ECZACILIK FAKÜLTESİ BÜLTENİ 10 ARALIK 2020

E-Gazi Farma

Cilt 5 Sayı 1

GAZİ ÜNİVERSİTESİ ECZACILIK FAKÜLTESİ

2020 YILI AR-GE BÜLTENİ

FAKÜLTEMİZ AKADEMİK FAALİYETLERİ (2020)

YAYINLAR

Araştırma Makaleleri

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PROJELER

- Gazi Üniversitesi BAP Projeleri
- TUBİTAK Projeleri

PATENTLER

TAMAMLANMIŞ TEZLER

ARAŞTIRMA MAKALELERİ

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MOLECULAR CANCER THERAPEUTICS | SMALL MOLECULE THERAPEUTICS

A Highly Potent TACC3 Inhibitor as a Novel Anticancer Drug Candidate

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ABSTRACT

TACC3, a transforming acidic coiled-coil (TACC) family member, is frequently upregulated in a broad spectrum of cancers, including breast cancer. It plays critical roles in protecting microtubule stability and centrosome integrity that is often dysregulated in cancers; therefore, making TACC3 a highly attractive therapeutic target. Here, we identified a new TACC3-targeting chemotype, BO-264, through the screening of in-house compound collection. Direct interaction between BO-264 and TACC3 was validated by using several biochemical methods, including drug affinity responsive target stability, cellular thermal shift assay, and isothermal titration calorimetry. BO-264 demonstrated superior antiproliferative activity to the two currently reported TACC3 inhibitors, especially in aggressive breast cancer subtypes, basal and HER2+, via spindle assembly checkpoint–dependent mitotic arrest, DNA damage, and apoptosis, while the cytotoxicity against normal breast cells was negligible. Furthermore, BO-264 significantly decreased centrosomal TACC3 during both mitosis and interphase. BO-264 displayed potent antiproliferative activity (~90% have less than 1 μmol/L GI_{50} value) in the NCI-60 cell line panel compromising of nine different cancer types. Noteworthy, BO-264 significantly inhibited the growth of cells harboring FGFR3–TACC3 fusion, an oncogenic driver in diverse malignancies. Importantly, its oral administration significantly impaired tumor growth in immunocompromised and immunocompetent breast and colon cancer mouse models, and increased survival without any major toxicity. Finally, TACC3 expression has been identified as strong independent prognostic factor in breast cancer and strongly prognostic in several different cancers. Overall, we identified a novel and highly potent TACC3 inhibitor as a novel potential anticancer agent, inducing spindle abnormalities and mitotic cell death.

Introduction

Microtubules have been important targets for cancer therapy because of their multifaceted functions in cell division, mitotic spindle formation, intracellular trafficking, and maintenance of cell shape and polarity (1). Microtubule-targeting agents (MTA), such as taxanes, maytansines, vinca alkaloids, colchicine, and combretastatin are therefore commonly used for the treatment of both hematologic and solid malignancies (2). However, the effectiveness of these agents has been impaired by various side effects, such as peripheral neuropathy (3) and possibly by acquisition of resistance to given therapy (4). Mitotic inhibitors, particularly those targeting Aurora kinases and Polo-like kinase 1 (PLK1), have demonstrated promising preclinical results, and several of these are currently being tested in clinics (5). However, the clinical benefit of most of these inhibitors is limited because of low therapeutic efficacy, necessitating the use of high doses that further leads to unwanted side effects. Therefore, discovery of novel therapeutic targets that are highly essential for mitotic cell division in cancer cells is urgently needed to achieve better antitumor efficacy with lower therapy-related side effects.

TACC3 is one of the most oncogenic members of the transforming acidic coiled-coil (TACC) family characterized by a conserved C-terminal motif, called the TACC domain that is required for binding to microtubules (6). TACC3 protein localizes at centrosomes and mitotic spindles and may also function as a plus-end tracking protein to regulate microtubule dynamics (7). Its depletion has been reported to inhibit microtubule nucleation at the centrosomes, form multipolar spindles during mitosis upon centrosome declustering (8), and results in chromosome misalignments leading to caspase-dependent apoptosis (9). Moreover, TACC3 inhibition may also reduce mitogenic signaling (10), block epidermal growth factor (EGF)-stimulated epithelial–mesenchymal transition (EMT; ref. 11), and mediate paclitaxel sensitization by triggering post-mitotic G_1-phase arrest via activating p53–p21 pathway (12). The mitotic functions of TACC3 are largely controlled by Aurora A kinase, which phosphorylates TACC3 at the Ser558 residue and ensures its recruitment to centrosomes and spindles in association with its interacting partner, ch-TOG (colonic and hepatic tumor overexpressed gene; ref. 13). This is followed by recruitment of clathrin, an endocytic and vesicle-trafficking protein, leading to the formation of the TACC3/ch-TOG/clathrin complex, which then acts as an intermicrotubule bridge stabilizing kinetochore fibers and preventing microtubule catastrophe (14).

Elevated levels of TACC3 have been observed in various cancers, including prostate cancer (15), hepatocellular carcinoma (HCC; ref. 16), non–small cell lung cancer (17), and breast cancer (18). Furthermore, downregulation of TACC3 with a small-molecule TACC3 inhibitor, KHS101 (19), reduced tumor growth of glioblastoma xenografts (20). TACC3 inhibition with KHS101 in breast cancer

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Surface enhanced Raman spectroscopy as a novel tool for rapid quantification of heroin and metabolites in saliva

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Background: Heroin can be detected and quantified by certain analytical methods, however, forensic professionals and criminal laboratories study for cheaper and faster detection tools. Surface-enhanced Raman spectroscopy (SERS) rises as a possible alternative tool with its widening application spectra. There are few studies regarding Raman and SERS spectra of heroin and its metabolites, which are unfortunately controversial. In this study, we compared five different surfaces in order to find out more efficient Raman-active substrate for opiate detection and rapid quantification of heroin and its metabolites in saliva.

Materials and methods: Morphine standard material was used to identify proper surface for SERS analysis of opiates. Heroin and its metabolites (morphine, morphine-3-ß-glucuronide and 6-monoacetyl morphine) were calibrated between 50 ppb and 500 ppm and quantified on AuNRs with signal enhancement of silver colloids in saliva. Raman microscope with a 785-nm laser source was used.

Results and Conclusion: Obtained results showed that heroin and its metabolites can be detected and quantified in saliva samples using a SERS-based system. Additionally, the present study revealed that synergetic effect of a specific gold nano-surface with ability controlling liquid motion and silver nanoparticles increase band numbers and intensities. Therefore, we suggest a fast, accurate and cost-effective method to detect and quantify heroin in biological fluids.

Keywords: Heroin and morphine identification, Heroin and morphine quantification, surface-enhanced Raman spectroscopy (SERS), Raman-active surface, gold nanorod arrays, silver nanoparticles

1. Introduction

Abuse of illicit drugs, including high-risk opioids, is still a major problem globally. It is responsible from increasing mortality and morbidity, particularly in young population. Heroin is one of the most commonly abused illicit drugs, which is diacetyl product of morphine that most commonly extracted from *Papaver somniferum* [1]. In a survey study from the United States [2], it has been stated that heroin use is extending in the population from city centers to urban areas and to different socio-cultural classes. According to World Drug Report 2017[1] and European Drug Report 2017[2] heroin is still the leading substance for addiction among high-risk opioids. Heroin addiction is still a widespread problem as a significant cause of morbidity and mortality due to increased risk of cardiopulmonary diseases, chronic infections including Hepatitis C and hepatic failure[2].

The use of surface enhanced Raman spectroscopy (SERS) increases in forensic sciences applications. SERS is a potentially fast and cost-effective analytical method requiring very little amount of sample. There is a large number of SERS based studies dealing with identification of chemical trace evidences and certain body fluids [3–10]. On the other hand, there are few SERS studies regarding identification of toxicological substances including morphine, cocaine and heroin directly dealing with

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Case report

Meropenem, rifampicin and gentamicin combination therapy in a patient with complicated urinary tract infection caused by extreme drug-resistant *P. aeruginosa*

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SUMMARY

In this article, we report a case of a 25-year-old male patient who was under follow-up for nephrolithiasis and repeated urological interventions. His last operation was carried out 9 months ago for insertion of a double-J catheter. *Pseudomonas aeruginosa*, which is susceptible to only colistin treatment, was detected in the urine culture. Before the removal of the double-J catheter, colistin and ceftazidime antibiotics were started to prevent the risk of bloodstream infection. However, the treatment was stopped urgently due to signs of nephrotoxicity. His treatment was restarted with colistin 300 mg once as the initial loading dose, followed by 150 mg/day. However, this time, colistin neurotoxicity has developed and the treatment was again stopped. Meropenem 6 g/day, gentamicin 2 mg/kg and rifampicin 300 mg were prescribed. Negative urine culture was achieved on the fifth day of treatment.

BACKGROUND

Management of nosocomial infections caused by Gram-negative bacteria with multiple drug resistance is becoming gradually difficult[1] due to the limited number of antibiotics that are effective in vitro. Use of polymyxin (colistimethate sodium), which is the only option for treatment of extreme drug-resistant (XDR), Gram-negative bacterial infections, is limited due to the risks of nephrotoxicity and neurotoxicity.[2] In this case, pharmacists aimed to emphasise coadministration of antibiotics by considering that their pharmacodynamic properties can be effective, even if the bacteria are resistant to these antibiotics in vitro.

CASE PRESENTATION

The patient, who is under follow-up due to nephrolithiasis and repeated urological interventions, was operated on in April 2018 at an infectious diseases outpatient clinic so as to insert a double-J catheter. The patient's complaints were dysuria, pollakiuria, fever and right costovertebral angle tenderness. Laboratory assessment showed that the patient's white cell count (WCC) was 5.8×10^3/L, C reactive protein (CRP) was 4.2 mg/dL, creatinine was 0.96 mg/dL and ALT was 34 U/L. Urinalysis showed positive nitrites in the urine and that the patient had pyuria. Urology physicians asked to remove the catheter, but the infection practitioners thought that the patient had a risk of bloodstream infection and septic shock if the biofilm in the infected catheter is removed. Therefore, the catheter was not removed until the urine culture became negative.

Pseudomonas aeruginosa, which is susceptible to only colistin treatment, was detected in the urine culture, so 300 mg colistin (colistimethate sodium equivalent to 300 mg colistin basic activity) was administered as the initial loading dose, followed by 150 mg/day maintenance therapy through infusion, plus ceftazidime 2 g twice in a day. An increase in blood creatinine levels (from 0.96 mg/dL to 2.23 mg/dL) and a reduction in GFR (52%) were seen on the second day of treatment, which might be signs of colistin nephrotoxicity. The treatment was stopped urgently. The patient, who had no sign of systemic infection, was monitored without any drug treatment over the period of time. The creatinine value decreased from 2.23 mg/dL to 1.3 mg/dL by means of hydration therapy with 0.09% NaCl administered parenterally. However, XDR *P. aeruginosa* was detected once more in the urine culture. Colistin treatment was restarted at 300 mg as the initial loading dose, followed by 150 mg/day. However, treatment was again stopped due to complaints of vertigo, numbness, itching around the mouth and irritability, which were considered signs of neurotoxicity caused by colistin.

According to E test (Epsilometer), the minimum inhibitory concentration (MIC) values were for meropenem 32 g/L and gentamicin 8 mg/L. They are considered to be resistant to the EUCAST (European Committee on Antimicrobial Susceptibility Testing) 2018 criteria (MIC breakpoint gentamicin, R>4 mg/L, MIC breakpoint meropenem R>8 mg/L). Although meropenem and gentamicin were resistant, they were used in the treatment due to their synergistic effects. Rifampicin was added to the combination due to its increased biofilm penetration and synergistic effect. Meropenem 6 g/day (dosage regimen divided into three steps) in slow infusion for 9 hours, gentamicin 2 mg/kg (intravenously, every 8 hours) and rifampicin 300 mg (orally, twice in a day) were prescribed. Negative urine culture was achieved on the fifth day of treatment. Medical examination showed WCC at $7.58 \times 10.e3/\mu L$, CRP of 8.01 mg/dL, creatinine of 0.93 mg/dL and ALT of 17 U/L (50% lower than the first measured ALT of the patient). The double-J catheter was removed from the patient's ureter. The treatment was continued after the urological intervention and urine culture resulted with no bacterial

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Research article

The impacts of prominent gene polymorphisms in DNA repair enzymes on Parkinson's disease

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ABSTRACT

Parkinson's Disease (PD), a chronic and progressive neurodegenerative disease of the brain, is associated with the loss of dopaminergic neurons. Its pathogenesis remains unclear; however, oxidative DNA damage due to reactive oxygen species (ROS) is believed to play a major role in the etiology of PD. DNA repair systems can mitigate oxidative DNA damage and help to maintain genomic stability and thus prevent neuronal death. However, gene polymorphisms on DNA repair enzymes may alter the functions of enzymes and increase the risk of PD. The present study aims to investigate a possible link between the *OGG1*, *XRCC1*, and *MTH1* gene polymorphisms and PD risk in 97 patients with PD and 102 controls in the Turkish population. Our genotyping study utilizing polymerase chain reaction-restriction fragment length polymorphism revealed no relationship between two gene polymorphisms (*OGG1Ser326Cys* and *MTH1Val83Met*) and PD risk. Participants with the *XRCC1* variant genotypes had a two to three and a half fold higher risk of PD than controls ($p = 0.046$, OR = 1.910, 95 % CI = [1.013–3.603] and $p = 0.006$, OR = 3.742, 95 % CI = [1.470–9.525], respectively). Our results suggested that *XRCC1 Arg399Gln* polymorphism is a risk factor for PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative process that affects approximately 1 % of the population over 65 years old. PD is a neurological disease with a multifactorial etiology that includes environmental (such as cigarette smoke, pesticides, herbicides, and heavy metals) and genetic factors [1–3]. The pathogenesis of PD still remains obscure; however, current evidence supports that an age-related increase in oxidative DNA damage may be the main risk factor [4]. Studies have shown that reactive oxygen species (ROS) are generated excessively in the brains of patients with PD and may attack macromolecules like DNA [5–7]. Many studies have also confirmed that ROS and oxidative DNA damage are part of pathological processes during PD [7,8], but it has not yet been determined whether this is a major event or a result of other cellular dysfunctions. Genetic polymorphisms may alter or decrease DNA repair capacity and affect the susceptibility to PD. Analysis of the polymorphisms of DNA repair enzymes can clarify whether PD may arise from a genetic predisposition to oxidative stress [8]. Enhanced production of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a marker of DNA damage induced by ROS in the midbrain of patients with PD, creates laboratory evidence of oxidative damage [5]. It is an oxidized form of guanine, yielding G:C to T:A transversion. Organisms have many protective mechanisms against oxidative DNA damage, including the base excision repair (BER) pathway. In BER, 8-oxoG DNA glycosylase (*hOGG1*), which is encoded by the human *OGG1* gene, recognizes and removes the altered base (8-OHdG) [6,9]. *OGG1* is polymorphic and has several polymorphisms. The higher expression levels of *OGG1* enzymes have been found in patients with PD [6].

Another repair enzyme that also has a major role in BER is X-ray repair cross-complementing 1, encoded by the *XRCC1* gene. The protein participates in the repair of DNA single-strand breaks and interacts with *OGG1*, poly (ADP-ribose) polymerase (PARP), DNA ligase III, and DNA polymerase β in BER [10–12]. Three polymorphisms (*Arg/Gln*, *Arg/His*, and *Arg/Trp*) have been described in the *XRCC1* gene. One of them is the *Arg399Gln* polymorphism that has been shown to alter DNA repair capacity [13]. The codon 399 polymorphism has been shown to affect DNA repair capacity, while the significance of the other two polymorphisms is not yet known in genotoxic measurement [14].

Human *MTH1*, an oxidized purine nucleoside triphosphatase, has a major role in BER, in that it hydrolyzes 8-oxo-dGTP and 2-hydroxy-dATP in the nucleotide pool. *MTH1* is considered a potential marker of oxidative DNA damage since its function is to reduce the accumulation of oxidized nucleotides in DNA [15]. Its activity can, therefore, be used

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REVIEWS

Natural products in drug discovery: advances and opportunities

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Abstract | Natural products and their structural analogues have historically made a major contribution to pharmacotherapy, especially for cancer and infectious diseases. Nevertheless, natural products also present challenges for drug discovery, such as technical barriers to screening, isolation, characterization and optimization, which contributed to a decline in their pursuit by the pharmaceutical industry from the 1990s onwards. In recent years, several technological and scientific developments — including improved analytical tools, genome mining and engineering strategies, and microbial culturing advances — are addressing such challenges and opening up new opportunities. Consequently, interest in natural products as drug leads is being revitalized, particularly for tackling antimicrobial resistance. Here, we summarize recent technological developments that are enabling natural-product-based drug discovery, highlight selected applications and discuss key opportunities.

the International Natural Product Sciences Taskforce

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Antiproliferative constituents from the aerial parts of *Chrysophthalmum montanum* (DC.) Boiss

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ABSTRACT

Three undescribed sesquiterpene lactones (1-3), 1β,4β-dihydroxy-guaia-10(14),11(13)-dien-8α,12-olide (1), 4α,6α-dihydroxy-9β,10β-epoxy-1βH-guaia-11(13)-en-8α,12-olide (2), and 4α,9β-dihydroxy-6α-acetoxy-1βH-guaia-10(14),11(13)-dien-8α,12-olide (3), as well as a known sesquiterpene lactone, (4α,5α,8β,10α)-4,10-dihydroxy-1,11(13)-guaiadien-12,8-olide (4), along with a lignan, pinoresinol (5), a flavonoid, chrysosplenol C (6), and two triterpenes, a mixture of isomers, taraxasterol acetate and Ψ-taraxasterol acetate (7a/7b), and a mixture of isomers taraxasterol and Ψ-taraxasterol (8a/8b) were isolated from the aerial parts of *Chrysophthalmum montanum* (DC.) Boiss. The structures of 1-6, 7a/7b, and 8a/8b were established on the basis of spectroscopic evidence, such as MS, NMR, UV, and IR spectroscopy. All isolated compounds, except for 5 and 8a/8b, were assayed for their antiproliferative activities against three human cancer cell lines, i.e. cervical (HeLa), breast (MCF-7), and lung (A549), and a normal human lung cell line (BEAS-2B) using MTT method. Compounds 1, 4, and 6 showed significant inhibitory effects on cancer cell growth at 20 μg/mL concentration, with cell viability ranging from 53 to 64 % against MCF-7 cell line. In addition, compounds 4, and 6 exhibited cytotoxicity against HeLa cancer cell line with the viability of approximately 64 %. In conclusion, compounds 1, 4, and 6 may serve as leads for further research towards the development of anticancer agents.

1. Introduction

Chrysophthalmum montanum (DC.) Boiss. (Asteraceae), called "tutça" or "nezle otu" in Turkish, is a perennial herbaceous plant growing in rock crevices and limestone cliffs, widely distributed in the Southeastern, and Eastern parts of Turkey (Grierson, 1975; Aytac and Anderberg, 2001). It is used in Turkish folk medicine to alleviate respiratory problems in flu, and common cold, as well as for wound healing of both humans, and animals (Yeşil and Akalın, 2009; Özkan and Koyuncu, 2005; Arasan and Kaya, 2015).

A few studies on preliminary biological activities such as cytotoxicity, antimicrobial, and acetylcholinesterase inhibitory effects, and chemical constituents of *C. montanum* have been reported (Kirbağ et al., 2009; Ozdemir et al., 2013; Gürbüz et al., 2016; Gecibesler et al., 2017; Gürbüz and Doğan, 2017). In our primary screening study, the *n*-hexane, and chloroform subextracts, obtained from the crude methanol extract of *C. montanum* aerial parts, were found to be significantly active against their cytotoxic and phytotoxic activities (Ayaz et al., 2017). In our further studies on this plant, the chloroform subextract exhibited the most potent cytotoxic activity against four human cancer cell lines [MCF 7, MDA-MB-231, PC3 (p53 mutant), and HT-29] by using SRB assay. As a part of our continued effort to discover potent anticancer constituents from the chloroform subextract of *C. montanum*, four cytotoxic guaianolides were isolated through bioassay-guided fractionation, and isolation procedures. Among these cytotoxic compounds, a C1(2)-en, 8,12-*cis*-guaianolide, (4α,5α,8β,10β)-4,10-dihydroxy-1,11(13)-guaidien-12,8-olide, showed strong, and selective cytotoxicity to HT-29 colon cancer cells, indicating significantly less toxicity towards the normal human lung cell line (BEAS-2B) (Ayaz et al., 2019). Similarly, in one of our other studies carried out on this plant,

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Anti-inflammatory Activity of Sesquiterpene Lactones from *Chrysophthalmum montanum* (DC.) Boiss.

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Abstract: The aerial parts of *Chrysophthalmum montanum* (DC.) Boiss. (Asteraceae) is traditionally used for wound healing, as well as for the treatment of common cold, sinusitis, and other inflammatory diseases. The objectives of this study were to identify potential anti-inflammatory effects of the methanol extract, and its different polarity subextracts (*n*-hexane, chloroform, *n*-butanol, and remaining aqueous), and guaianolide-type sesquiterpene lactones [6*α*-acetoxy-4*α*-hydroxy-1*β*H-guaia-9.11(13)-dien-12.8*α*-olide (**1**), 6*α*-acetoxy-4*α*-hydroxy-9*β*.10*β*-epoxy-1*β*H-guaia-11(13)-en-12.8*α*-olide (**2**), 4*α*,6*α*-dihydroxy-1*β*,5*α*,7*α*H-guaia-9(10),11(13)-dien-12,8*α*-olide (**3**), and (4*α*,5*α*,8*β*,10*β*)-4,10-dihydroxy-1,11(13)-guaidien-12,8-olide (**4**)] from the aerial parts of *C. montanum*. In order to evaluate the anti-inflammatory activity of *C. montanum*, carrageenan- and PGE_2-induced hind paw edema, and acetic acid-induced increase in capillary permeability mice models were used. The methanol extract, the chloroform subextract, and compounds **3**, and **4** were shown to possess anti-inflammatory activity in *in vivo* models at 100 mg/kg dose. The results provide a biological, and phytochemical basis for the traditional use of *C. montanum* aerial parts for inflammatory conditions in Turkish folk medicine.

Keywords: Asteraceae; *Chrysophthalmum montanum;* sesquiterpene lactones; anti-inflammatory; carrageenan; prostaglandins.

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ORIGINAL ARTICLE Open Access

N-glycolyl chondroitin synthesis using metabolically engineered *E. coli*

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Abstract

N-glycolyl chondroitin (Gc-CN) is a metabolite of *N*-glycolylneuraminic acid (Neu5Gc), a sialic acid that is commonly found in mammals, but not humans. Humans can incorporate exogenous Neu5Gc into their tissues from eating red meat. Neu5Gc cannot be biosynthesized by humans due to an evolutionary mutation and has been implicated in causing inflammation causing human diseases, such as cancer. The study Neu5Gc is important in evolutionary biology and the development of potential cancer biomarkers. Unfortunately, there are several limitations to detecting Neu5Gc. The elimination of Neu5Gc involves a degradative pathway leading to the incorporation of *N*-glycolyl groups into glycosaminoglycans (GAGs), such as Gc-CN. Gc-CN has been found in humans and in animals including mice, lamb and chimpanzees. Here, we present the biosynthesis of Gc-CN in bacteria by feeding chemically synthesized *N*-glycolylglucosamine to *Escherichia coli*. A metabolically engineered strain of *E. coli* K4, fed with glucose supplemented with GlcNGc, converted it to *N*-glycolylgalactosamine (GalNGc) that could then be utilized as a substrate in the chondroitin biosynthetic pathway. The final product, Gc-CN was converted to disaccharides using chondroitin lyase ABC and analyzed by liquid chromatography–tandem mass spectrometry with multiple reaction monitoring detection. This analysis showed the incorporation of GalNGc into the backbone of the chondroitin oligosaccharide.

Keywords: Sialic acid, Biotransformation, *N*-glycolyl chondroitin, Metabolite, *N*-glycolyl glucosamine

Key points

1. *N*-glycolyl chondroitin (Gc-CN) is a stable metabolite of Neu5Gc.
2. Metabolic engineering of *E. coli* K4.
3. *E. coli* has promiscuous enzymes involved in CN biosynthesis.
4. Feeding *E. coli* K4 with GlcNGc affords Gc-CN.

Introduction

Sialic acids constitute a family of acidic sugars with a 9-carbon backbone found at the terminal end of glycan chains attached to many soluble glycoproteins (Schauer 2000; Wang and Brand-Miller 2003). Their presence at the terminal end of sugars gives them an advantage in performing their biological roles, providing structure, serving as a ligand for intrinsic and extrinsic receptors, as a binding site for pathogens and toxins, and in molecular mimicry for host invasion (Varki 2008). Sialic acids are mainly expressed in vertebrates and certain bacteria (Angata and Varki 2002). In mammals, the two most common sialic acids found are *N*-acetylneuraminic acid (Neu5Ac) and *N*-glycolylneuraminic acid (Neu5Gc). An enzyme called cytidine monophosphate *N*-acetylneuraminic acid hydroxylase (Cmah), encoded by the *CMAH* gene, is responsible for converting CMP-Neu5Ac to CMP-Neu5Gc through the addition of an oxygen atom

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ORIGINAL ARTICLE

Reversal of deleterious effect of hypertension on the liver by inhibition of endoplasmic reticulum stress

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Abstract
Hypertension is an important risk factor for cardiovascular diseases. Besides cardiovascular system, it could cause damage to liver. It has been shown that endoplasmic reticulum stress (ERS) plays a crucial role in the pathogenesis of hypertension. ERS inhibitor tauroursodeoxycholic-acid (TUDCA) has favorable effects on various pathologies including cardiovascular, metabolic and hepatic diseases. In this study, the hepatoprotective effect and mechanism of TUDCA were investigated in the deoxycorticosterone acetate (DOCA)-salt-induced hypertension. Male Wistar rats were used and divided into four groups: Control, DOCA, TUDCA and DOCA + TUDCA. Hypertension was induced by DOCA-salt administration for twelve weeks after the unilateral nephrectomy. TUDCA was given for the last 4 weeks. Systolic blood pressure was measured by using tail-cuff method. At the end of the treatment, liver was isolated and weighed. The expressions of various proteins and histopathological evaluation were examined in the liver. TUDCA markedly decreased systolic blood pressure in the hypertensive animals. Hypertension caused increase in the expressions of glucose-regulated protein-78 (GRP78), matrix metalloproteinase-2 (MMP-2) and phospho-inhibitor κB-α (p-IκB-α) and the decrease in the expression of sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase2 (SERCA2) and phospho-extracellular signal-regulated kinase (p-ERK) in the liver. Alterations in these protein expressions were not detected in the TUDCA-treated hypertensive group. Also, hepatic ballooon degeneration, inflammation and fibrosis were observed in the hypertensive group. TUDCA improved inflammation and fibrosis in the hypertensive liver. Our findings indicate that the detrimental effect of DOCA-salt-induced hypertension on the liver was defended by the inhibition of ERS. Hepatic ERS and its treatment should be taken into consideration for therapeutic approaches to hypertension.

Keywords Hypertension · Liver · Endoplasmic reticulum stress · TUDCA

Introduction

Hypertension, which is a common cardiovascular disease, is an important public health problem leading to morbidity and mortality worldwide [1]. Hypertension is a systemic disease that disturbs the physiological balance of body, and affects several organs such as heart, vessels, kidneys, brain and liver [2]. Although hypertension-induced molecular and structural pathologies have been searched in main organs, liver pathologies have not been investigated in detail yet.

The endoplasmic reticulum (ER) modulates protein synthesis, folding and trafficking as well as intracellular calcium homeostasis. Several conditions, for example the accumulation of unfolded/misfolded proteins into the ER, depletion of calcium deposition, starvation and hypoxia can deteriorate the functioning of the ER, which leads to endoplasmic reticulum stress (ERS) [3]. Known as unfolded protein response for restoration of ER homeostasis, various signal pathways are triggered by ERS. When the deterioration is moderate, the UPR promotes the improvement of ER function and helps the adaptation of the cells to the altered situations. However, if the perturbation is excessive and prolonged, the UPR initiates apoptotic signaling pathways that contribute to the pathogenesis of various diseases [4, 5]. Previous studies have reported that ERS also activates

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Research Article

Filiz Bakar-Ates*, Berna Hoti, Ilhan Gurbuz, Tugba Gunbatan, Hayri Duman and Ceyda Sibel Kilic

The cytotoxic and apoptotic effects of *Ferulago* W. Koch extracts on various cancer cell lines

[Ferulago W. Koch Türlerinin Çeşitli Kanser Hücre Hatlarında Sitotoksik ve Apoptotik Etkinlikleri]

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Abstract

Background: The studies investigating the anticancer activities of natural products have accelerated to produce new solutions in the face of increasing cancer cases. Various *Ferulago* species are reported to exhibit antioxidant, antiulcer and antimicrobial activities.
Objective: This study aimed to evaluate the cytotoxic and apoptotic activities of ethanolic extracts of roots of five *Ferulago* species on various human cancer cell lines.
Material and methods: HPLC analyses were performed by HP Agilent 1,100. The cytotoxicity were determined by MTT assay. The cell cycle arrest and Annexin V binding analyses were performed by Muse Cell Analyzer (Millipore).
Results: All examined species except *F. setifolia* inhibited cell viability in PC3 and SW480 cells at 0.01 mg/mL and higher concentrations ($p<0.05$). *Ferulago* species inhibited cell cycle at different stages for treated cell lines. The ethanolic extracts of *Ferulago* species also increased Annexin V binding significantly, resulted in apoptosis ($p<0.05\%$). In this context, *F. syriaca* showed the highest apoptotic activity in MCF-7 cells by increasing the apoptotic cell population to 23.54 ± 2.10% ($p<0.0001$).
Conclusion: The findings of present study have shown that *Ferulago* species included in the study have potent anticancer effects and this work have the potential to result in further studies.

Keywords: antiproliferative; apiaceae; apoptosis; cell cycle; Ferulago sp; medicinal plant.

Öz

Amaç: Doğal ürünlerin antikanser aktivitelerini araştıran çalışmalar, artan kanser vakaları karşısında yeni çözümler üretmek için giderek hız kazanmıştır. Çeşitli Ferulago türlerinin antioksidan, antiülser ve antimikrobiyal aktiviteler sergilediği bildirilmiştir. Bu çalışmada, beş Ferulago türünün köklerinin etanolik ekstraktlarının çeşitli insan kanser hücre hatları üzerindeki sitotoksik ve apoptotik aktivitelerinin değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntem: HPLC analizleri, HP Agilent 1,100 ile yapıldı. Sitotoksisite, MTT testi ile belirlendi. Hücre döngüsü tutulumu ve Annexin V bağlanma analizleri, Muse Cell Analyzer (Millipore) ile gerçekleştirildi.
Bulgular: Elde edilen bulgulara göre, *F. setifolia* dışında incelenen tüm türler, PC3 ve SW480 hücrelerinde 0,01 mg/mL ve daha yüksek konsantrasyonlarda hücre canlılığını inhibe etmiştir ($p<0,05$). Ferulago türlerinin, ekstre uygulanan hücre hatları için farklı aşamalarda hücre döngüsünü inhibe ettiği gözlenmiştir. Ferulago türlerinin etanolik ekstreleri, Annexin V bağlanmasını önemli ölçüde artırmış ve apoptozu indüklediği belirlenmiştir ($p<\%0,05$).

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The evaluation of the oxidative stress index of reproductive tissues and serum thiol/disulphide homeostasis during estrous cycle in bitches

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Abstract: The aim of this study was firstly to determine the relationship between estrous cycle and oxidative stress in reproductive tissues in bitches. This research was performed in twenty-nine healthy bitches from different breeds and of varied ages (the range was 2-5 years) that were brought to the clinic for routine ovariohysterectomy. The stages of estrous cycle were detected using by vaginal cytology, blood progesterone level and histological findings. Ovarian, oviduct and uterine tissues were taken into Eppendorf tubes for oxidative stress index and stored at -80°C until analyses. Also, another part of these tissues were fixed in 10% formalin solution. There were no significant differences ($P > 0.05$) among total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI) values in the reproductive tissues in concerning estrous cycle stages. However, there were remarkable correlations between oxidative stress parameters and reproductive tissues in different estrus stages in bitches. In conclusion, the physiological values of TAS and TOS concentration, and OSI in the ovarian, oviduct and uterine tissues during estrous cycle were firstly defined in this article. The serum thiol/disulphide homeostasis was also determined in the estrous cycle of bitches. We have found that there are remarkable variations of oxidative stress balance in the ovary, oviduct and uterus concurrently, during estrous cycle in the bitches. Besides, significant correlations between oxidative stress parameters and estrous cycle stages in the reproductive tissues were observed in the present study.
Keywords: Bitch, estrous cycle, oxidative stress index, progesterone, thiol/disulphide.

Köpeklerde östrus siklusu boyunca reprodüktif dokularda oksidatif stres indeksi ve serum tiyol/disülfit homestazının değerlendirilmesi

Özet: Bu çalışmada, köpeklerde östrus siklusu ile reprodüktif organlardaki oksidatif stres arasındaki ilişkinin ilk olarak ortaya konulması amaçlandı. Bu araştırma, rutin ovaryohisterektomi için kliniğe getirilen farklı ırklardan ve değişik yaşlardan (2-5 yıl arasında) sağlıklı yirmi dokuz köpekte gerçekleştirildi. Östrus siklusunun evreleri vajinal sitoloji, kan progesteron seviyesi ve histolojik bulgular ile tespit edildi. Ovaryum, ovidukt ve uterus dokuları, oksidatif stres indeksinin belirlenmesi için Eppendorf tüplerine alındı ve analiz edilene kadar -80°C'de saklandı. Ayrıca, bu dokuların diğer bir kısmı %10 formalinde fikse edildi. Reprodüktif organlardaki total antioksidan durum (TAS), total oksidan durum (TOS) ve oksidatif stres indeksi (OSI) düzeylerinde östrus siklusu evreleri bakımından istatistiksel bir fark bulunmadı ($P > 0,05$). Ancak östrus siklusunun farklı evrelerinde oksidatif stres parametreleri ile reprodüktif dokular arasında dikkat çekici korelasyonlar belirlendi. Sonuç olarak, bu araştırma ile köpeklerde östrus siklusu boyunca ovaryum, ovidukt ve uterus dokusundaki TAS, TOS ve OSI'nin fizyolojik değerleri ilk kez ortaya konuldu. Ayrıca köpeklerde östrus siklusunun evrelerine göre serum thiol/disülfit homeostazisi de belirlendi. Bununla birlikte, reprodüktif dokulardaki oksidatif stres parametreleri ile östrus siklusunun evreleri arasında önemli korelasyonların olduğu gözlendi.
Anahtar sözcükler: Dişi köpek, oksidatif stres indeksi, östrus siklusu, progesteron, tiyol/disülfit.

Introduction

Domestic canids are typically classified as monoestrus, and have three estrous cycle every two years. However, in domestic bitches, most females display two estrous cycle in one year. The estrous cycle of bitches is much longer than those of other animals, and consists of proestrus, estrus, diestrus and anestrus stages (22). Endocrine mechanism of canine cycle differs from other mammalian species; ovulation occurs 2-3 days after LH surge at the end of proestrus or at the beginning of estrus

molecules

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Article

Cognitive Facilitation and Antioxidant Effects of an Essential Oil Mix on Scopolamine-Induced Amnesia in Rats: Molecular Modeling of In Vitro and In Vivo Approaches

Razvan Stefan Boiangiu [1], Ion Brinza [1], Monica Hancianu [2], Ilkay Erdogan Orhan [3], Gokcen Eren [4], Elife Gündüz [5], Halis Ertas [5], Lucian Hritcu [1,*] and Oana Cioanca [2]

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Abstract: The present study investigated the capability of an essential oil mix (MO: 1% and 3%) in ameliorating amnesia and brain oxidative stress in a rat model of scopolamine (Sco) and tried to explore the underlying mechanism. The MO was administered by inhalation to rats once daily for 21 days, while Sco (0.7 mg/kg) treatment was delivered 30 min before behavioral tests. Donepezil (DP: 5 mg/kg) was used as a positive reference drug. The cognitive-enhancing effects of the MO in the Sco rat model were assessed in the Y-maze, radial arm maze (RAM), and novel object recognition (NOR) tests. As identified by gas chromatography–mass spectrometry (GC–MS), the chemical composition of the MO is comprised by limonene (91.11%), followed by γ-terpinene (2.02%), β-myrcene (1.92%), β-pinene (1.76%), α-pinene (1.01%), sabinene (0.67%), linalool (0.55%), cymene (0.53%), and valencene (0.43%). Molecular interactions of limonene as the major compound in MO with the active site of butyrylcholinesterase (BChE) was explored via molecular docking experiments, and Van der Waals (vdW) contacts were observed between limonene and the active site residues SER198, HIS438, LEU286, VAL288, and PHE329. The brain oxidative status and acetylcholinesterase (AChE) and BChE inhibitory activities were also determined. MO reversed Sco-induced memory deficits and brain oxidative stress, along with cholinesterase inhibitory effects, which is an important mechanism in the anti-amnesia effect. Our present findings suggest that MO ameliorated memory impairment induced by Sco via restoration of the cholinergic system activity and brain antioxidant status.

Keywords: essential oil mix; scopolamine; memory; oxidative stress; molecular docking simulation

1. Introduction

Neurodegeneration can be defined as forfeiture of neuron structure and function in a progressive way, which is associated with various diseases such as Alzheimer's disease (AD), Parkinson's disease, Huntington disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), etc. [1]. Among them, AD is estimated to affect approximately 40 million people all over the world, with an increasing

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RESEARCH ARTICLE

A Series of New Hydrazone Derivatives: Synthesis, Molecular Docking and Anticholinesterase Activity Studies

İrem Bozbey[1,*], Zeynep Özdemir[2], Harun Uslu[3], Azime Berna Özçelik[4], Fatma Sezer Şenol[5], İlkay Erdoğan Orhan[5] and Mehtap Uysal[1,4]

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Abstract: ***Background***: Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are known to be serine hydrolase enzymes responsible for the hydrolysis of acetylcholine (ACh), which is a significant neurotransmitter for regulation of cognition in animals. Inhibition of cholinesterases is an effective method to curb Alzheimer's disease, a progressive and fatal neurological disorder.

Objective: In this study, 30 new hydrazone derivatives were synthesized. Then we evaluated their anticholinesterase activity of compounds. We also tried to get insights into binding interactions of the synthesized compounds in the active site of both enzymes by using molecular docking approach.

Methods: The compounds were synthesized by the reaction of various substituted/nonsubstituted benzaldehydes with 6-(substitute/nonsubstituephenyl)-3(2*H*)-pyridazinone-2-yl propiyohydrazide. Anticholinesterase activity of the compounds was determined using Ellman's method. Molecular docking studies were done by using the ADT package version 1.5.6rc3 and showed by Maestro. RMSD values were obtained using Lamarckian Genetic Algorithm and scoring function of AutoDock 4.2 release 4.2.5.1 software.

Results: The activities of the compounds were compared with galantamine as cholinesterase enzyme inhibitor, where some of the compounds showed higher BChE inhibitory activity than galantamine. Compound $\mathbf{F1_{11}}$ was shown to be the best BChE inhibitor effective in 50 μM dose, providing 89.43% inhibition of BChE (IC_{50}=4.27±0.36 μM).

Conclusion: This study supports that novel hydrazone derivates may be used for the development of new BChE inhibitory agents.

Keywords: Alzheimer's disease, AChE inhibitor, BChE inhibitor, 3(2*H*)-Pyridazinone, hydrazone, molecular docking.

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1. INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in the elderly [1]. Although the pathophysiology of AD is still unknown, it is thought that the disease results from an unidentified cause of brain cell loss. Among the characteristic pathological findings of the disease are extracellular senile plaques in the brain, neurofibrillary tangles inside neurons, loss of neurons and synapses [2]. Biochemical studies indicate that some neuromediators decrease in the cortex, particularly acetylcholine. Neuronal and axonal losses, which co-occur at the beginning of the disease, cause a release of lower levels of acetylcholine, therefore, nerve conduction may be interrupted, which could be explained by "the cholinergic hypothesis". This hypothesis puts an emphasis on acetylcholine deficiency leading to an increase in the symptoms of disease. One of the methods to be applied to increase the level of acetylcholine is the suppression of the acetylcholinesterase (AChE) and buthyrilcholinesterase (BChE) enzymes, which are known as cholinesterases (ChEs) taking place in serine hydrolase enzyme series. The main task of AChE in cholinergic synapses is to hydrolyze

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Evaluation of Activity of Some 2,5-Disubstituted Benzoxazole Derivatives against Acetylcholinesterase, Butyrylcholinesterase and Tyrosinase: ADME Prediction, DFT and Comparative Molecular Docking Studies

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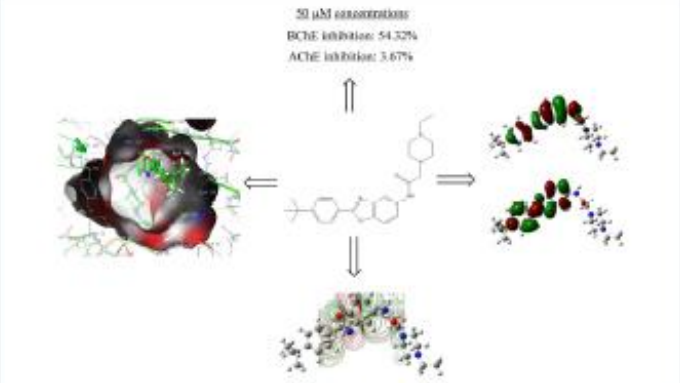
ABSTRACT

In this study, *p*-tert-butyl at position 2 and acetamide bridged 4-substituted piperazine/piperidine at position 5 bearing benzoxazole derivatives were evaluated for their *in vitro* inhibitory activity against AChE, BChE and Tyrosinase, which are important targets in reducing the adverse effects of Alzheimer's disease. The most active **1g** inhibited the BChE at a concentration of 50 µM by 54 ± 0.75%. Molecular docking studies of the compounds against BChE (PDB: 4BDS) were performed with Schrödinger and AutoDock Vina and the results were compared. Schrödinger docking scores were found to be more consistent. Estimated ADME profiles and bioactivity scores of the compounds were calculated and found to be compatible with Lipinski and other limiting rules. Geometric optimization parameters, MEP analysis and HUMO and LUMO quantum parameters of the most active **1g** were calculated by using DFT/B3LYP theory and 6-311G (d,p) base set and results was viewed.



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KEYWORDS
Alzheimer's disease; butyrylcholinesterase; DFT; MEP; molecular docking

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ORIGINAL ARTICLE

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Assessment of Bisphenol A Levels in Preschool Children: Results of a Human Biomonitoring Study in Ankara, Turkey

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What is already known on this topic?

Bisphenol A (BPA) is an endocrine disrupting chemical and exposure to BPA is almost inevitable in daily life. Relationships between BPA exposure and various health risks have begun to be established. In different societies, BPA levels in young children seem to be higher in comparison with adolescents and adults.

What this study adds?

This first study of biomonitoring in preschool children from Turkey is an important contribution to the limited information about childhood exposure to BPA in Turkey and the world. The magnitude of exposure of BPA by children, estimated daily intake was calculated first time for Turkish children in this study.

Abstract

Objective: There is general concern regarding environmental chemical exposure and the impact it may have on human health. This is particularly important for vulnerable populations such as infants and children during critical periods of development. Bisphenol A (BPA) is an endocrine disrupting chemical used worldwide over the last 30 years in many consumer products. Evidence points to widespread human exposure to BPA. The aim of this study was to evaluate the exposure of Turkish preschool children to BPA.

Methods: This study was conducted as a preliminary investigation of BPA in urine, collected from 3-6 year old children living in Ankara. After spot urine samples were taken from preschool children, free BPA, β-D-glucuronide and total BPA were determined using high-performance liquid chromatography tandem mass spectrometry and adjusted by creatinine concentration.

Results: Preschool children from Ankara (n = 125; males n = 70, females n = 55; mean age: 4.50 ± 1.26) were recruited. BPA was detected in 76.8% of children from Ankara city, with urinary concentrations ranging from < limit of quantification to 18.36 µg/g creatinine. Total BPA levels were not statistically different between boys (1.26 µg/g creatinine) and girls (2.24 µg/g creatinine) ($p > 0.05$).

Conclusion: This study is an important contribution to the limited information about childhood exposure to BPA. The estimated daily BPA intake in this study is substantially lower than the European Food Safety Authority derived tolerable daily intake of 4 µg/kg BW/day.

Keywords: Bisphenol A, urine, children, liquid chromatography-mass spectrometry, Turkey

Introduction

There is general concern regarding environmental chemical exposure and its impact on human health, but this is particularly important for vulnerable populations, such as infants and children during sensitive periods of development. In 1997 the leaders of the G8 countries stated, "*We acknowledge that, throughout the world, children face significant threats to health from an array of environmental hazards. The protection of human health remains a fundamental objective of environmental policies to achieve sustainable development. We increasingly understand that the health and well-being of our families depends upon a clean and healthy environment. Nowhere is this more true than in the case of children, who are particularly vulnerable to pollution*" (1). In addition, one of the biggest concerns of the World Health Organization (WHO) for children is exposure to chemicals during the

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Multiplex enumeration of *Escherichia coli* and *Salmonella enteritidis* in a passive capillary microfluidic chip

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Multiplex detection and quantification of bacteria in water by using portable devices are particularly essential in low and middle-income countries where access to clean drinking water is limited. Addressing this crucial problem, we report a highly sensitive immunoassay sensor system utilizing the fluorescence technique with magnetic nanoparticles (MNPs) to separate target bacteria and two different types of quantum dots (CdTe and Ni doped CdTe QDs) incorporated into a passive microfluidic chip to transport and to form sandwich complexes for the detection of two target bacteria, namely *Escherichia coli* (*E. coli*) and *Salmonella enteritidis* (*S. enteritidis*) in less than 60 min. The assay is carried out on a capillary driven microfluidic chip that can be operated by merely pipetting the samples and reagents, and fluorescence measurements are done by using a handheld fluorescence spectrophotometer, which renders the system portable. The linear range of the method was found to be 10^1 to 10^5 cfu mL^{-1} for both *E. coli* and *S. enteritidis*. The limit of detection (LOD) was calculated to be 5 and 3 cfu mL^{-1} for *E. coli* and *S. enteritidis*, respectively. The selectivity of the method was examined by testing *Enterobacter dissolvens* (*E. dissolvens*) and *Staphylococcus aureus* (*S. aureus*) samples, and no significant interference was observed. The method was also demonstrated to detect bacteria in tap water and lake water samples spiked with target bacteria.

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1 Introduction

Pathogen caused diseases due to the usage of contaminated water is a severe public health problem, especially in low and middle-income countries where access to clean drinking water is limited.[1–3] Since different species of bacteria can be found in contaminated water, the simultaneous detection of multiple types of water-borne bacteria by using a simple, fast, and reliable technique is vital to decrease the number of people suffering from such diseases. Classical methods require lengthy incubation times (24–48 h), and it is not easy to enumerate several species of bacteria simultaneously. Nanoparticles have been tremendously used for the development of an alternative reliable detection technique for pathogenic bacteria in the last few decades.[4–9] Many different analytical methods such as fluorescence,[10,11] surface-enhanced Raman spectroscopy (SERS),[12,13] enzyme-linked immunosorbent assay (ELISA),[14] surface plasmon resonance (SPR)[15] and amperometry[16] have been used for detection of pathogenic bacteria. Among these methods, fluorescence is one of the most promising analytical techniques because it offers high sensitivity and facilitates on-site measurements. Semiconductor QDs have been frequently used as fluorescent labels in many studies in the last decade due to their high quantum yield values, which improves the sensitivity and the resistance against photo-degradation.[17,18] Moreover, size-controlled emission spectra of QDs with narrow emission peaks and a broad excitation wavelength range enable the detection of different types of bacteria, simultaneously.[19]

On the other hand, when the analyte concentration is low, a selective preconcentration step is needed both to separate the analyte from the sample matrix and to increase the sensitivity of the analytical technique. In this sense, MNPs are advantageous due to their magnetic properties and their ease of modification specific to target bacteria. Besides, the low toxicity and biocompatibility of MNPs allow their utilization in the

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Clinical Infectious Diseases

MAJOR ARTICLE

Development and Validation of a Nomogram for Assessing Survival in Patients With COVID-19 Pneumonia

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Background. The outbreak of coronavirus disease 2019 (COVID-19) has spread worldwide and continues to threaten peoples' health as well as put pressure on the accessibility of medical systems. Early prediction of survival of hospitalized patients will help in the clinical management of COVID-19, but a prediction model that is reliable and valid is still lacking.

Methods. We retrospectively enrolled 628 confirmed cases of COVID-19 using positive RT-PCR tests for SARS-CoV-2 in Tongji Hospital, Wuhan, China. These patients were randomly grouped into a training (60%) and a validation (40%) cohort. In the training cohort, LASSO regression analysis and multivariate Cox regression analysis were utilized to identify prognostic factors for in-hospital survival of patients with COVID-19. A nomogram based on the 3 variables was built for clinical use. AUCs, concordance indexes (C-index), and calibration curves were used to evaluate the efficiency of the nomogram in both training and validation cohorts.

Results. Hypertension, higher neutrophil-to-lymphocyte ratio, and increased NT-proBNP values were found to be significantly associated with poorer prognosis in hospitalized patients with COVID-19. The 3 predictors were further used to build a prediction nomogram. The C-indexes of the nomogram in the training and validation cohorts were 0.901 and 0.892, respectively. The AUC in the training cohort was 0.922 for 14-day and 0.919 for 21-day probability of in-hospital survival, while in the validation cohort this was 0.922 and 0.881, respectively. Moreover, the calibration curve for 14- and 21-day survival also showed high coherence between the predicted and actual probability of survival.

Conclusions. We built a predictive model and constructed a nomogram for predicting in-hospital survival of patients with COVID-19. This model has good performance and might be utilized clinically in management of COVID-19.

Keywords. coronavirus; COVID-19; nomogram; prediction; survival.

In December 2019, an unknown pneumonia emerged in Wuhan, China, coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus [1]. Since its emergence, COVID-19 has spread across China and globally, with high morbidity and mortality [2]. With the progression of this pandemic, public health is greatly threatened and healthcare systems worldwide are under great pressure. Progress in vaccine development has brought hope of potentially preventing the disease [3]. However, effective drugs are still lacking for clinical treatment. Prediction of patients' outcomes as early as admission will help to identify those at high risk of a poor outcome, and active supportive treatment may be given to these patients to improve their prognosis. Considering this, a predictive model with reliable efficacy is of great importance for the clinical management of COVID-19.

Recently, a number of models or factors have been proposed to predict the severity or survival of patients with confirmed COVID-19. For example, 1 study reported that severe cases of COVID-19 tend to have a higher neutrophil-to-lymphocyte

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From nutrition to medicine: Assessing hemorrhoid healing activity of *Solanum melongena* L. via *in vivo* experimental models and its major chemicals

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ABSTRACT

Ethnopharmacological relevance: *Solanum melongena* L. (eggplant) is used for treatment of rheumatism, beriberi, itching, toothache, bleeding, asthma, bronchitis, cholera, neuralgia and hemorrhoids in traditional medicine (Turkish, Chinese, and Indian). Hemorrhoids from these diseases, are common illness in all over the world, which are treated with various approaches including ethnobotanicals.

Aim of the study: This study aimed to evaluate the anti-hemorrhoidal activity of eggplant, an edible plant, which is commonly utilized around the world.

Materials & methods: *In vivo* anti-hemorrhoidal activity of the methanolic extract prepared from eggplant was evaluated by experimental hemorrhoid model, subsequently histological and biochemical analysis. Hemorrhoid, which was induced by applying croton oil to the anal area of the rats. Furthermore, the extract was screened for anti-inflammatory activity which is based on the inhibition of acetic acid-induced increase in capillary permeability. The healing potential was comparatively assessed with a reference Pilex® tablet and cream. Phytochemical analysis performed by HPLC. The amount of the major phenolic compound (chlorogenic acid) in extract was found by using HPLC method.

Results: Histological and biochemical analysis demonstrated that eggplant extract is highly effective against hemorrhoid in comparison to the controls and the commercial preparation. In addition, the methanolic extract demonstrated significant inhibitory effect on acetic acid-induced increase in capillary permeability.
The phytochemical studies identified major compound as chlorogenic acid (2.86%) by liquid chromatography.

Conclusion: The eggplant calyxes, not edible, are easy to reach, by products/vast from the food sources. This is the first scientific evidence revealing that the eggplant extract has significant anti-hemorrhoidal and anti-inflammatory activity.

1. Introduction

The term *hemorrhoids*, derived from the words "haema (blood)" and "rhoos (flow)" originated from Greek, was first used by Hippocrates (BC 460) to describe vascular bleeding from the anus (Leff, 1987). Although hemorrhoids do not pose a risk to vita, they are one of the most common diseases. Even though the clear prevalence of hemorrhoidal disease is not known, some epidemiological studies encountered after the 19th century showed that the prevalence of hemorrhoids was 4.4%, mostly in individuals aged between 45 and 65 years (Johanson and Sonnenberg,

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Surface molecularly-imprinted magnetic nanoparticles coupled with SERS sensing platform for selective detection of malachite green

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ABSTRACT

Herein, a novel analytical method was reported for sensitive and selective quantification of malachite green (MG) in tap water and carp samples based on a combination of surface-enhanced Raman spectroscopy (SERS) and molecular imprinting technology. For this purpose, surface molecularly-imprinted magnetic nanoparticles (MIP@Fe_3O_4 NPs) were synthesized through recently developed living/controlled radical polymerization mechanism referred to as reversible chain transfer catalyzed polymerization (RTCP). Surface characterization of MIP@Fe_3O_4 NPs was carried out in detail by using the combination of several analytical techniques and the results showed the presence of a thin polymer layer on the nanoparticles. Rebinding properties, selectivity and reusability of the nanoparticles were investigated and the obtained results indicated the prepared nanoparticles had excellent selectivity, high adsorption capacity, fast adsorption kinetics and multiple-uses with an imprinting factor of 3.86. Then, silver dendrites (Ag NPs) were deposited on silicon wafers and used as SERS sensing platform. Moreover, surface properties of the SERS substrate were also investigated in detail in terms of stability, reusability and homogeneity. After that, the eluted MG from the imprinted nanoparticles was dropped on the sensing platform and SERS analysis was carried out. Under optimized conditions, limit of detection and limit of quantification were determined to be 1.50 pM and 4.96 pM for tap water, respectively and 1.62 pM and 5.38 pM for carp samples, respectively within acceptable recovery rates and standard deviations. The overall results indicated that the proposed method can be effectively used for the quantification of trace amounts of MG in tap water and carp samples. Moreover, the proposed method is promising for development of new ways to prepare MIPs via surface-initiated RTCP.

1. Introduction

Malachite green (MG) is a type of triphenylmethane dye which has been widely used for more than 50 years, with a high degree of fungicide ability even at very low doses [1]. It is a powerful antifungal, antibacterial and antiparasitic agent widely used in fish farms as well as being an effective tropical antiprotozoal disinfectant [2]. Besides its wide fungicidal and antiparasitic spectrum, its effectiveness against trout proliferative kidney disease has made it extremely popular for fish farmers [3]. However, it was reported that there were spine, head, fin, and tail abnormalities in trout fry from eggs exposed to MG and also MG can easily enter the food chain and cause enerogenic, mutagenic and teratogenic abnormalities in humans [4]. Due to the serious side effects, the use of MG in the agriculture industry in U.S. and the European Commission has been banned [5]. However, because of easily availability and low cost, MG can still be used illegally in industry. Thus far, rapid, selective and sensitive analytical methods are necessary for the detection of MG in water samples.

Recently, several analytical methods such as immunoassays [6,7], high-performance liquid chromatography (HPLC) [8], HPLC-mass spectrometry (HPLC-MS) [9], gas chromatography (GC) [10], capillary electrophoresis [11], surface enhanced Raman spectroscopy (SERS) [12] and electrochemical methods [13,14] have been reported for the determination of MG. Though, low detection limits (LODs) can be achieved with the reported methods, chromatographic methods suffer time-consuming sample pre-treatment steps and expensive instruments

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Research Article

Determination of Tryptophan and Kynurenine by LC−MS/MS by Using Amlodipine as an Internal Standard

Burcu Eser,* Yeşim Özkan, and Aylin Sepici Dinçel

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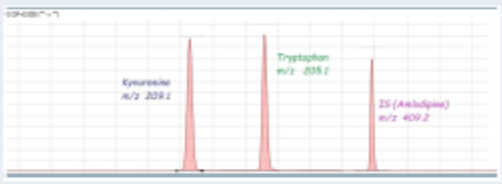
ABSTRACT: Tryptophan is an essential amino acid that plays an important role in cell metabolism, and kynurenine is its main metabolic pathway. By using ultra-high-performance liquid chromatography coupled to electrospray ionization triple−quadrupole mass spectrometry, tryptophan and kynurenine were determined using amlodipine as an internal standard. The analysis was carried out on an ACE-C18 (4.6 mm × 50 mm, 5 μm) reversed-phase analytical column using the gradient elution mode. For quantitative determination, amlodipine was used as an internal standard. Detection was performed using multiple reaction monitoring in electrospray ionization mode at m/z 205.1 → 117.7 and 187.9 for tryptophan, m/z 209.1 → 146 and 93.9 for kynurenine, and m/z 409.2 → 294.1 for the internal standard. Good linearity of the analyte to internal standard peak area ratios was seen in the concentration range 1.25−4000 ng/mL for tryptophan and 0.5−1600 ng/mL for kynurenine. The method showed excellent linearity with regression coefficients of 0.99 for kynurenine and 0.996 for tryptophan. The limits of quantification were 0.55 ng/mL for tryptophan and 0.47 ng/mL for kynurenine. The % RSD for all analytes ranged from 0.3 to 3.4% for intraday and 0.4 to 8.9% for interday experiments. A simple LC−MS/MS method has been developed and validated for measuring Kyn and Trp by using an affordable and more easily available internal standard, which is amlodipine.



KEYWORDS: *tryptophan, kynurenine, amlodipine, LC−MS/MS*

INTRODUCTION

Tryptophan (Trp) is an essential amino acid that has an important role in cell metabolism. A very small amount of dietary Trp is used for protein synthesis, and the rest is reduced to different biomolecules through hydroxylation and decarboxylation (serotonin, melatonin), transamination, deamination (indican), and oxidation (kynurenine).[1] There are three pathways in Trp metabolism: serotonin (5-HT), indole-3-acetic acid, and kynurenine (Kyn).[2] About 80−90% of Trp is from the diet and is metabolized by the kynurenine pathway.[3] The metabolism of Kyn and Trp, which has been the subject of many studies in recent years, plays an important role in various physiological and pathological conditions such as infections, autoimmunity, inflammatory bowel disease (IBD and IBS), neurological disorders, metabolic disorders (diabetes, obesity, insulin resistance, and atherosclerosis), neuropsychiatric affections, including anxiety, depression, and autism, cancer, and pregnancy. Most catabolites are biologically active and play a role in the pathogenesis of many disease processes. Moreover, the interrelationship between metabolic pathways is of profound pharmacological and physiological importance because changes in one pathway may have secondary effects on others.[3] New physiological roles and correlations between different pathways can only be identified by the simultaneous detection of these metabolites.[4]

Today, liquid chromatography−mass spectrometry (LC−MS) is widely used in many areas, including clinical and biological analyses. Electrospray-ionized (ESI) LC−MS provides an opportunity to quantify Trp, Kyn, and metabolites in various biological samples. In addition, the tandem mass spectrometer also has been widely used in recent years, with its high sensitivity and selectivity, and is accepted as the gold standard method.

The internal standard (IS) method is used to increase the intensity of the analysis. The aim of using an IS is both to behave analogously to the examined analyte and to provide a signal that can be distinguished from the analyte. Different studies have suggested that any of the shortcomings affecting the analyte signal will also affect the IS signal. The use of an IS is particularly important when there has been a need for complex sample preparation processes.[18,29]

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Nanoparticle-assisted pyrrolidonyl arylamidase assay for a culture-free Group A *Streptococcus pyogenes* detection with image analysis

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ABSTRACT

Existing techniques for the detection of Group A *Streptococcus pyogenes* (GAS) have drawbacks in rapidness, accuracy or in high-cost. Considering the clinical importance of GAS, we have developed a culture-free detection method based on pyrrolidonyl arylamidase (PYR) activity with the aid of magnetic gold nanoparticles (AuNPs). GAS is the reason for pharyngitis and sampling starts from the throat with cotton swabs. After swab sampling, the target was collected with antibody modified magnetic AuNPs and transferred into 500 μL of PYR-broth without any antigen extraction or pure colony isolation. Then, the assay was finished by adding 25 μL of 4-(dimethylamino)-cinnamaldehyde (DMACA) reagent after 4-h incubation. A red color formation was evaluated as the presence of GAS comparing to blank, however, image analysis was employed for the interpretation of color changes clearly. For this purpose, a formula related to image data was proposed and analytical validation parameters were defined. Thus, the correlation was found to be linear with the R^2 of 0.9685 between the log of bacteria concentration and the image data with the limit of detection of 3.3×10^2 CFU/mL of GAS. In addition, the assay worked efficiently in the abundance interference of *Enterococcus faecalis*. The results represent a new feature to nanoparticles eliminating the selective growth media for a bacteria and this study provided a detection with intact cells of bacteria without any antigen or DNA/RNA extraction. The proposed work has been the most similar to the gold standard but a faster method in this field.

1. Introduction

Streptococcus pyogenes which belongs to Lancefield group A is a gram-positive, beta-hemolytic cocci, and the reason for inflammation of the pharynx, called pharyngitis [1]. Today, fast and accurate analysis of GAS can be achieved with rapid antigen test strips and this is important for the proper time of antibiotic therapy [2]. Although these tests provide results in 20–30 min, throat swab samples are required to evaluate with the culture technique for confirmed results. The specificity of the rapid test is high, however, there is still a risk of the false-negative result, and in any case, it takes up to two days for the final result [3]. The exact diagnosis of GAS infections mostly performed with the gold standard, culturing bacteria from swab samples on a blood agar plate [1]. GAS is detected on blood agar plates with the formation of white colonies with beta-hemolytic zones after 24–48 h [4]. In addition, definitive identification of GAS includes biochemical tests: mainly, pyrrolidonyl arylamidase (PYR) activity test, bacitracin susceptibility test and Lancefield group A antigen test [5].

PYR activity is conventionally tested with a reference broth or a disk [6] which are based on the same chemical reaction. Since there is a risk of false-positive reactions caused by other PYR active pathogens, all PYR tests are required to perform with a pure culture. It is the limitation for the PYR test which enables the only differentiation and identification of the bacteria after a long period of growth on an agar [5]. The detection of PYR activity started with the description of L-pyrrolidonyl-α- and β-naphthylamide as chromogenic substrates [7,8] and up-to-date PYR activity was tested with different microorganisms. For instance, Bombicno et al. [9] evaluated PYR activity for non-fermenting gram-negative rods and 293 isolates were tested for this purpose. Each test had the 24-h culture of each bacteria and conventional PYR disks were used for the definitive identification of these microorganisms. In another study [10], it was shown that PYR was the single test to distinguish *Staphylococcus aureus* (SA) from *Staphylococcus intermedius* and *Staphylococcus delphini*. Reference broth testing was preferred and the PYR broth was inoculated with each isolated colony to perform the test. Buchan et al. collected blood cultures containing gram-positive bacteria and they used the PYR test to identify some species in order to different the infections clearly [11]. In a case presentation for the infection of

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Original article

The inhibitory effects of isolated constituents from *Plantago major* subsp. *major* L. on collagenase, elastase and hyaluronidase enzymes: Potential wound healer

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ABSTRACT

Plantago major L. which is a medicinal plant with important biological activities, commonly used as traditional medicine. Potential inhibitory activities of the aqueous extract and three isolated constituents calceorioside B (**1**), homoplantaginin (hispidulin-7-O-glucoside) (**2**) and plantamajoside (**3**) from the aerial parts of *Plantago major* subsp. *major* L. (Plantaginaceae) have been tested against hyaluronidase, collagenase, and elastase, which play critical roles in wound pathogenesis. Even though, the extract (27.04%), and among the isolated compounds, calceorioside B (41.16%) exerted significant inhibition against hyaluronidase enzyme, homoplantaginin and plantamajoside were found to be inactive. Similar results were obtained from collagenase enzyme inhibition test. The extract (21.92%) and calceorioside B (28.34%) also caused notable inhibition in this test. However, no remarkable inhibition was observed in the presence of elastase enzyme. The experimental data revealed that *P. major* subsp. *major* displayed remarkable inhibitory activity against hyaluronidase and collagenase enzymes. *In vitro* enzyme activity of *P. major* subsp. *major* is reported for the first time in the current study.

1. Introduction

Plantago major L. (Plantaginaceae) belongs to the genus *Plantago*, which is represented by 21 species in Turkey and 2 of them are endemic (Davis, 1982). Many species of *Plantago* genus have been documented as medicinal plants in numerous countries including Turkey for centuries (Baytop, 1999; Jankovic et al., 2012; Goncalves and Romano, 2016). *P. major* (common plantain) is the most known and widely used species in traditional medicine for treatment of wound, abscess, acnes, diabetes, and cancer (Yesilada et al., 1995; Sezik et al., 1997; Sezik et al., 2001; Goncalves and Romano, 2016; Kuranel et al., 2016). Due to conspicuous veins on the leaves, *P. major* is named as "sinirli ot" in Turkey. There are three subspecies of *P. major*; *P. major* subsp. *major*, *P. major* subsp. *intermedia* and *P. major* subsp. *winteri* (Adom et al., 2017). *P. major* subsp. *major* and *P. major* subsp. *intermedia* have been commonly used as a traditional medicine in Anatolia (Baytop, 1999). The presence of iridoid glucosides, phenylethanoid glycosides, flavonoids, terpenoids, phenolic acids and polysaccharides in *Plantago* species has been reported up to date (Jankovic et al., 2012; Harput et al., 2012; Grubesic et al., 2013; Goncalves and Romano, 2016; Adom et al., 2017).

Though there has been an extensive investigation going on discovery of new collagenase, elastase and hyaluronidase enzyme inhibitory compounds of both synthetic and natural origins, a great essential still remains for new inhibitors of these enzymes owing to either side effects or low efficacy of present inhibitors. Further, the number of the current these enzyme inhibitors is quite limited, and new inhibitors are in demand mainly for cosmetics industry and wound healer. To date, we have investigated a large number of medicinal plants as well as natural compounds using several *in vivo* and *in vitro* experiments and as a result of these efforts we have find different collagenase, elastase, hyaluronidase enzyme inhibitors such as *Eucalyptus globulus* Labill., *Marsdenia erecta* R. Br., *Podospermum canum* C.A. Mey. etc. (Tumen et al., 2017; Acıkara

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The Effect of Boron-Containing Nano-Hydroxyapatite on Bone Cells

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Abstract

Metabolic diseases or injuries damage bone structure and self-renewal capacity. Trace elements and hydroxyapatite crystals are important in the development of biomaterials to support the renewal of bone extracellular matrix. In this study, it was assumed that the boron-loaded nanometer-sized hydroxyapatite composite supports the construction of extracellular matrix by controlled boron release in order to prevent its toxic effect. In this context, boron release from nanometer-sized hydroxyapatite was calculated by ICP-MS as in large proportion within 1 h and continuing release was provided at a constant low dose. The effect of the boron-containing nanometer-sized hydroxyapatite composite on the proliferation of SaOS-2 osteoblasts and human bone marrow-derived mesenchymal stem cells was evaluated by WST-1 and compared with the effects of nano-hydroxyapatite and boric acid. Boron increased proliferation of mesenchymal stem cells at high doses and exhibited different effects on osteoblastic cell proliferation. Boron-containing nano-hydroxyapatite composites increased osteogenic differentiation of mesenchymal stem cells by increasing alkaline phosphatase activity, when compared to nano-hydroxyapatite composite and boric acid. The molecular mechanism of effective dose of boron-containing hydroxyapatite has been assessed by transcriptomic analysis and shown to affect genes involved in Wnt, TGF-β, and response to stress signaling pathways when compared to nano-hydroxyapatite composite and boric acid. Finally, a safe osteoconductive dose range of boron-containing nano-hydroxyapatite composites for local repair of bone injuries and the molecular effect profile in the effective dose should be determined by further studies to validation of the regenerative therapeutic effect window.

Keywords Bone · Boron · Nano-hydroxyapatite · SaOS-2 · Mesenchymal stem cell · Transcriptome

Introduction

Bone loss due to diseases such as osteoporosis, tumors and trauma is currently replaced by autografts and allografts; however, these methods have limitations [1] and complications [1, 2]. A recent approach is to replace bone with synthetic bioceramics such as calcium sulfate, tri-calcium phosphate (TCP) [3], and hydroxyapatite (HAp) with or without cells [1]. The inorganic extracellular matrix (ECM) of bone is of trace elements such as zinc, cooper, magnesium, iron, and boron (B) containing nano-HAp (nHAp) [1, 4, 5]. Nano-HAp is a bioactive, biocompatible, glass-like bioceramic that replaces the ECM of bone in clinical practice [2, 6].

Dietary boron increases bone strength [7] and bone mineral density (BMD) [8] in diabetic rats and broiler chicken, respectively [9]. Dietary boron furthermore modulates vitamin D metabolism [10], increases BMD in rat alveolar bone [11], and increases serum osteocalcin (OCN) levels in postmenopausal women [12]. Previous studies [13–15] integrated boron into biomaterials to improve new bone formation. B-nHAp-

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Article

Microwave-assisted synthesis and pharmacological screening of some triazolothiadiazole derivatives

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In this study, twenty-two new [1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (5a-n, 6a-h) were synthesized under microwave irradiation (MWI). The chemical structures of the compounds were elucidated by their IR, ^{1}H-NMR, LC-MS, and elemental analysis. The compounds were tested for antinociceptive activity by using the tail clip, tail flick, hot plate, and writhing methods in mice. The varying levels of antinociceptive activity of the compounds were compared with those of aspirin. Among these compounds, compound **5g** and **5j** were found to be significantly more active than the other compounds and the standard in the tests. Also, inhibitory effects of the test compounds on COX-1 and COX-2 activities were investigated. DuP-697 for COX-2 and SC-560 for COX-1 were used as reference standards.

Keywords: 2(3*H*)-Benzoxazolone. Triazolothiadiazole. Antinociceptive activity. Microwave-assisted synthesis.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) represent a heterogeneous family of pharmacologically active compounds used to alleviate acute and chronic inflammation, pain, and fever. Their clinical efficacy is closely related to their ability to inhibit both COX-1 and COX-2 isoforms of the enzyme cyclooxygenase (COX) which is also referred to as prostaglandin H2 synthase since it catalyzes the conversion of arachidonic acid to prostaglandin H2 (PGH2) (Dannhardt, Kiefer, 2001).

A large number of N-bridged heterocycles derived from 1,2,4-thiadiazole nucleus are important pharmacological agents and there is a significant amount of research on this class of compounds. 1,2,4-Thiadiazole ring is associated with a wide variety of biological activities named antimicrobial, antimycobacterial, anticonvulsant, antidepressant, antihypertensive, and analgesic agents. Moreover, some 1,2,4-triazoles and 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles derived from 4-amino-3-thioxo-1,2,4-triazoles are associated with diverse pharmacological activities such as anti-Alzheimer's (Shiradkar, *et al*., 2007), anti-inflammatory, analgesic (Mathew, Keshavayya, Vaidya, 2006; Sarıgöl *et al*., 2015; Haider *et al*., 2014; Akhter, Hassan, Amir, 2014), antiviral (Kritsanida *et al*., 2002), antifungal and antibacterial (Kumar *et al.,* 2010a; Hussein *et al*., 2011; Aggarwal, Kumar, Dureja, 2011; Mathew *et al*., 2007), antitubercular (Kumar *et al.,* 2010b; Mathew *et al*., 2007), and anticancer (Ibrahim, 2009) activities.

On the other hand, some compounds having small and simple 2(3H)-benzoxazolone ring show a broad spectrum of biological activity such as antimicrobial (Gülkok *et al.,* 2012; Koksal *et al*., 2002), antitubercular (Gulkok *et al*., 2012), antioxidant (Aichaoui *et al*., 2009; Satyendra *et al*., 2011), anticonvulsant (Ucar *et al*., 1998), cytotoxic (Petrov *et al*., 2008), anti-inflammatory (Unlu *et al*., 2003; Dogruer *et al*., 1997), and analgesic (Onkol *et al*., 2002; Gokhan-Kelekci, Koksal, Univar, 2009; Abdelazeem *et al*., 2015) activities.

Design of new drugs can be based on the development of hybrid molecules by linking different pharmacophore fragments in a single structure, which may lead to compounds with interesting biological profiles.

These observations prompted us to synthesize new 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives, which were attached to position-3 of the 2(3*H*)-benzoxazolone ring through a methylene bridge. Also, the structure of the

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Activity-guided isolation of α-amylase, α-glucosidase, and pancreatic lipase inhibitory compounds from *Rhus coriaria* L

Hasya Nazlı Gök, Didem Deliorman Orhan, İlhan Gürbüz, and Mustafa Aslan

Abstract: The leaves and fruits of *Rhus coriaria* are traditionally used in Turkey for the treatment of diabetes. The aim of the present study is to determine α-amylase, α-glucosidase, and pancreatic lipase inhibitory activities of *R. coriaria* leaf and fruit ethanol extracts (80%), and to isolate active compounds against these enzymes. As a result of the activity-guided isolation, the active compounds were determined as the amentoflavone, agathisflavone, and 1,2,3,4,6-penta-*O*-galloyl-β-glucopyranose. Agathisflavone, amentoflavone, and penta-*O*-galloyl-β-glucopyranose inhibited α-glucosidase with 11.4 ± 0.9, 11.3 ± 0.7, and 4.1 ± 0.1 μM IC_{50} values, respectively. Furthermore, penta-*O*-galloyl-β-glucopyranose inhibited α-amylase with 6.32 ± 0.18 μM IC_{50}. These three compounds also significantly inhibited ($P < 0.05$) pancreatic lipase. The results of high-performance liquid chromatography analysis showed that penta-*O*-galloyl-β-D-glycopyranose was one of the main compounds in both fruit and leaf extracts. Therefore, it may be considered that *R. coriaria* fruit and leaf extracts can be standardized on this substance and used in the development of both medicinal products and functional food for diabetes.

Keywords: Agathisflavone, amentoflavone, HPLC, pentagalloyl glucose, *Rhus coriaria*

Practical Application: *Rhus coriaria* (Sumac) is one of the plants that is well known and used around the world as a spice. It is also used against diabetes traditionally. The determination of effective compounds can lead to the standardization and development of both medicinal products and functional foods for diabetes.
While the fruits of the plant are used as a spice all around the world, the leaves are generally throw away; therefore, the usage of the leaves to the food and medical industry can lead to beneficial effects on the economy.

1. INTRODUCTION

Anacardiaceae family is only represented in Turkey by three genera, which are *Rhus*, *Cotinus*, and *Pistacia* (Choulak et al., 2019; Davis, 1965). While the genus *Rhus* contains approximately 250 species (Min & Barfod, 2008) in the World, there is only *Rhus coriaria* in Turkey (Davis, 1965). *R. coriaria* L. (Sicilian sumac) is generally known as "sumak" in Anatolia. The powdered fruits are used as a spice. The fruit macerate of the plant is used as a sauce for salads and meals (Abu-Reidah, Ali-Shtayeh, Jamous, Arraez-Roman, & Segura-Carretero, 2015).

It is known that folk remedies play a key role in the development of new drugs candidate in pharmaceutical research. Relevant biological activity researches on folk medicines used in various disorders are often the first step in the development of new drugs of natural origin (Gürbüz et al., 2019). From this perspective, it is seen that the *R. coriaria* has an important potential as a folk medicine. *R. coriaria* is used for the treatment of diabetes, kidney stones, diarrhea, hypertension, dysentery, peptic ulcer, hemorrhoids, wounds, burns, rash, edema, and bruise as folk medicines in Turkey. It is also used to treat insect bites, bee stings, and maturation of abscess (Honda et al., 1996; Paksoy, Selvi, & Savran, 2016; Polat, Çakılcıoğlu, & Satıl, 2013; Şimşek, Aytekin, Yeşilada, & Yıldırımlı, 2002; Tabata et al., 1994; Tuttolomondo et al., 2014; Yeşilada et al., 1995). The various biological activity of *R. coriaria* was also demonstrated in many *in vivo*, *in vitro*, and clinical studies (Sakhr & El Khatib, 2020).

Although the leaf decoction of *R. coriaria* has traditionally been used against diabetes, to the best of our knowledge, no previous studies have been found on the antidiabetic effect of leaves and antiobesity effect of leaves and fruits *in vivo* or *in vitro*. There are a number of *in vitro* and *in vivo* studies in the literature on the antidiabetic effect of fruits of *R. coriaria*. (Abedi Gaballu et al., 2015; Anwer et al., 2013; Giancarlo, Rosa, Nadjafi, & Francesco, 2006; Mohammadi, Kouhsari, & Feshani, 2010; Salimi, Eskandary, Headari, Nejati, & Kalhori, 2015). Additionally, the antidiabetic and anti-atherosclerotic activity of *R. coriaria* on humans was proven in a double-blind randomized controlled clinical study conducted by Shidfar et al. (2014). The effects of *R. coriaria* on α-amylase α-glucosidase and pancreatic lipase enzymes were investigated in this study.

α-Amylase is an enzyme that can be found in animals, plants, and microorganisms. Carbohydrates are cleaved to oligosaccharides by α-amylase. It hydrolyzes complex polysaccharides such as starch by cutting off α-1,4-glucan chain. The resulting oligosaccharides are cleaved by the α-glucosidase enzymes to the glucose, and then glucose passes into the blood, which causes postprandial hyperglycemia especially in diabetic patients. The inhibition of the digestion of polysaccharides by the inhibition of α-amylase and α-glucosidase plays an important role in the control of blood sugar levels (D. Liu, Gao, Tang, & Nie, 2017).

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REVIEW ARTICLE

A Recent Look into Natural Products that have Potential to Inhibit Cholinesterases and Monoamine Oxidase B: Update for 2010-2019

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Abstract: With respect to the unknowns of pathophysiology of Alzheimer's Disease (AD)-, and Parkinson's Disease (PD)-like neurodegenerative disorders, natural product research is still one of the valid tools in order to provide alternative and/or better treatment options. At one hand, various extracts of herbals provide a combination of actions targeting multiple receptors, on the other hand, the discovery of active natural products (*i.e.*, secondary metabolites) generally offers alternative chemical structures either ready to be employed in clinical studies or available to be utilized as important scaffolds for the design of novel agents. Regarding the importance of certain enzymes (*e.g.* cholinesterase and monoamine oxidase B), for the treatment of AD and PD, we have surveyed the natural product research within this area in the last decade. Particularly novel natural agents discovered within this period, concomitant to novel biological activities displayed for known natural products, are harmonized within the present study

Keywords: Acetylcholinesterase, butyrylcholinesterase, monoamine oxidase B, Alzheimer's disease, Parkinson's disease, natural products.

1. INTRODUCTION

There are a number of disease states categorized under the Central Nervous System (CNS) diseases. Some of them are further subcategorized as neurodegenerative diseases. Alzheimer's Disease (AD) and Parkinson's Disease (PD) are within this category [1, 2]. Although it has been more than a century following the first description and diagnosis of these diseases, their treatment mainly employs symptomatic drug therapies with respect to the unknowns in their etiologies. Among these therapies, certain targets have been validated considering the basic clinical outcomes [3-5].

Cholinergic system and the functioning of acetylcholine (ACh) on both muscarinic and nicotinic receptors are well-known for the continuation of regular cognitive functions. Besides, the deficiency of cholinergic system is well-categorized throughout the development of AD [6, 7]. From this point of view, a strategy to increase the cholinergic function within CNS is to increase ACh levels through the inhibition of cholinesterase enzymes [8]. ACh lacks drug-like properties, ruling out the possibility to use it as a drug molecule [9]. Therefore, donepezil, rivastigmine, and galantamine are the cholinesterase inhibitory molecules used today for the symptomatic treatment of AD [10]. It is noteworthy to state that there are two cholinesterase enzymes used as the targets [*i.e.*, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE)] and selectivity of these drugs towards the mentioned sister enzymes display differences as well [10, 11]. BChE is an esterase-type of enzyme, which also displays selectivity to ACh hydrolysis, while AChE is the dominant form in the CNS for the hydrolysis of ACh and the termination of its activity. Studies indicated that throughout the development of AD, the levels of AChE and BChE are inversely proportional, pointing out that AChE levels decrease, while BChE levels increase to compensate it [12, 13]. Donepezil and galantamine are AChE-selective inhibitors, while rivastigmine is a BChE-selective inhibitor [11, 14].

Regarding its pathophysiology, PD development indicates an imbalance in the levels of ACh and dopamine in CNS [15]. Particularly, lower dopamine levels throughout the development of PD result in some syndromes including, but not limited to, shaking, rigidity, slowness of movement, and difficulty in walking. Therefore, PD treatment mainly involves the targets increasing dopamine levels [16]. Levadopa, a dopamine receptor agonist, and co-employment of a decarboxylase inhibitor are some of the treatment strategies followed for the treatment. Besides, monoamine oxidase (MAO) inhibition is an alternative strategy to increase the levels of dopamine in CNS [17, 18]. Like ACh molecule, dopamine also lacks bioavailability with respect to

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Investigations on the anti-ulcerogenic activity of *Sideritis caesarea* H. Duman, Aytaç & Başer

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ABSTRACT

Ethnopharmacological relevance: Aerial parts of *Sideritis caesarea* H. Duman, Aytaç & Başer are used for complaints such as stomach-aches, and intestinal spasms as traditional medicine in Kayseri, Turkey.

Aim of study: To investigate the anti-ulcerogenic activity by using bioassay guided fractionation technique (BAGF) and to identify the compound(s) that are responsible for anti-ulcerogenic activity through ethanol-induced anti-ulcerogenic activity model in vivo.

Materials and methods: Liquid-liquid partition and then different chromatographic techniques were utilized for the BAGF of the ethanol (80%) extract of the aerial parts of *Sideritis caesarea*. Ethanol-induced gastric ulcer method on rats was employed for the determination of the anti-ulcerogenic activity, and the ulcer index was also calculated for anti-ulcerogenic activity detection.

Results: The ethanol (80%) extract of *S. caesarea* showed statistically potent anti-ulcerogenic activity (95.9% ulcer inhibition, $p < 0.001$). Among the liquid-liquid fractions, strongest anti-ulcerogenic activity was observed with the ethyl acetate fraction (91.4% inhibition, $p < 0.001$) and therefore BAGF studies were proceeded with the ethyl acetate fraction. Two anti-ulcerogenic flavonoids {4′-*O*-methylhypolaetin-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside and isoscutellarein-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-6″-*O*-acetyl-β-D-glucopyranoside} were isolated from this fraction together with a sesquiterpene glycoside [(2*E*,6*E*)-2,6,10-trimethyl-2,6,11-dodecatriene-1,10-diol-1-*O*-β-D-glucopyranoside] and two additional flavonoids {4′-*O*-methylhypolaetin-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside and isoscutellarein-7-*O*-[6‴-*O*-acetyl-β-D-allopyranosyl-(1→2)]-β-D-glucopyranoside}.

Conclusions: Traditional use of *S. caesarea* in the treatment of stomach-aches was supported by this study and four flavonoids were isolated by using BAGF method and two of them were determined to have significant anti-ulcerogenic activity. Additionally, (2*E*,6*E*)-2,6,10-trimethyl-2,6,11-dodecatriene-1,10-diol-1-O-β-D-glucopyranoside was obtained from a *Sideritis* genus for the first time.

This study was conducted as a part of a doctoral thesis [Tuğba Günbatan, "*Sideritis caesarea* H. Duman, Aytaç & Başer bitkisinin antiülserojenik aktivitesi üzerinde araştırmalar", Gazi University Institute of Health Sciences, Ankara, 2017] and was partly presented as posters at The International Gazi Pharma Symposium (Günbatan et al., Two anti-ulcerogenic flavonoid glycosides from *Sideritis caesarea* H. Duman, Aytaç & Başer, Antalya, Turkey, 2015) and The 19th International Congress Phytopharm (Gürbüz et al., In vivo anti-ulcerogenic effect evaluation of *Sideritis caesarea* H. Duman, Aytaç & Başer Lamiaceae, Bonn, Germany, 2015).

1. Introduction

Lamiaceae family, distributed nearly worldwide, includes powerful aromatic herbs which have been in use for culinary, medicinal purposes and especially in making beverages, herbal teas, since ancient times (Fecka and Turek, 2007). Various species of the genera *Salvia*, *Thymus*, *Stachys*, *Lavandula*, *Origanum*, *Marrubium*, *Satureja* and *Sideritis* are commonly used to make herbal teas in Turkey and around (Dirmenci et al., 2018; Gürbüz et al., 2019; Tuzlacı, 2011). Among them, *Sideritis* species stand out with their excellent flavour and fragrance profile and

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Article

Antidepressant Potential of *Lotus corniculatus* L. subsp. *corniculatus*: An Ethnobotany Based Approach

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Abstract: As a Turkish traditional medicinal plant, aerial parts of *Lotus corniculatus* L. subsp. *corniculatus* (Fabaceae) are used as a painkiller, antihemoroidal, diuretic and sedative. In this study, the antidepressant potential of the plant has been attempted to clarify. Extracts with water, *n*-Hexane, ethyl acetate, and methanol were prepared respectively from the aerial parts. Antidepressant activity of the extracts were researched by using three different in vivo test models namely a tail suspension test, antagonism of tetrabenazine-induced hypothermia, ptosis, and suppression of locomotor activity and forced swimming test on male BALB/c mice and in vitro monoamine oxidase (MAO)-A and B inhibition assays. The results were evaluated through comparing with control and reference groups, and then active compounds of the active extract have been determined. Bioassay-guided fractionation of active fraction led to the isolation of three compounds and structures of the compounds were elucidated by spectroscopic methods. The data of this study demonstrate that the MeOH extract of the aerial parts of the plant showed remarkable in vivo antidepressant effect and the isolated compounds medicarpin-3-*O*-glucoside, gossypetin-3-*O*-glucoside and naringenin-7-*O*-glucoside (prunin) from the active sub-fractions could be responsible for the activity. Further mechanistic and toxicity studies are planned to develop new antidepressant-acting drugs.

Keywords: antidepressant; *Lotus corniculatus*; Fabaceae; forced swimming test; monoamine oxidase; tail suspension test; tetrabenazine

1. Introduction

Depression is a common but serious mood disorder and its etiology has not yet been elucidated. The studies to date have shown that the onset of this disease may be associated with several genetic, biological and psychosocial risk factors [1]. The symptoms of depression can vary from mild to severe and include emotional, cognitive, behavioral and physical changes and all of these can cause disruptions in normal daily activities of individuals [2,3]. In addition to psychosocial problems, it can lead to some other additional diseases such as asthma, diabetes, obesity and cancer [4]. The World Health Organization estimate that over 300 million people suffer from depression and about 800,000 people die each year in suicide cases due to it [5]. The treatment of this serious public health problem is very important because of its financial and moral damages.

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Identification of the main active antidepressant constituents in a traditional Turkish medicinal plant, *Centaurea kurdica* Reichardt

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ABSTRACT

Ethnopharmacological relevance: In Turkish folk medicine, infusions and decoctions prepared from the flowers, fruits and aerial parts of *Centaurea kurdica* Reichardt (Asteraceae) are used as sedative and antidepressant-like effects of various sedative plants have been identified in many studies. The present study was designed to evaluate the antidepressant activity of this plant.

Materials and methods: *n*-Hexane, ethyl acetate (EtOAc), and methanol (MeOH) extracts were prepared from the branches with leaves and also flowers of the plant. Antidepressant potentials of these extracts were researched by using the forced swimming test, tail suspension test, and antagonism of tetrabenazine-induced ptosis, hypothermia, and suppression of locomotor activity.

Results: After determination of high antidepressant potentials of MeOH extract prepared from flowers and *n*-hexane extract prepared from branches with leaves, isolation studies were carried out on these two extracts and the main active components were determined as β-amyrin, mixture of β-sitosterol and stigmasterol and costunolide for the branches with leaves and quercitrin, isoquercetin and naringenin-7-*O*-glucopyranoside for the flowers.

Conclusions: As a result of the mechanistic and toxicity studies planned on this plant, it is thought that *C. kurdica* may be a glimmer of hope for depressed patients.

1. Introduction

Depression derives from the verb "deprimo", which means "being under pressure" in Latin and in medical terminology this term is defined as "emotional depression, lack of interest and energy" (Terziivanova et al., 2018). Although its etiology is not yet fully elucidated, depression is a complex disease associated with psychosocial, biological, and genetic risk factors that are closely interacted each other (Fig. 1) (Yemez and Alptekin, 1998).

Suicide risk and concomitant health problems are mainly considered in the treatment of depression and there are three types of options that can be applied sometimes in combination; electroconvulsive therapy (ECT), psychotherapy and pharmacotherapy (Keller, 2003). Psychotherapy, which is the first choice in the treatment of depression, aims to save the patient from low self-esteem and social isolation. Clinical studies have shown that the combination of psychotherapy with pharmacotherapy is more effective than administering both treatments alone (Thase et al., 1997). There are various antidepressant drugs used in the pharmacotherapy of depression which have different mechanisms such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs). Depression continues to be one of the important health problems waiting for a solution because of the delay in the effectiveness of the therapeutics used for treatment, negative side effect profiles of them and the risk of recurrence of the disease at the end of the treatment (Polyakova et al., 2015). Because of recurrent depressive attacks, the patient's belief in treatment is broken. Therefore, many studies have been carried out to develop alternative therapeutics with higher efficacy and lower side-effect profile for the treatment of depression (Zis and Goodwin, 1979).

The genus *Centaurea* (Asteraceae) is commonly found in Turkey with 180 species, 109 of which are endemic (Wagenitz, 1975; Duran and Duman, 2002). This genus has been used in traditional folk medicine because of its antipyretic, anti-inflammatory, antidiabetic, antibacterial, diuretic, antidiarrhetic, digestive, stomachic, choleretic, colagog, antirheumatic, astringent, hypotensive and cytotoxic properties (Farrag et al., 1993; Gurkan et al., 1998; Kaij-A-Kamb et al., 1992; Orallo et al., 1998). Several biological activities of this genus and its

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The investigation of the potential antidepressant-like activity of *Xanthium orientale* subsp. *italicum* (Moretti) Greuter in rodents

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ARTICLE INFO

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ABSTRACT

Ethnopharmacological relevance: Ethnobotanical surveys revealed that *Xanthium orientale* subsp. *italicum* (Moretti) Greuter has been used against central nervous system disorders in Turkish folk medicine. The aim of the present study is to verify the folkloric assertion on this plant. The compounds responsible for the activity were investigated using bioassay-guided fractionation procedures.

Materials and methods: The antidepressant activity of the aqueous, *n*-hexane, ethyl acetate (EtOAc), methanol (MeOH) extracts; fractions and isolated compounds from active MeOH extract were evaluated by using the *in vitro* MAO inhibition assay and three different *in vivo* models namely forced swimming test, tail suspension test, and antagonism of tetrabenazine-induced ptosis, hypothermia, and suppression of locomotor activity. The results were compared with control and reference groups, and active compounds of the plant have been determined. Through the bioassay-guided fractionation procedures, two compounds were isolated from the active fraction and their structures were elucidated by spectroscopic methods.

Results: The MeOH extract of the plant was found to possess antidepressant-like activity. This extract was then subjected to chromatographic techniques. Isolated sesquiterpene lactones were elucidated as xanthatin (1) and xanthinosin (2), which were responsible for the antidepressant-like activity.

Conclusions: This study discovered the antidepressant potential of *X. orientale* subsp. *italicum*. Using bioassay-guided fractionation and isolation techniques, xanthatin (1) and xanthinosin (2) were determined as the main active components of the leaves.

1. Introduction

Depression is a common, chronic and recurrent mental disorder which is one of the leading cause of disability and suicide (Singh et al., 2009). It is a complex disease whose etiology is not yet fully explained, but the occurrence of the disease is thought to be related to psychosocial, biological and genetic risk factors (Yemez and Alptekin, 1998). Clinical symptoms observed in depression could be emotional, cognitive, behavioral and physical. Emotional symptoms like depressed mood and feelings of guilt and worthlessness; cognitive signs like anhedonia and recurring death thoughts; behavioral signs like appetite changes and sleep disorders; physical ones like weight changes and fatigue could be observed in depressed people but this type of symptoms is not sufficient for the diagnosis. Clinical signs should be supported by biological markers which are based on genetic, epigenetic, molecular studies and radiological neuroimaging studies (Huprich, 2009; Schmidt et al., 2001).

According to WHO's 2018 data, more than 300 million people worldwide suffer from depression and about 800,000 people die each year in cases of depression-induced suicide (WHO Fact Sheet, 2018). Therefore, the treatment of this public health problem is essential because of its financial and moral burdens. There are various drugs that show activity with different mechanisms are used in the treatment of depression. Since these synthetic antidepressant drugs do not provide the expected effect at the expected level and have serious side effects, various studies have been carried out to develop more effective and safer drug molecules in treatment (Bet et al., 2013). Ethnopharmacological information is considered as an important resource in these type of studies on the road from nature to medicine (Zhang, 2004).

Xanthium genus belongs to Asteraceae family and includes 30

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RESEARCH ARTICLE

The Struggle with Rheumatism through *Dracunculus vulgaris* Schott: In the Light of Ethnobotanical Information

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Abstract: ***Background***: The fruits with the seeds of *Dracunculus vulgaris* Schott. (Araceae) are used against inflammatory diseases in Turkey.

Objective: The present study was designed to justify this folkloric usage of the plant. Therefore, the aim of this study was to investigate the anti-inflammatory activity of *D. vulgaris*.

Methods: Petroleum ether, ethyl acetate and methanol extracts were prepared from the fruits, successively. Carrageenan-, serotonin-, and prostaglandin E_2-induced hind paw edema; acetic acid-induced capillary permeability and 12-*O*-tetradecanoyl-phorbol-13-acetate–induced mouse ear edema models were used to assess the anti-inflammatory activity of the extracts. The analgesic activity was observed by using *p*-benzoquinone-induced abdominal constriction test.

Results: The petroleum ether extract displayed the highest activities in all of the used test models compared with the control group. Therefore, the constituents of this extract were determined by using gas chromatography-mass spectroscopy (GC–MS). Linoleic acid was found to be the major constituent of the petroleum ether extract of *D. Vulgaris*.

Conclusion: This study has provided some justification for the folkloric use of the plant.

Keywords: : Analgesics, anti-inflammatory, araceae, *Dracunculus vulgaris*, ethnopharmacology, rheumatism.

1. INTRODUCTION

Rheumatism is a systemic inflammatory disease characterized by pain in joints, tendons, ligaments, bones and muscles [1]. Thousands of people worldwide suffer from pain and deformity because of this disease [2]. No definitive remedy for this disease exists and even the most effective available treatment options based on controlling the pain and reducing the inflammation are not ideal. Consequently, rheumatism has been included in the group of chronic, incurable diseases. Although several potential antirheumatic agents are available, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic agents (DMARDs), methotrexate and cyclosporine, none of them has been found to be safe. All of them cause certain side effects [3]. For instance, NSAIDs-related gastrointestinal problems [4]; corticosteroid-induced mental, hematologic, immunologic, gastrointestinal, hepatic, and ophthalmologic disturbances [5] and toxicity profile of DMARDs on the kidney and liver [6] make these options inappropriate. Therefore, the investigation of the antirheumatic potential of traditionally used plants as new alternatives in the treatment is necessary.

The genus *Dracunculus* belongs to the Araceae family represented by large tuberous perennial plants [7]. Phytochemical studies on this genus have detected various types of chemical compounds such as fatty acids [8], saponin, coniine alkaloids [9], methyl chavicol, estragole, phellandrene, iodine, tannin, coumarin, and flavonoid [10].

Dracunculus vulgaris Schott., which is named locally as "yılan bıçağı, yılan kaması" in Turkey [11], is one of the poisonous species of *Dracunculus* genus used in traditional Turkish medicine against infections [12], inflamed wounds, hemorrhoids, eczema, cancer, edema, headache [13] and rheumatic pain [11]. Only a few biological activity studies have been conducted on this genus despite its wide use worldwide. Biological activity studies have established the antioxidant, anticancer [14] and antibacterial [15] activities of this genus. The present study was performed to justify the folkloric use of *D. vulgaris* against rheumatism in Turkish folk medicine.

2. MATERIALS AND METHODS

2.1. Collection of the Plant Materials

Fruits of *D. vulgaris* were collected in the month of May from İzmir, Turkey, in 2017. A voucher specimen is kept in the Herbarium of the Faculty of Pharmacy, Gazi University, Ankara, Turkey (Herbarium Number: GUE-3465).

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RESEARCH ARTICLE

Spiro Heterocyclic Compounds as Potential Anti-Alzheimer Agents (Part 2): Their Metal Chelation Capacity, POM Analyses and DFT Studies

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Abstract: ***Background***: One of the best methods to treat Alzheimer disease (AD) is through the effective use of cholinesterase inhibitors as vital drugs due to the identification of acetylcholine deficit in the AD patients.

Objective: The present study aims the investigation of spiro heterocyclic compounds as potential AD agents supported by their metal chelation capacity, POM analyses and DFT studies, respectively.

Method: The cholinesterase inhibition and metal chelation ability were performed on ELISA microtiter assay. Whereas, the B3LYP method with 6-31+G(d,p) basis set was implemented to study HOMO-LUMO energy calculations. The pharmacokinetic properties of the synthesized molecules were studied through Petra, Osiris and Molinspiration (POM).

Results: The six spiro (**1-6**) skeletons were tested for their inhibitory potential and metal-chelation capacity. Our findings revealed that the tested spiro skeletons exerted none or lower than 50% inhibition against both cholinesterases, while compound **4** proved to be the most active molecule with 57.21±0.89% of inhibition toward BChE. The spiro molecule **3** exhibited the highest metal-chelation capacity (9.12±5.26%). Molecular docking model for the most active molecule exhibited promising bindings with AChE and BChE's active site pertained to hydrophobic hydrogen bonds and positive ionizable interactions. The POM analyses gave the information about the flexibility at the site of coordination of spiro compounds (**1-6**).

Conclusion: The screening of spirocompounds (**1-6**) against cholinesterases revealed that some of them show considerable potential to inhibit AChE and BChE. Herein, we propose that the spiro molecules after further derivatization could serve interesting AD inhibitor drugs.

Keywords: Spiro molecules, anti-Alzheimer; cholinesterase, POM analysis, DFT studies, metal chelation.

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Article

Sedative Effects of Latexes Obtained from Some *Lactuca* L. Species Growing in Turkey

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Abstract: *Lactuca* L. species belong to the Asteraceae family and these plants are traditionally used for therapeutic purposes around the world. The dried milky latex of *L. serriola* is known as "lettuce oil" and is used as a sedative in Turkey. This study aimed to evaluate the sedative effects and analyze the chemical compositions of latexes obtained from some *Lactuca* species growing in Turkey. The sedative effects were evaluated through various behavioral tests on mice. For this purpose, latexes were obtained from *L. glareosa* Boiss., *L. viminea* (L.) J. Presl and C. P, *L. mulgedioides* (Vis and Pančić) Boiss. and Kotschy ex. Boiss., *L. saligna* L., and *L. serriola* L. The latex from *L. saligna* showed the highest sedative effects, whilst *L. serriola* and *L. viminea* latexes also displayed significant sedative effects compared to the control group at a dose of 100 mg/kg. However, the latexes from *L. glareosa* and *L. mulgedioides* did not exhibit any sedative effects on mice. Characteristic sesquiterpene lactones (lactucin, lactucopicrin, 11,13β-dihydrolactucin, and 11,13β-dihydrolactucopicrin) were determined qualitatively and quantitatively by high-performance liquid chromatography (HPLC). Lactucin was identified as the main component.

Keywords: Asteraceae; *Lactuca*; sedative effect; sesquiterpene lactone; HPLC

1. Introduction

Sleep is the state of rest that is necessary for all people to lead healthy lives. Many physical, environmental, psychological, and physiological factors can positively or negatively affect the quality and quantity of sleep. Insomnia is considered an important health problem because of its negative effects on people's quality of life and it often has psychiatric or medical causes [1]. Chronic sleep disorders are often defined as difficulties in initiating and maintaining sleep; consequently, the quality and quantity of sleep are low. Insomnia is often seen and treated as a symptom rather than a disease. Antidepressants and sedative and hypnotic drugs are used for insomnia, especially benzodiazepines,

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Original Article

The regression of endometriosis with glycosylated flavonoids isolated from *Melilotus officinalis* (L.) Pall. in an endometriosis rat model

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ABSTRACT

Objective: *Melilotus officinalis* (L.) Pall. is commonly used for treating bronchitis, painful menstruation, hemorrhoids, kidney stones, ulcers of the eyes, earache, and hardening and swelling of uterus. The European Medicines Agency reported the use of *M. officinalis* orally against stomach ache, gastric ulcer, and disorders of the liver and uterus in folk medicine. The present study aimed to appraise the activity of *M.* (L.) Pall. aerial parts in endometriosis rat model.

Materials and methods: The endometriosis rat model was used to evaluate the potential activity of *M. officinalis* aerial parts based on its folkloric usage. The aerial parts of *M. officinalis* were extracted with *n*-hexane, ethyl acetate (EtOAc), and methanol (MeOH), respectively. The adhesion scores, endometrial foci areas, and cytokine levels were measured in all treated groups. After the biological activity studies, phytochemical studies were performed on the active extract and the fractions obtained from the active extract.

Results: The MeOH extract significantly decreased the endometrial foci areas and cytokine levels in rats with endometriosis. Fractionation was performed on the MeOH extract to achieve bioactive molecules. Following the fractionation, the fractions obtained from the MeOH extract were tested. Fraction C showed the highest activity in the rat endometriosis model. Phytochemical investigation of the active fraction (Fraction C) resulted in isolation and elucidation of some quercetin and kaempferol glucoside derivatives.

Conclusion: Fraction C obtained from the MeOH extract of *M. officinalis* showed the highest activity, yielding four glycosylated flavonoids.

Introduction

Melilotus officinalis (L.) Pall. (Fabaceae) is native in Europe and Asia and known as "yellow melilot, yellow sweet clover, and medicinal sweet clover" [1,2]. *M. officinalis* is commonly used for treating hemorrhoids, bronchitis, kidney stones, painful menstruation, earache, ulcers of the eyes, and hardening and swelling of uterus [3,4]. The European Medicines Agency reported the traditional use of *M. officinalis* orally against stomach ache, gastric ulcer, and complaints of liver and uterus [5].

Biological activity studies demonstrated the antioxidant, anti-inflammatory, and antiproliferative effects of *M. officinalis* [6,7]. Some studies showed that this plant prevented skin aging, promoted tissue regeneration, and reduced fat deposition [8]. Previous studies about phytochemical profile of *M. officinalis* reported that *M. officinalis* contains kaempferol, quercetin, and coumarin derivatives [3–5,9].

Endometriosis is defined as the condition in which a tissue resembling the uterine mucous membrane, or endometrium, if found outside of the uterus. It can develop in the uterine ligaments, ovaries, pelvic peritoneum, rectovaginal septum, covering the sigmoid colon, uterus, rectum, tubes or bladder, umbilicus, laparotomy and episiotomy scars, tubal stumps, hernial sacs, appendix, cervix, vagina, vulva or lymph glands [10]. The incidence of endometriosis has increased in the last few decades. This increase is most probably

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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Isolation and identification of triterpenes from *Anthemis austriaca* Jacq. through bioactivity-guided fractionation on polycystic ovary syndrome rat model

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Abstract

Purpose This study aimed to assess the activity of *A. austriaca* flowers in treating polycystic ovary syndrome (PCOS) in rats.

Methods A letrozole-induced PCOS rat model was used to evaluate the activity potential of *A. austriaca* flowers. For this purpose, extracts of different polarity were prepared from *A. austriaca* flowers using *n*-hexane, ethyl acetate, and methanol. Serum luteinizing hormone, follicle-stimulating hormone, progesterone, testosterone, estradiol, serum leptin, lipid, and glucose levels were tested. Moreover, the antioxidant activity was evaluated by calculating superoxide dismutase, malondialdehyde, catalase, and glutathione peroxidase levels. Following the biological activity studies, phytochemical studies were conducted on the active extract to detect the compound(s) responsible for the activity.

Results The treatment with *n*-hexane extract contributed to regulating serum gonadotropin and steroid hormone levels. The plasma level of high-density lipoprotein cholesterol was significantly higher than that of the control group, while the levels of low-density lipoprotein cholesterol, leptin, and glucose were significantly lower than those of the control group. Also, the *n*-hexane extract showed significant antioxidant activity in the PCOS rat model. Since the *n*-hexane extract was found to be active, isolation studies were performed on this extract and three main fractions were obtained from the *n*-hexane extract. Those fractions also were tested on letrozole-induced PCOS rat model. As a result, three triterpenoids, *β*-amyrin palmitate, taraxasterol acetate, and taraxasterol were isolated and identified from Fr. B which is the most active fraction.

Conclusion *n*-Hexane extract and Fr. B obtained from this extract showed statistically significant activity in the letrozole-induced PCOS rat model and three triterpene-type compounds were isolated from Fr. B.

Keywords *Anthemis austriaca* · Asteraceae · Polycystic ovary syndrome · Letrozole · Triterpenoids

Introduction

Fifty-two species of *Anthemis* L. genus are found in Flora of Turkey. The genus includes annual, biennial, or perennial herbs, and sometimes suffruticose or small shrubs, which are sparsely or densely pubescent or sericeous. The stems of the genus are simple or branched. Leaves are usually pinnatisect and rarely simple. The leaves of *Anthemis austriaca* Jacq. are pinnatisect and lobes of the plant are 1.5–3 mm long [1].

A. austriaca of the Asteraceae family is indigenous to Austria and distributed widely from Europe to Turkey. *A. austriaca* flowers have been used traditionally to treat hemorrhoids, abdominal pain, and pneumonia [2–4]. The plant is also used against cough and ovary diseases as an infusion in folk medicine [5–7]. According to the biological activity studies, *Anthemis* species showed antimicrobial, antioxidant, antiviral, and cytotoxic effects [8,

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In vivo bioactivity assessment on *Epilobium* species: A particular focus on *Epilobium angustifolium* and its components on enzymes connected with the healing process

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ABSTRACT

Ethnopharmacological relevance: Epilobium species are generally known as "Yakı Otu" in Turkey, which mens "plaster herb" in English. Young shoots of *Epilobium angustifolium* L., *Epilobium stevenii* Boiss., and *Epilobium hirsutum* L. are consumed as salad or meal. These species have been used as a poultice for the treatment of mouth wounds in traditional medicine. An ointment prepared from leaves is used for skin disorders in children.

Aim of the study: We aimed to evaluate the ethnopharmacological use of *Epilobium angustifolium*, *E. stevenii*, and *E. hirsutum* by using *in vivo* and *in vitro* experimental models, and to identify the active wound-healer compound (s) and to explain the probable mechanism of the wound-healing activity.

Materials and methods: Evaluation of wound healing effects of plant extracts was performed in rats and mice by linear incision and circular excision wound models. Determination of total phenolic constituents and antioxidant capacities, which are known to promote the wound healing process, were carried out through Folin-Ciocalteau method and 2,2 Diphenyl 1 picrylhydrazyl (DPPH) scavenging assay as well as determination of total antioxidant status (TAS) and total oxidant status (TOS) on the treated tissues. The active ethyl acetate (EtOAc) sub-extract of *E. angustifolium* was fractionated by different chromatographic separation techniques. The structures of isolated compounds were elucidated via detailed analyzes (NMR and LC/MS). In addition, *in vitro* collagenase, hyaluronidase, and elastase enzymes inhibitory activity tests were performed on the isolated compounds to discover the activation pathways of the samples.

Results: Among the methanol (MeOH) extracts, *E. angustifolium* had the highest wound healing activity. Among the sub-extracts, EtOAc showed the highest wound healing activity. Thus, EtOAc sub-extract was subjected to chromatography to isolate the active compounds. Five known flavonoids namely hyperoside (quercetin-3-*O*-β-D-galactoside) (1), kaempferol (2), kaempferol-3-*O*-α-L-rhamno pyranoside (3), quercetin-3-*O*-α-L-rhamno pyranoside (4), and quercetin-3-*O*-α-L-arabino pyranoside (5) were isolated from the EtOAc sub-extract of *E. angustifolium*. *In vitro* tests showed that hyperoside could be the compound responsible for the wound-healing activity by its significant anti-hyaluronidase, anti-collagenase, and antioxidant activities.

Conclusion: The EtOAc sub-extract of the aerial part of *Epilobium angustifolium* displayed remarkable wound-healing activity with anti-hyaluronidase, anti-collagenase, and antioxidant activities. Hyperoside was detected as the primary active compound of the aerial parts. According to the results, we suggest that EtOAc sub-extract of *E. angustifolium* and hyperoside may be a potent nominee to be used for the improvement of a wound-healing agent.

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RESEARCH PAPER

Investigation of Formulation and Process Parameters of Wet Media Milling to Develop Etodolac Nanosuspensions

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ABSTRACT

Purpose Etodolac (ETD) is one of the non-steroidal anti-inflammatory drugs which has low aqueous solubility issues. The objective of this study was to develop ETD nanosuspensions to improve its poor aqueous solubility properties while investigating formulation and process parameters of wet media milling method via design of experiment (DoE) approach.

Methods The critical formulation parameters (CFP) were selected as ETD amount, stabilizer type and ratio as well as critical process parameters (CPP) which were bead size, milling time and milling speed. The two-factorial-2^3 and The Box-Benkhen Designs were generated to evaluate CFP and CPP, respectively. Particle size (PS), polydispersity index (PDI) and zeta potential (ZP) were analyzed as dependent variables. Characterization, physical stability and solubility studies were performed.

Results Optimum nanosuspensions stabilized by PVP K30 and Poloxamer 188 showed 188.5 ± 1.6 and 279.3 ± 6.1 nm of PS, 0.161 ± 0.049 and 0.345 ± 0.007 PDI, 14.8 ± 0.3 and 16.5 ± 0.4 mV of ZP values, respectively. The thermal properties of ETD did not change after milling and lyophilization process regarding to DSC analysis. Also, the crystalline state of ETD was preserved. The morphology of particle was smooth and spherical on SEM. The dry-nanosuspensions stayed physically stable for six months at room temperature. The solubility of nanosuspensions increased up to 13.0-fold in comparison with micronized ETD.

Conclusions In conclusion, it is found that the poor solubility issue of ETD can be solved by nanosuspension. DoE approach provided benefits such as reducing number of experiments, saving time and improving final product quality by using wet media milling.

KEY WORDS design of experiment · etodolac · nanosuspension · solubility enhancement · wet media milling

ABBREVIATIONS

ETD	Etodolac
NS	Nanosuspension
CFP	Critical Formulation Parameters
CPP	Critical Process Parameter
PS	Particle Size
PDI	Polydispersity Index
ZP	Zeta Potential
Conc.	Concentration
PVP	Polyvinylpyrrolidone
BBD	Box-Benkhen Design
DoE	Design of Experiment

INTRODUCTION

Low aqueous solubility of drug compounds limits drug application through oral (1) or dermal (2) routes of application due to low bioavailability. Also, new drug candidates are coming out more and more insoluble. Over 40% of commercialized drugs and many more drug candidates are found to have highly lipophilic properties with aqueous solubility less than 100 µg/mL, which is characterized as highly insoluble in water (3). The dissolution rate limiting compounds for absorption are identified as Biopharmaceutical Classification System

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RESEARCH ARTICLE

Preparation, characterization and antimicrobial activity evaluation of electrospun PCL nanofiber composites of resveratrol nanocrystals

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ABSTRACT

The objective of this study was to develop resveratrol nanocrystals to solve low water solubility issues of resveratrol and adsorb them to the polycaprolactone nanofibers. Nanocrystals were prepared by microfluidization. Particle size, polydispersity index and zeta potential values were evaluated as dependent variables. Polycaprolactone (PCL) nanofibers were prepared via electrospinning method and the flow rate, electrical voltage and tip-to-collector distance were set to 3 mL/h, 13 kV and 15 cm, respectively. Optimum resveratrol nanocrystals were lyophilized and re-suspended in water and physically adsorbed to PCL nanofibers with two different concentrations (0.2 and 1 mg/cm^2). Bioadhesion, wettability, solubility, drug loading and antimicrobial activity against *Propionibacterium acnes* studies were carried out. Final nanocrystals showed 800 nm of particle size, 0.4 of polydispersity index, and −8 mV of zeta potential. Nanocrystals successfully adsorbed to PCL nanofibers proven on SEM images with adsorption efficiencies >70%. Adsorption of resveratrol nanocrystals decreased the contact angle of PCL from 128° to 50°. The solubility of resveratrol nanocrystals enhanced ~5-fold in comparison with coarse powder. Effective antimicrobial activity against *P. acnes* was observed. It is concluded that nanocrystal loading on nanofibers brings advantage into preparing easy to use dermal patches for acne treatment or skin disorders.

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KEYWORDS
Resveratrol; nanocrystal; nanofiber; solubility enhancement; dermal delivery

Introduction

Human skin has a large surface area which prevents the body from organisms and also maintains the body heat. Drug application from skin is a suitable route for local or systemic effect (Oktay et al. 2018). However, poorly soluble drug compounds show limited penetration through the skin due to inadequate concentration gradient between formulation and skin. Generation of higher concentration gradient by improving solubility leads to increased skin penetration (Müller et al. 2019). The use of nanotechnology in topical products provides many advantages such as lower doses for application, higher skin penetration, providing local or systemic effects of the preparations. Also, the poorly soluble, irritant, volatile, or photosensitive compounds can be formulated for dermal delivery using nanotechnological approaches (Rai et al. 2018). Although liposomes, transfersomes, niosomes, nanosponges, microneedles or ethosomes, which are developed for this purpose, increase the passage of the active substances topically, these systems have some disadvantages such as stability problems, skin irritation, patient incompliance or high cost (Elsayed et al. 2007; Arora and Nanda 2019). Among nanotechnological drug delivery systems, nanocrystals have benefits for increasing saturation solubility and stability of the Biopharmaceutical Classification System (BCS) Classes II or IV active pharmaceutical compounds as well as enhancing skin penetration by reducing particle size below micrometer range. They can be defined as nano-sized drug particles prepared with minimum quantity of suitable surfactants, polymers or combination of them. The main advantage of the system is the increasing solubility and surface area leading to an enhanced dissolution velocity and hence enhancing passive diffusion through biological membranes due to increased concentration gradient (Pelikh et al. 2018). Mainly top-down approaches such as high pressure homogenization or wet ball milling methods or precipitation as a bottom-up technique can be used to obtain nanocrystals (Müller et al. 2011). The stability of the nanocrystal formulations can be achieved by using surfactants and/or polymers at different ratios (Merisko-Liversidge and Liversidge 2011; Wu et al. 2011). Design of experiment (DoE) approach can be used in order to select suitable stabilizer, reduce the number of experiments and improve final product quality (Tashan et al. 2019). Nanocrystals are dispersed systems typically in water and they can be lyophilized or spray-dried to improve physical stability and also to prepare solid dosage forms. Nanocrystals can physically adsorb on the nanofibers to generate solid dermal patches, which brings advantages to improve patient compliance, enhance skin penetration of drug substance, and increase physical stability (Hamlett et al. 2008).

Electrospinning method, in which electrostatical forces from synthetic or natural polymers are used, is one of the most preferred fabrication method of nanofibers. Basically, electrical charging of polymer solution causes charged polymer jets which are collected on the grounded collector while the solvent evaporates. In pharmaceutical area, active ingredients loaded nanofibers have gained popularity due to their large surface area to volume ratio, customized porosity, increasing solubility of active ingredients and customized release behaviours (Torres-Martinez et al. 2018). There are different methods for producing active ingredients loaded nanofibers such as physical adsorption, embedded loading

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Supplemental data for this article can be accessed here.

Neuroprotective Potential of the Tubers of *Corydalis triternata* Zucc. Growing in Turkey

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Summary: The continuing research for the determination of bioactive secondary metabolites from Turkish geophytes as therapeutic agents for dementia is mainly based on the need for drug candidates affected to brain areas. In this study, the *in vitro* anticholinesterase activity of the alkaloidal fractions of the tubers of *Corydalis triternata* Zucc. was investigated for their neuroprotective potential. Furthermore, the content of the active alkaloid fractions of the tubers was determined by LC-Q-TOF-MS. The tubers of *Corydalis triternata* Zucc. were collected from Hatay province of Turkey. The plant species were also preserved as *ex-situ* in Yalova-Turkey. The alkaloidal extract was prepared from the tubers. The anticholinesterase activities of the extracts and fractions were tested by modification of the Ellman's method. The optimization of LC-MS conditions was used in ESI in the positive ion mode. The *in vitro* tests were highlighted that the alkaloidal extract of the tubers exhibited the highest activity against AChE and BuChE with IC_{50} values of 17.56 ± 1.0 µg/mL and 326.23 ± 2.6 µg /mL (galanthamine 6.8 ± 0.5 µg /mL and 344.4 ± 8.2 µg /mL as positive control), respectively. The fractions CK-3 and 4 were showed the highest inhibitory activity against AChE with the IC_{50} value (6.88 ± 0.3 µg mL and 7.26 ± 0.3 µg /mL), the fractions CK-5,6,7 and 8 have indicated potent inhibitory activities by compared with galanthamine, which was used as positive control with IC_{50} value 6.8 ± 0.5 µg /mL. Among the fractions obtained from the alkaloidal extract, protoberberine-type alkaloids were exerted the most promising activity against both cholinesterases. The present study was described for the first time the *in vitro* anticholinesterase activity of *Corydalis triternata* Zucc. as neuroprotective potential and their metabolite profile by LC-Q-TOF-MS. Besides, the anticholinesterase assays on alkaloidal extract and its fractions showed that protoberberine-type alkaloids were determined the most potent inhibitor against AChE and BuChE.

Keywords: Alkaloids, Anticholinesterase, *Corydalis triternata* Zucc., isoquinolines.

Introduction

Neurological disorders generally affect the elderly population. Alzheimer's disease (AD) is characterized clinically by advancing memory deficits and impaired cognitive function [1,2]. AD is predicted to account for between 50 and 60 % of dementia cases in persons over 65 years of age and according to the United Nations, the number of people bearing age-related neurodegeneration, will enduringly increase from 25.5 million in 2000 to an estimated 114 million in 2050 [3]. It is a major public health concern in developed countries due to the increasing number of sufferers, placing strains on caregivers as well as on economical resources [2]. A deficiency in levels of the neurotransmitter acetylcholine (ACh) has been observed in the brains of AD patients, and inhibition of acetylcholinesterase (AChE), the key enzyme hydrolysing ACh, is a majör treatment option for AD [4]. Galantamine, originally isolated from plants of the Amaryllidaceae family, has become significant in the treatment of AD [5]. The AChE inhibitory activity of this drug is the principal mode of action to ensure symptomatic relief. Galantamine increases the availability of ACh in the cholinergic synapse by competitively inhibiting the enzyme responsible for its breakdown, AChE. The binding of galantamine to AChE slows down the catabolism of ACh and, as a result, ACh levels in the synaptic cleft are increased [6-9]. Therefore, current drug therapies are based on the cholinergic hypothesis. However, the β - amyloid hypothesis has been gaining attention in the last few years. To date, several secondary metabolites from natural sources have been identified as showing acetylcholinesterase inhibitory (AChEI) activity and are thus potential drug candidates [10]. The genus *Corydalis* (Papaveraceae) comprises of 470 species distributed mainly in temperate regions of the Northern Hemisphere, mostly in Eurasia; represented by one species in the subarctic Russia and North America, one species in the mountains of eastern Africa, 3 species in the subtropical Indo-China, and 17 species with 22 taxons in the Flora of Turkey [11]. Members

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Antioxidant effects of dexmedetomidine against hydrogen peroxide-induced DNA damage in vitro by alkaline Comet assay

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Background/aim: Dexmedetomidine (DEX) is an alpha-2 adrenergic agonist that is commonly used as a sedative and anesthetic. The protective effects of DEX against oxidative damage under both in vitro and in vivo conditions have been demonstrated. It was aimed to evaluate and compare the protective effects of DEX and vitamin C (Vit C) on DNA against H_2O_2-induced DNA damage in human lymphocyte cell cultures in vitro by alkaline Comet assay.

Materials and methods: Lymphocyte cell cultures were divided into 5 groups, as the negative control, solvent control, positive control, hydrogen peroxide (H_2O_2; 150 μM) + DEX (1 μM; 2.5 μM; 5 μM), and H_2O_2 (150 μM) + Vit C (1 μM; 2.5 μM; 5 μM), and incubated at 37 °C for 1 h. Cell viability was measured using the Trypan blue test. DNA damage was measured using the Alkali Comet Technique and the % percent tail intensity was evaluated. Statistical analysis was performed using 1-way ANOVA and the Tukey multiple comparison test.

Results: It was observed that H_2O_2 significantly induced DNA damage in the lymphocytes and this damage was decreased significantly with Vit C and DEX. It was observed that Vit C at doses of 1 μM and 2.5 μM had a significantly stronger antioxidant effect, but there was no significant difference between the antioxidant effects of Vit C and DEX with a dose of 5 μM. The dose of 5 μM DEX was found to be the most effective in reducing oxidative DNA damage.

Conclusion: There is limited data on the protective effects of DEX against oxidative DNA damage. The primary effect might be cytoprotection. The results herein showed that DEX was protective against H_2O_2-induced in vitro oxidative DNA damage in lymphocyte cell cultures in a dose-dependent manner. DEX might have a potential therapeutic value in the prevention of oxidative DNA damage in patients.

Key words: Antioxidant, dexmedetomidine, DNA damage

1. Introduction

Dexmedetomidine (DEX) is a highly selective alpha-2 adrenergic receptor agonist that is commonly used in clinical practice as a sedative and anesthetic agent due to its sedative, analgesic, hemodynamic stabilizing, and diuretic effects [1,2]. In addition to its sedative and anesthetic effects, its antiinflammatory and antioxidant effects on vital organs, such as the heart [3,4], lungs [5–7], kidneys [8], spinal cord [9], and brain [10], have been demonstrated. DEX has antiinflammatory and protective effects against oxidative damage that have been shown under both in vitro and in vivo conditions [11,12]. It shows these effects probably by inhibiting the toll-like receptor (TLR) [4,13], suppressing high-mobility group box 1 (HMGB1) factor [14], and inhibiting the nuclear factor (NF)-κB and phosphoinositide-3 kinase (PI3K-) signaling pathway [3,15].

Oxidative stress, which is induced by ischemia, mechanical stress, or toxins, is a condition that results from an imbalance between the production of reactive oxygen species (ROS) and free radicals, as well as inappropriate antioxidant functions. The ROS-induced oxidative stress in cells trigger a mechanism that, through the release of cytochrome c and activation of caspase-3, leads to intrinsic apoptosis. ROS play a critical role in maintaining homeostasis and cell signaling [16]. Hydrogen peroxide (H_2O_2), a reactive ROS derivative, is considered to be the radical that is most responsible for oxidative damage. It has been widely used to mimic in vitro oxidative stress in many different cell types [17].

ROS can lead to DNA-strand breaks by loss of DNA bases, known as apurinic/apyrimidinic sites, and inhibits transcription. Moreover, the DNA strand break, an

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Reinvestigation of *Herniaria glabra* L. saponins and their biological activity

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Enzyme inhibitory activity

ABSTRACT

Twelve undescribed triterpenoid pentacyclic glycosides, medicagenic acid (3-*O*-β-D-glucuronopyranosyl-28-*O*-{[β-D-glucopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)]-[α-L-rhamnopyranosyl-(1 → 3)]-4-*O*-acetyl-β-D-fucopyranosyl-(1→)}-2β,3β-dihydroxyolean-12-ene-23,28-dioic acid, 3-*O*-β-D-glucuronopyranosyl-28-*O*-{[α-L-rhamnopyranosyl-(1 → 2)]-[β-D-apiofuranosyl-(1 → 3)]-4-*O*-acetyl-β-D-fucopyranosyl-(1→)}-2β,3β-dihydroxyolean-12-ene-23,28-dioic acid, 3-*O*-β-D-glucuronopyranosyl-28-*O*-{[α-L-rhamnopyranosyl-(1 → 2)]-3,4-*O*-diacetyl-β-D-fucopyranosyl-(1→)}-2β,3β-dihydroxyolean-12-ene-23,28-dioic acid, 28-*O*-{[6-*O*-acetyl-β-D-glucopyranosyl-(1 → 2)]-[2-*O*-acetyl-α-L-rhamnopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 6)]-β-D-glucopyranosyl-(1→)}-2β,3β-dihydroxyolean-12-ene-23,28-dioic acid, 28-*O*-{[6-*O*-acetyl-β-D-glucopyranosyl-(1 → 2)]-[3-*O*-acetyl-α-L-rhamnopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 6)]-β-D-glucopyranosyl-(1→)}-2β,3β-dihydroxyolean-12-ene-23,28-dioic acid, 28-*O*-{[6-*O*-acetyl-β-D-glucopyranosyl-(1 → 2)]-[4-*O*-acetyl-α-L-rhamnopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 6)]-β-D-glucopyranosyl-(1→)}-2β,3β-dihydroxyolean-12-ene-23,28-dioic acid, 28-*O*-{[6-*O*-acetyl-β-D-glucopyranosyl-(1 → 2)]-[β-D-glucopyranosyl-(1 → 6)]-β-D-glucopyranosyl-(1→)}-2β,3β-dihydroxyolean-12-ene-23,28-dioic acid, 28-*O*-{[β-D-glucopyranosyl-(1 → 2)]-[β-D-glucopyranosyl-(1 → 6)]-β-D-glucopyranosyl-(1→)}-2β,3β-dihydroxyolean-12-ene-23,28-dioic acid), zanhic acid (3-*O*-β-D-glucuronopyranosyl-28-*O*-{[β-D-glucopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)]-[α-L-rhamnopyranosyl-(1 → 3)]-4-*O*-acetyl-β-D-fucopyranosyl-(1→)}2β,3β,16α-trihydroxyolean-12-ene-23,28-dioic acid, 3-*O*-β-D-glucuronopyranosyl-28-*O*-{[β-D-glucopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)]-β-D-fucopyranosyl-(1→)}-2β,3β,16α-trihydroxyolean-12-ene-23,28-dioic acid), 29-hydroxy-medicagenic acid (3-*O*-β-D-glucuronopyranosyl-28-*O*-{[β-D-glucopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)]-[α-L-rhamnopyranosyl-(1 → 3)]-4-*O*-acetyl-β-D-fucopyranosyl-(1→)}-2β,3β,29β-trihydroxyolean-12-ene-23,28-dioic acid) and herniaric acid (28-*O*-{[6-*O*-acetyl-β-D-glucopyranosyl-(1 → 2)]-[α-L-rhamnopyranosyl-(1 → 4)-β-D-glucopyranosyl-(1 → 6)]-β-D-glucopyranosyl-(1→)}-2β,3β-dihydroxyolean-18-ene-23,28-dioic acid) were isolated from the whole plant extract of *Herniaria glabra* L. (Caryophyllaceae), wild growing in the Ukraine. In addition, five known triterpenoid saponins; i.e. herniariasaponins 1, 4, 5, 6, and 7 were also isolated. Their structures were elucidated by HRESIMS, 1D and 2D NMR spectroscopy, as well as by comparison with the literature data. Twelve herniariasaponins, the purified crude extract, and the saponin fraction were evaluated *in vitro* for their xanthine oxidase, collagenase, elastase, and tyrosinase inhibitory activity. Moreover, herniariasaponins 4, 5, and 7 were screened for their cholinesterase inhibitory potential. As a result, no or low inhibition towards the mentioned enzymes was observed.

1. Introduction

Herniaria glabra L. (syn. *H. suavis* Klokov (Fedoronchuk and Didukh, 2002; Marhold, 2011; "The Plant List (2010). Version 1. Published on the Internet," 2010); common name: smooth rupturewort) is an annual or biennial plant, a member of the family Caryophyllaceae, native in Northern Africa, Asia-Temperate and Europe, naturalized in Japan and Northern America ("USDA, Agricultural Research Service, National

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Effect of *Sorbus domestica* and its active constituents in an experimental model of colitis rats induced by acetic acid

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ARTICLE INFO

Keywords:
Sorbus domestica
Rosaceae
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Myeloperoxidase
Caspase-3
Inflammation

ABSTRACT

Ethnopharmacological relevance: In Turkish folk medicine, leaves of *Sorbus domestica* are used for the treatment of burns, cough, stomachache, bradyuria, kidney stone. The fruits of this plant are used for diarrhoea.
Aim of the study: This study was carried out to investigate the effect of *S. domestica* on ulcerative colitis induced by acetic acid in rats.
Materials and methods: The crude methanolic extract of fruits was sequentially fractionated into five subextracts; dichloromethane, diethyl ether, ethyl acetate, *n*-butanol and aqueous extracts. Effects of the extract, subextracts and fractions were investigated in acetic acid–induced rat colitis model. The colonic interleukin-6 (IL-6), tumor necrosis factor (TNF-α), nitrite, superoxide dismutase (SOD), glutathione (GSH), lipid peroxidation (LPO), catalase (CAT), and malondialdehyde (MDA) levels as well as the caspase-3 and myeloperoxidase (MPO) activities were measured to determine the activity. Histopathological analyzes were also performed on the colon tissue of rats.
Results: The methanolic extract and diethylether subextract have led to a noteworthy decrease in MPO, caspase-3, IL-6, TNF-α, MDA, and nitrite levels in the colon tissue and blood. In addition, histopathological analysis results were supported by biochemical parameters. After confirmation of the activity against ulcerative colitis, the diethyl ether subextract was subjected to more chromatographic separation for the isolation of compounds **1**, **2** and **3**. The structures of these three compounds were elucidated as vanillic acid 4-O-α-L-rhamnopyranoside (**1**), protocateuic acid anhydrite (**2**) and trivanilloyl-(1,3,4-trihydroxybenzol) ester (**3**).
Conclusion: In this study, the potential of *S. domestica* in the treatment of colitis was investigated. Fruits of this plant were found to have important anti-inflammatory and antioxidant activities. Through isolation techniques, vanillic acid 4-O-α-L-rhamnopyranoside, protocateuic acid anhydrite and trivanilloyl-(1,3,4-trihydroxybenzol) ester were determined as the main active components of the fruits. Consequently, *S domestica* might be a promising candidate for upcoming use the prevention and treatment of various disorders, such as inflammatory bowel diseases, irritable bowel syndrome and *Clostridium difficile* infection.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic immune mediated illnesses with unidentified etiology which are evaluated in the context of inflammatory bowel diseases (IBD). Even though the etiology and pathogenesis of IBD continue to be uncertain, the effect of genetic factors and also environmental factors cannot be denied. Current epidemiological data show that the incidence of IBD is increasing in many parts of the world, and this situation has been linked to changing lifestyles of people and the rate of industrialization of societies (Cota et al., 2019). The pathological findings related to UC are increasing in oxidative stress, certain inflammatory mediators, intestinal permeability or sulfide production; decreasing in oxidation of short chain fatty acids or methylation; degeneration of the mucosa and alteration of glycosaminoglycan content in it (Gupta et al., 2015). Oxidative stress has also been demonstrated in the pathogenesis of UC in preclinical studies.

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molecules

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Article

Sedative and Anxiolytic Activities of *Opuntia ficus indica* (L.) Mill.: An Experimental Assessment in Mice

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Abstract: Ethnobotanical field surveys revealed the use of fruits of *Opuntia ficus indica* (L.) Mill. for treating diabetes, burns, bronchial asthma, constipation, kidney stones, and rheumatic pains and as a sedative in Turkish folk medicine. This study aimed to verify the efficacy of the fruits of *O. ficus indica* experimentally and to define components responsible for the activity using bioassay-guided procedures. The crude methanolic extract of the fruits was sequentially fractionated into five subextracts: *n*-hexane, dichloromethane, ethyl acetate, *n*-butanol, and water. Further experiments were carried out on the most active subextract, that is, the ethyl acetate (EtOAc) subextract, which was further subjected to fractionation through successive column chromatographic applications on Sephadex LH-20. For activity assessment, each extract or fraction was submitted to bioassay systems; traction test, fireplace test, hole-board test, elevated plus-maze test, and open-field test were used for sedative and anxiolytic effects, and a thiopental-induced sleeping test was used for the hypnotic effect. Among the subextracts obtained from the methanolic extract, the EtOAc subextract showed significant sedative and anxiolytic effects in the bioassay systems. From the EtOAc subextract, major components were isolated, and their structures were determined as isorhamnetin, isorhamnetin 3-*O*-glucoside, isorhamnetin 3-*O*-rutinoside, and kaempferol 3-*O*-rutinoside using spectral techniques. In conclusion, this study confirmed the claimed use of the plant against anxiety in Turkish folk medicine.

Keywords: anxiolytic; cactaceae; hypnotic; mice; *Opuntia ficus indica*; sedative

1. Introduction

Common anxiety disorder is the most common among mental disorders in patients of advanced age group [1]. In general, anxiety disorders can be treated with certain psychotherapeutic drugs. Sedatives and hypnotics are medications that can reduce anxiety and induce the onset of sleep and maintain sleep time [2]. Benzodiazepines are commonly used because of their muscle-relaxant, sedative-hypnotic, and anticonvulsant effects [3]. However, the continued use of these currently available sedative-hypnotic treatments has serious side effects, from respiratory, digestive, and immune

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Beneficial effects of *Ajuga chamaepitys* (L.) Schreber subsp. *chia* (Schreber) and its iridoids on the colitis model: Histopathological and biochemical evidence

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ARTICLE INFO

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ABSTRACT

In Turkish folk medicine, aerial parts of *Ajuga chamaepitys* (L.) Schreber subsp. *chia* (Schreber) are used for the treatment of diarrhea. The crude methanolic extract of aerial parts of *A. chamaepitys* subsp. *chia* was sequentially fractionated into five subextracts; *n*-hexane, dichloromethane, ethyl acetate, *n*-butanol and aqueous extracts. Effects of the methanol extract, subextracts and fractions were investigated in acetic acid-induced rat colitis model. The MeOH extract and *n*-BuOH subextract have regulated the caspase-3, myeloperoxidase, TNF-α, IL-6 levels and antioxidant parameters. After confirmation of the activity against ulcerative colitis, *n*-BuOH subextract was subjected to more chromatographic separation for the isolation of compounds ajugoside (**1**), asperulosidic acid (**2**) and deacetyl-asperulosidic acid (**3**). As a conclusion, *A. chamaepitys* subsp. *chia* can be used in cell, tissue, or individual-specific treatments that will be developed in the future treatment of IBD, or as a complementary therapeutic agent that contributes to these treatments.

1. Introduction

Ulcerative colitis (UC) is a chronic disease of the gastrointestinal (GI) system which characterized by acute non-infectious inflammation of the colonic mucosa (Ordas et al., 2012). UC is one of types of inflammatory bowel diseases (IBDs), the other is Crohn's disease (CD). Genetic backgrounds and environmental factors both promote the damage. UC develops in the second or third decade of lifetime and causes clinical symptoms such as bloody diarrhea and rectal urgency tenesmus (Danese and Fiocchi, 2011).

The mucosal immune system, is incessantly exposed to antigens, such as dietary (exogenous) and bacterial (endogenous). Activation of T cells by antigens may lead to the production of inflammatory cytokines and inflammation and tissue damage in IBDs. In addition to immune factors other mediators of inflammation, such as cytokines, eicosanoids, nitrogen- and oxygen-reactive metabolites etc. are reported in the disease (Di Paola et al., 2009). The primary purpose in treatment strategies of UC is to provide a better quality of life for a long period of time with minimal steroid exposure, induce a clinical remission and relieve clinical symptoms and mucosal inflammation (Di Paola et al., 2009). Many plants, such as *Aloe vera* (Langmead et al., 2004), *Boswellia serrata* (Dahmen et al., 2001), *Curcuma longa* (Hanai et al., 2006), *Cynara*

Abbreviations: UC, Ulcerative colitis; GI, Gastrointestinal; IBD, Inflammatory bowel disease; MeOH, methanol; CH_2Cl_2, Dichloromethane; EtOAc, Ethyl acetate; *n*-BuOH, *n*-Butanol; CMC, Carboxymethyl cellulose; GSH, Reduced glutathione; SOD, Superoxide dismutase; CAT, Catalase; LPO, Lipid peroxide; MPO, Myeloperoxidase; TNF, Tumor necrosis factor; IL, Interleukin; iNOS, Inducible nitric oxide synthase; COX, Cyclooxygenase; NF-kB, Nuclear Factor Kappa Beta; TNBS, Trinitorbenzene sulfonic acid; CD, Crohn's disease.

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plants

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Article

Insecticidal Activity of *Hyoscyamus niger* L. on *Lucilia sericata* Causing Myiasis

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Abstract: Background: *Hyoscyamus niger* L. (Solanaceae) generally known as henbane, is commonly distributed in Europe and Asia. In Turkey, henbane seeds have been used in folk medicine to remove worms from the eyes. The present study aimed to investigate the insecticidal activity of *H. niger* seeds. Methods: *n*-hexane, ethyl acetate, methanol and alkaloid extracts were prepared from the seeds of the plant and their insecticidal activities on *Lucilia sericata* larvae were evaluated. EC_{50} and EC_{90} values of the alkaloid extract were calculated and morphological abnormalities were investigated. Results: Alkaloid extract prepared from the seeds of this plant displayed significant insecticidal activity. EC_{50} values of *H. niger* seeds alkaloid extract were found to be 8.04, 8.49, 7.96 µg/mL against first, second and third instar, respectively. It was determined that malformations of larvae included damaged larvae with small size, contraction and weak cuticle. Furthermore, HPLC analysis was performed on alkaloid extract of *H. niger* seeds and main components of the extract were determined. It was determined that alkaloid extract mainly contain hyoscyamine and scopolamine. Conclusions: These results confirm the folkloric usage of the plant and suggest that the alkaloid content of the plant could be responsible for the insecticidal activity.

Keywords: black henbane; *Hyoscyamus niger*; *Lucilia sericata*; myiasis; Solanaceae

1. Introduction

Hyoscyamus genus has six species in the flora of Turkey, *H. aureus*, *H. albus*, *H. leptoclyx*, *H. niger*, *H. pusillus* and *H. reticulatus* [1]. The genus belongs to Solanaceae family. *Hyoscyamus niger* L. (black henbane) is the most popular species of *Hyoscyamus* genus. It has been used as a medicinal plant since ancient Greece [2]. The mature corolla of *H. niger* is lurid yellow, usually veined purple; the fruiting calyx is constricted at the middle; and the upper cauline leaves are amplexicaul [1]. *H. niger* leaves are used as an antispasmodic for overfed animals and the seeds are used for itching, reddening in eyes, and earache [3,4]. One of the most popular uses of *H. niger* in folk medicine is to expel worms in the mouth or eyes [3,5–9]. Seeds are spread on

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Research Article

Enzymatic Synthesis of Chondroitin Sulfate E to Attenuate Bacteria Lipopolysaccharide-Induced Organ Damage

Jine Li, Erica M. Sparkenbaugh, Guowei Su, Fuming Zhang, Yongmei Xu, Ke Xia, Pen He, Sultan Baytas, Shannon Pechauer, Anand Padmanabhan, Robert J. Linhardt, Rafal Pawlinski,* and Jian Liu*

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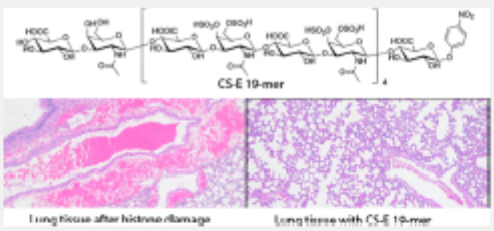
ABSTRACT: Chondroitin sulfate E (CS-E) is a sulfated polysaccharide that contains repeating disaccharides of 4,6-disulfated *N*-acetylgalactosamine and glucuronic acid residues. Here, we report the enzymatic synthesis of three homogeneous CS-E oligosaccharides, including CS-E heptasaccharide (**CS-E 7-mer**), CS-E tridecasaccharide (**CS-E13-mer**), and CS-E non-adecasaccharide (**CS-E 19-mer**). The anti-inflammatory effect of **CS-E 19-mer** was investigated in this study. **CS-E 19-mer** neutralizes the cytotoxic effect of histones in a cell-based assay and in mice. We also demonstrate that **CS-E 19-mer** treatment improves survival and protects against organ damage in a mouse model of endotoxemia induced by bacterial lipopolysaccharide (LPS). **CS-E19-mer** directly interacts with circulating histones in the plasma from LPS-challenged mice. **CS-E 19-mer** does not display anticoagulant activity nor react with heparin-induced thrombocytopenia antibodies isolated from patients. The successful synthesis of CS-E oligosaccharides provides structurally defined carbohydrates for advancing CS-E research and offers a potential therapeutic agent to treat life-threatening systemic inflammation.



INTRODUCTION

Chondroitin sulfate (CS) is a glycosaminoglycan (GAG) found in all animals exhibiting essential physiological functions. The CS polysaccharide consists of a disaccharide repeating unit of →3) *N*-acetyl-β-D-galactosamine (GalNAc) (1 → 4) β-D-glucuronic acid (GlcA) (1 →, and both saccharide residues can carry sulfo groups. Four major subtypes of CS polysaccharides have been isolated: (1) chondroitin sulfate A (CS-A); (2) chondroitin sulfate C (CS-C); (3) chondroitin sulfate D (CS-D); and (4) chondroitin sulfate E (CS-E). Each subtype is characterized by a single sulfation pattern. CS-A contains 4-*O*(oxygen)-sulfated GalNAc residue, CS-C contains 6-*O*-sulfated residue, CS-D contains 2-*O*-sulfated GlcA, and CS-E contains 4,6-*O*-disulfated GlcNAc residue. CS plays important roles in neuroplasticity, cell communication, osteoblast differentiation, immunological response, and viral infection.[1,2] Among CS subtypes, CS-E has a low abundance in mammals but plays a critical role in modulating angiogenesis through interacting with chemokines and growth factors[3] and regulating tumor progression and metastasis.[4,5] These activities of CS-E are governed by its unique sulfation pattern.[6] CS-E isolated from biological tissues is a mixture of GAG chains with different lengths and sulfation patterns.[7] The lack of homogeneous CS-E oligosaccharides of defined structure and size has limited in-depth investigation of the function and structure relationship of CS-E.

Systemic inflammation is a major contributor to sepsis[8−10] impacting 31 million people globally and resulting in 5 million deaths annually.[10] Currently, there are no specific drugs to treat sepsis. A murine model of endotoxemia, induced by administration of bacterial lipopolysaccharide (LPS), is widely used to study the systemic inflammatory responses that are a critical part of the complex pathology associated with sepsis.[11] Upon administering bacterial LPS, neutrophils or injured cells release histones, nuclear DNA-binding proteins, into extracellular space and blood circulation.[12−14] Extracellular histones activate immune cells and trigger the release of pro-inflammatory cytokines through toll-like receptors.[15,16] Extracellular histones also mediate intravascular coagulation[17] and cause endothelial dysfunction,[18] leading to organ damage under hyper inflammatory conditions.[19−21] Treatment with antibodies neutralizing histones resulted in an improved survival and reduced organ injury in septic mice.[11] Therefore, targeting extracellular histones represents a promising strategy for the treatment of sepsis. Although heparin and heparan sulfate have been used to target to histone to attenuate

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Tamoxifen/raloxifene loaded liposomes for oral treatment of breast cancer

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Breast cancer
Oral delivery

ABSTRACT

Breast cancer is the most common type of cancer and it is the second common cause of cancer-related deaths in women. Hormonal therapy is a quite well-tolerated treatment, for estrogen receptor (ER) and progesterone receptor-positive breast cancers. Selective estrogen receptor modulators (SERM) is a specific drug group, structurally different from estrogen, configured as nonsteroidal estrogen with the ability to bind estrogen receptors competitively. They are not readily soluble in biological fluids and have some bioavailability problems. In this study, liposome formulations of tamoxifen and raloxifene were developed with penetration enhancers dimethyl-β-cyclodextrin (DM-β-CD) or sodium taurocholate (NaTC). These formulations were subjected to in vivo and in vitro tests. Raloxifene and DM-β-CD liposomes showed almost 3.5 folds higher permeability coefficients through Caco-2 cell lines. Tamoxifen DM-β-CD liposomes representing particle size with a value of 244.7 ± 8.1 nm (polydispersity index was 0.332, the zeta potential was −14.8 mV and encapsulation efficiency was 45.1%) have shown higher tumor size reduction (92.5%) and therapeutic efficacy (50%). All these results indicate that SERM drug-containing liposomes with a penetration enhancer can be a better therapeutic alternative for oral treatment of breast cancer.

1. Introduction

Breast cancer is the most common type of cancer as well as the second common cause of death from cancer in women in many countries [1–3]. 1.38 million women are diagnosed with breast cancer every year worldwide [4]. The common reason for breast cancer-related mortality is known to be the development of metastases [3]. Lymph nodes, lung, liver, bone, and brain are the most common sites which are susceptible to breast cancer metastases [5].

According to the different subtypes and phases of the disease, different treatment approaches are available [6]. Breast cancer treatment is often a combination of several different treatment approaches. If the tumor is appropriate to the operation, surgical procedures constitute the first step of treatment as the most effective approach [7] and then followed by chemotherapy and/or radiotherapy which usually leads to unselective damages on healthy tissues [8]. Chemotherapeutics usually fail in the treatment because of a lack of effectiveness and also side effects [9]. Inefficient chemotherapy is considered to be directly associated with multidrug resistance (MDR), which is most frequently associated with inadequate drug concentration at the tumor site [10].

Another treatment approach in breast cancer is hormonal therapy which is a quite well-tolerated treatment, for estrogen receptor (ER) and progesterone receptor-positive breast cancers. It has been established that 75% of breast cancers are ER-positive (ER +), while 65% of ER-negative type (ER -) are progesterone receptor-positive. The success of the treatment is reported as 50–60% for ER +, and 65–70% for progesterone and estrogen-positive tumors [11–13]. There are two main drug classes for hormonal therapy which are aromatase inhibitors and estrogen receptor modulators [14,15]. Aromatase inhibitors suppress circulating estrogen up to 90% by inhibiting peripheral aromatase [16]. The second group, selective estrogen receptor modulators (SERM) is a specific chemical group that is structurally different from estrogen and defined as nonsteroidal estrogens [17]. They bind to estrogen receptor and act as agonist or antagonist to estrogen by interacting with the receptors in many different tissues by inhibiting the estrogen binding to mimic or block its effects [18,19]. The first representative of SERM group is tamoxifen [20]. Tamoxifen has been approved by FDA to be used in breast cancer prevention and adjuvant therapy. Raloxifene from the same group approved for osteoporosis, to prevent or treat bone loss in postmenopausal women [21]. While tamoxifen is effective for

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RESEARCH PAPER

Cytotoxicity of Novel Redox Sensitive PEG_{2000}-*S-S*-PTX Micelles against Drug-Resistant Ovarian and Breast Cancer Cells

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ABSTRACT

Purpose Since the last decade, it is established that nonspecific delivery of chemotherapeutics fails to effectively treat cancer due to systemic cytotoxicity, poor biodistribution at tumor site and most importantly the development of drug resistance (MDR). Stimuli-sensitive drug delivery systems gained significant attention in recent years for effective tumor therapy and reversal of MDR. The aim of this study was developing a redox sensitive micellar prodrug system, by taking the advantage of the significant difference in GSH levels between extracellular and intracellular environments, but more importantly in healthy and tumor tissues.

Methods Redox sensitive PEG_{2000}-*S-S*-PTX micelles were developed for intracellular paclitaxel delivery and characterized *in vitro*. *In vitro* release studies were carried out and followed by cytotoxicity studies in chemo-resistant ovarian and breast cancer cells in various reducing environments for different time periods to confirm their potential.

Results PEG_{2000}-*S-S*-PTX, was synthesized and characterized as a redox sensitive micellar prodrug system. The reduction sensitivity and *in vitro* PTX release properties were confirmed in reducing environments comparatively with physiological conditions. Cytotoxicity studies suggested that ovarian (SK-OV-3) cells could be better candidates for treatment with redox-sensitive drug delivery systems than breast (MCF-7) cancer cells.

Conclusions The results of this study highlights the importance of personalized therapy since no fits-for-all system can be developed for different cancer with significantly different metabolic activities.

KEY WORDS stimuli-sensitive drug delivery systems · redox-sensitive nanocarriers · MDR in cancer · paclitaxel

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INTRODUCTION

Paclitaxel (PTX) is one of the most potent natural microtubule stabilizing agents which is widely used for the treatment of various tumors including, ovarian, breast, non-small cell lung, head, neck cancers, as well as Kaposi's sarcoma. However, its low solubility, rapid clearance and adverse effects limits its clinical use. In the past decades, there had been serious side effects and solubility issues associated with the formulation of its widely used commercial products (1,2). It is common fact that systematically administered hydrophobic drugs, especially chemotherapeutics, fail in clinic as result of their systemic cytotoxicity, insufficient ability to bypass biological barriers, poor biodistribution at tumor site and nonspecific delivery. In addition, chemotherapy with a single reagent, also dubbed as mono-therapy is known to result in development of drug resistance (MDR) (3).

Numerous research has been done on PTX delivery to tumors with various nano-preparations including liposomes, micelles, nanoparticles, bioconjugates and dendrimers. However, the vast number of research is aimed to improve its solubility, reduce the administered dose, hence reduce its side effects (4). Nanocarriers overcome some of the limitations of conventional cancer chemotherapy by increasing solubility of the hydrophobic drugs, but only a small fraction of applied dose reaches to tumor tissue, because there are multiple challenges to be overcome following systemic administration

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Article

Discovery of Novel 5-Lipoxygenase-Activating Protein (FLAP) Inhibitors by Exploiting a Multistep Virtual Screening Protocol

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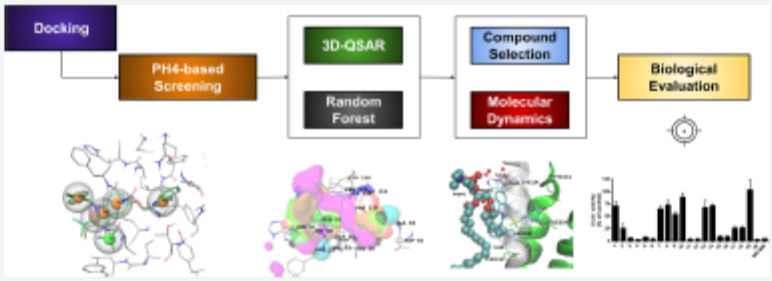

ABSTRACT: Leukotrienes (LTs) are proinflammatory mediators derived from arachidonic acid (AA), which play significant roles in inflammatory diseases. The 5-lipoxygenase-activating protein (FLAP) is an integral membrane protein, which is essential for the initial step in LT biosynthesis. The aim of this study was to discover novel and chemically diverse FLAP inhibitors for treatment of inflammatory diseases requiring anti-LT therapy. Both ligand- and structure-based approaches were applied to explain the activities of known FLAP inhibitors in relation to their predicted binding modes. We gained valuable insights into the binding modes of the inhibitors by molecular modeling and generated a multistep virtual screening (VS) workflow in which 6.2 million compounds were virtually screened, and the molecular hypotheses were validated by testing VS-hit compounds biologically. The most potent hit compounds showed significant inhibition of FLAP-dependent cellular LT biosynthesis with IC_{50} values in the range from 0.13 to 0.87 μM. Collectively, this study provided novel bioactive chemotypes with potential for further development as effective anti-inflammatory drugs.

INTRODUCTION

The 5-lipoxygenase-activating protein (FLAP) has been the subject of extensive research for next-generation anti-inflammatory drugs over the last two decades.[1,2] FLAP is an integral membrane protein, which facilitates the transfer of the substrate arachidonic acid (AA) to 5-lipoxygenase (5-LO) to produce leukotrienes (LTs), and is shown to be indispensable for cellular LT biosynthesis.[3,4] Despite the fact that the structural basis for activation of 5-LO by FLAP is still not completely understood, accumulating evidence suggests that FLAP may operate as a nuclear membrane anchor scaffold for 5-LO, and activation involves a physical interaction between 5-LO and FLAP.[5−7] AA is converted to the unstable epoxide LTA_4 in a two-step process mediated by 5-LO with the aid of FLAP (Figure 1). LTA_4 is then rapidly transformed into either LTB_4 by LTA_4 hydrolase or LTC_4 through a reaction with LTC_4 synthase. LTB_4 binds to the GPCRs BLT1 and BLT2 eliciting neutrophil and eosinophil chemotaxis and subsequent activation of downstream inflammatory responses. LTC_4 is further metabolized to LTD_4 and LTE_4, collectively called cysteinyl leukotrienes (CysLTs), causing bronchoconstriction, airway edema, and hypersecretion of mucus via their GPCRs CysLT1 and CysLT2. Since LT involvement is implicated in the pathophysiology of many diseases,[8−11] FLAP has become an attractive target as its inhibition would prevent the biosynthesis of both LTB_4 and CysLTs and as such has proven to be a valuable therapy for asthma and other respiratory diseases[12] as well as allergic and cardiovascular diseases[13,14] and certain types of cancers.[15,16]

Although the study of FLAP inhibitors in human clinical trials goes back to the early 1990s, exemplified by MK-591,[17] no FLAP inhibitor has yet progressed beyond phase 2 clinical

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Preparation and in vitro / in vivo evaluation of flurbiprofen nanosuspension-based gel for dermal application

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ABSTRACT

Flurbiprofen (FB) is an analgesic and anti-inflammatory drug, but its low water solubility (BCS Class II) limits its dermal bioavailability. The aim of this study is to develop a FB nanosuspension (NS) based gel and to evaluate its analgesic and anti-inflammatory activities in rats. FB-NS was produced by the wet milling method with Plantacare 2000®, as stabilizer. The FB-NS was then incorporated in different carrier gels such as hydroxypropyl methyl cellulose (HPMC), polycarbophil, oleogel, and chitosan. To select the optimum gel type, visual examinations, pH and rheological property measurements, texture profile analysis, in vitro release and ex vivo permeation studies were performed. Following these tests, the analgesic and anti-inflammatory activities of the optimum NS based gel were evaluated using the tail flick and carrageenan-induced paw edema methods consecutively. The NS was successfully prepared with the wet milling method, and the PS, PDI and ZP values were found to be 237.7 ± 6.8 nm, 0.133 ± 0.030, and -30.4 ± 0.7 mV; respectively. Among the NS-based gels, HPMC gel showed more suitable rheological and mechanical properties, also the percentage of permeated FB and the flux value observed for HPMC gel were higher for HPMC than for the other gels. Thus, HPMC gel was selected as a carrier gel for in vivo pharmacodynamics studies. The anti-inflammatory activity of FB-NS HPMC gel was higher than that of the physical mixture gel and that of the coarse suspension gel. Results of our analgesic activity studies showed that, in the 180th min of FB nanosuspension treatment, the latency time was significantly prolonged compared to that of the control group ($p < 0.05$). As a conclusion, while nanosuspensions increased the in vivo pharmacodynamics effect of FB by means of nanosized particles and a large surface area, the HPMC gel as a carrier prolonged the contact time of NSs with skin and eased the dermal application.

1. Introduction

Pain and inflammation are among the most common disorders that contemporary clinical medicine is trying to solve. Pain is one of the essential defensive mechanisms of the body, and it is defined as an unpleasant sensation that can be classified as acute and chronic, resulting from complex neurochemical processes (Patel et al., 2016). Inflammation is an essential protective response of the body, that develops against tissue damage caused by physical trauma, irritant chemicals or microbiological agents, in order to neutralize infectious organisms, remove harmful metabolites, and repair tissue. Inflammation is initiated by chemical mediators such as prostaglandins secreted from damaged cells, and protective cells from the damaged tissue (Henderson, 1994; Manconi et al., 2011; Pireddu et al., 2016; Standiford, 2000). Prostaglandins are generally locally effective in the tissue, and they are not found in high concentration in the bloodstream. In addition, prostaglandins increase regional blood flow and a leukocyte migration to the inflammation site, thus causing edema and redness in that region (Howland et al., 2006).

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used clinically to prevent the production of prostaglandins. NSAIDs demonstrate their analgesic, antipyretic, and anti-inflammatory activities by inhibiting cyclooxygenase$_2$ (COX_2), which is the first step in prostaglandin synthesis (Fukumoto et al., 2018; Kawabata, 2011; Narumiya et al., 1999).

Flurbiprofen (FB) is also included in this NSAIDs group, and has been found effective in the prevention of pain-related diseases such as osteoarthritis and rheumatoid arthritis. The widespread oral usage of NSAIDs may cause some undesirable side effects, and dermal and transdermal formulations are therefore preferred today

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Screening of stabilizing agents to optimize flurbiprofen nanosuspensions using experimental design

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ABSTRACT

Although flurbiprofen (FB), as one of non-steroidal anti-inflammatory drugs, has various pharmacological applications, it shows low dermal bioavailability due to its low water solubility. To overcome this solubility problem, FB nanosuspensions were developed and the effects of stabilizers were investigated with regard to critical quality attributes. While PVP K30 and HPMC 3cps were used as non-ionic polymeric stabilizer, Tween 80 and Plantacare 2000 (PL) were used as non-ionic surfactants. The influence of these types of stabilizers and their different ratios were tested. The selected formulations according to results of experimental design were also characterized by SEM, FTIR, XRPD, DSC, and the stability studies were performed. According to results of characterization studies, PL was selected as the appropriate stabilizer. The determined nanosuspension stabilized with PL had the nanosized, spherical, and homogenous dispersed particles. There is no polymorphic change on the crystalline state of FB while producing nanosuspension stabilized with PL. It also retained its stability compared with PVP stabilized nanosuspensions for one month. It was concluded that the design of experimental approach is a useful tool to determine the effect of stabilizer on quality attributes of nanosuspensions and to select the optimum type and ratio of stabilizer for obtaining more stable nanosuspensions.

1. Introduction

Flurbiprofen (FB) is one of the non-steroidal anti-inflammatory drugs and has various pharmacological applications, such as gout and osteoarthritis [1]. It is a lipophilic molecule and poorly soluble in water. The drug substances that are poorly water soluble have delivery problems such as low dermal bioavailability [2]. To overcome this solubility problem, many approaches have been applied, such as using cosolvent [3,4] and preparing in the forms of solid dispersions, liposomes, emulsions, and nanoparticles [5–8]. Because possible toxicity is related with the use of large amounts of organic solvents and excipients, their advantages are limited.

To increase solubility of lipophilic drug substance, another promising approach is the preparation of nanosuspension systems. Nanosuspensions can be defined as nano-sized (10–1000 nm) drug particles (crystalline or amorphous) covered by minimum amount of suitable surfactants, polymers or combination of them [9]. By means of decreasing particle size and increasing surface area, nanosuspensions enhance the physicochemical properties, such as dissolution, saturation solubility, biological performance, and physical stability of formulations [10]. Moreover, nanosuspensions have such advantages as high amount of drug content, low excipient side effects, ease of scale up and low cost of production [11]. Thus, nanosuspensions bring benefits in regard to applicability to various dosing routes, such as oral, parenteral, ocular, pulmonary, and dermal delivery [12].

Nanosuspension can be produced by using top down and bottom up techniques [13]. High pressure homogenization (microfluidization) is one of the top down techniques to produce nanosuspension, which can be easily adapted to industrial production [14]. The critical process parameters of this method are homogenization cycle, homogenization pressure, chamber type and size, and temperature. During the application of high level of pressure and homogenization cycles at this technique, it generates cavitation forces, which may lead to a reduction in particle sizes and an increase in Gibbs energy. Because of the increased Gibbs free energy of the system, surface area and interfaces are formed together [15]. This formation of high-energy surfaces may increase saturation solubility, dissolution velocity and improves bioavailability [16]. Also, this high surface energy may cause particle size growth which is known as Ostwald ripening effect [17]. For this reason, nanosuspensions, which have tendency for crystal growth and agglomeration, are thermodynamically unstable colloidal systems [18]. In order to protect the nanosuspension system against stability problems, the use of a stabilizer is needed. Stabilizers prevent the aggregation and agglomeration of nanosuspensions by surrounding the nanosized drug

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Molecular approach to promising cholinesterase inhibitory effect of several amaryllidaceae alkaloids: Further *re*-investigation

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ABSTRACT

All cholinesterase (ChE) inhibitory drugs in clinical use are nitrogenous compounds and among them, galanthamine as the latest anticholinesterase drug, contains a tetrahydroisoquinoline structure. For this reason, isoquinoline alkaloids seem to be attractive in search for novel drug candidates towards Alzheimer's disease (AD). Therefore, in the current work, we investigated inhibitory capacity of several alkaloids representing expanding group of biogenetically-related isoquinoline alkaloids from the Amaryllidaceae including lycorine, (+)-9-O-demethylhomolycorine, 6-hydroxybuphanisine, 9-O-demethoxymontanine, 3-epi-hydroxy-bulbispermine, tazettine, haemanthamine, (+)-haemanthidine, (-)-crinine, 8-hydroxy-9-methoxycrinine, and *N*-norgalanthamine against ChEs by microtiter enzyme inhibition assays. Our findings indicated that *N*-norgalanthamine is the most active one inhibiting both acetylcholinesterase (AChE, IC_{50} = 2.42 ± 0.16 μg/mL) and butyrylcholinesterase (BChE, IC_{50} = 20.87 ± 1.01 μg/mL) at 100 μg/mL, whereas IC_{50} values of galanthamine used as the reference were 1.33 ± 0.11 μg/mL and 37.69 ± 2.93 μg/mL for AChE and BChE, respectively. Beside this, 8-hydroxy-9-methoxycrinine was a strong inhibitor of AChE (IC_{50} = 6.92 ± 0.51 μg/mL), while (+)-9-O-demethylhomolycorine displayed a moderate BChE inhibition (IC_{50} = 83.57 ± 1.36 μg/mL). Relevantly, 8-hydroxy-9-methoxycrinine and *N*-norgalanthamine were docked into active gorges of hAChE (PDB: 4EY6) and hBChE (PDB: 4TPK), which pointed out the detail that *N*-norgalanthamine displayed a very similar binding mode of to that of galanthamine. Moreover, both AChE-inhibiting alkaloids were found to stably bind to hAChE active site occupying the middle of the gorge between the catalytic site and the peripheral anionic site. 8-Hydroxy-9-methoxycrinine was also docked into the active site of BChE. We can conclude that among the tested alkaloids, *N*-norgalanthamine with dual ChE inhibitory effect seems to be the most promising anti-Alzheimer candidate molecule for future experiments.

1. Introduction

Alzheimer's disease (AD) is a progressive neurological disorder with partly identified pathology. Due to complexity of the disease, only symptomatic treatment is available up to present. There have been two hypotheses to explain the multifactorial pathology of AD, known as "amyloid hypothesis" and "cholinergic hypothesis" (Chen and Mobley, 2019; Hampel et al., 2019). According to cholinergic hypothesis, deficit in level of acetylcholine (ACh) has been observed in the brains of AD patients, which could be prevented by inhibiting acetylcholinesterase (AChE) that hydrolyzes ACh (Saxena & Dubey, 2019). Consequently, cholinesterase (ChE) inhibition is an important option for the treatment of AD, which is the most common type of dementia, as well as glaucoma and myasthenia gravis. All ChE inhibitory drugs in clinical use are so far nitrogen-containing compounds, *i.e.* physostigmine, tacrine, donepezil, and galanthamine (Hogan, 2014; Sharma, 2019). Since ChE enzyme inhibitors are the first-generation drugs for anti-AD pharmacotherapy, acetyl- (AChE) and butyrylcholinesterase (BChE) are the most-targeted enzymes at the moment. AChE in particular, containing the active site (with catalytic anionic and esteratic subsites), aromatic gorge and peripheral anionic site (PAS) in its structure, is the primary goal for AD as aforementioned (Thapa et al., 2017).

On the other hand, many natural products, *i.e.* coumarins, flavonoids, stilbenes, alkaloids, and triterpenes, have been reported with potent ChE-inhibiting properties at pre-clinical level (Loizzo et al., 2008; Huang et al., 2013; Orhan and Gulcan, 2015; Nabavi et al., 2019). Among them, galanthamine isolated initially from *Galanthus woronowii* (snowdrop) of Amaryllidaceae family was approved as a clinically available and well-tolerable drug for the treatment of AD with mild adverse effects such as nausea, vomiting, and diarrhea (Birks, 2006; Gulcan et al., 2015). Considering the potent ChE inhibitory as well as non-competitive nicotinic receptor agonist effect of galanthamine, its hybrids with various chemical structures such as camphene, ferulic acid, memantine, etc. were also synthesized in order to find much stronger inhibitors (Storch et al., 1995; Vezenkov et al., 2012; Fang et al., 2016; Prati et al., 2016; Stavrakov et al., 2017).

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Veterinary Research Forum

The Effectiveness of *Teucrium chamaedrys* L. extracts on endometriotic implant regression in rat endometriosis model

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Abstract

The aim of the present study was to investigate the therapeutic effects of *Teucrium chamaedrys* L. (Lamiaceae) in the experimentally induced endometriosis in rats. Endometrial tissue was implanted into the abdominal wall of thirty Sprague Dawley rats; the rats with endometriosis were randomized into five groups and treatment procedure was performed for three weeks. The treatment groups were orally treated with three different extracts of *Teucrium chamaedrys*. Buserelin acetate (20.00 mg) was given as a reference drug. Vehicle was administered alone to the control group. All rats were sacrified at the end of the experiment. The endometriotic implants were measured, intra-abdominal adhesions were scored and the tissue samples were histopathologically investigated. After the treatment procedure, the volumes of endometrial implant and adhesions were detected to be significantly decreased in the *T. chamaedrys* extracts treated groups compared to the control group. Therapeutic effect of the *T. chamaedrys* extracts could be attributed to the both nonpolar and polar secondary metabolites. The study conceived that the different polarity extracts of *T. chamaedrys* could be beneficial in the treatment of endometriosis.

Introduction

Endometriosis is the growth of endometrial tissue outside the uterus. It is one of the most common gynecological diseases negatively affecting the quality of life.[1-3] It is known that endometriosis plays an important role in the fertility of both women and animals.[2,4,5] This disease affects approximately 6.00-10.00% of the women population.[6] Etiopathogenesis of this disorder is yet uncertain.[7] The diagnosis of endometriosis in the cow and mare with infertility is accomplished by endometrial biopsy.[4,8] In bitches and cats, endometriosis is a rare and sporadic disease. Generally, this disorder is accidentally discovered during the ovariohysterectomy procedure.[5,9,10] Previous studies have exhibited that ovarian endometriosis is associated with inadequate corpus luteum function.[11,12] Accordingly, spontaneous abortion was reported due to ovarian endometriosis in a bitch.[5] The patients with endometriosis are treated according to the symptoms and fertility needs.[7] Pharmacological, non-pharmacological, and surgical methods are treatment options for endometriosis. Most of the pharmacological methods cause pregnancy prevention due to their contraceptive action.[13] Moreover, available medical therapies mainly focus on treating the symptoms rather than curing the disease itself. These therapies cannot be employed for a long time owing to their severe secondary side effects.[14] Surgical approach may damage the ovarian reserve. Thus, there is a definite need to develop new drugs to provide specific and more efficient therapeutic options eliminating endometriotic lesions, preventing recurrences, and not interfering with the fertility potential.[15] New complementary therapies, perhaps combined with established medical and surgical therapies, could prevent the progression of the disease and improve fertility.

Despite the presence of drug medication and surgical methods, more recently natural remedies are gaining popularity among patients having such gynecological problems due to the unwanted effects of conventional

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Identification of small-molecule urea derivatives as novel NAMPT inhibitors via pharmacophore-based virtual screening

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ABSTRACT

Nicotinamide phosphoribosyltransferase (NAMPT) catalyzes the condensation of nicotinamide (NAM) with 5-phosphoribosyl-1-prophosphate (PRPP) to yield nicotinamide mononucleotide (NMN), a rate limiting enzyme in a mammalian salvage pathway of nicotinamide adenine dinucleotide (NAD^+) synthesis. Recently, intracellular NAD^+ has received substantial attention due to the recent discovery that several enzymes including poly(ADP-ribose) polymerases (PARPs), mono(ADP-ribose) transferases (ARTs), and sirtuins (SIRTs), use NAD^+ as a substrate, suggesting that intracellular NAD^+ level may regulate cytokine production, metabolism, and aging through these enzymes. NAMPT is found to be upregulated in various types of cancer, and given its importance in the NAD^+ salvage pathway, NAMPT is considered as an attractive target for the development of new cancer therapies. In this study, the reported NAMPT inhibitors bearing amide, cyanoguanidine, and urea scaffolds were used to generate pharmacophore models and pharmacophore-based virtual screening studies were performed against ZINC database. Following the filtering steps, ten hits were identified and evaluated for their in vitro NAMPT inhibitory effects. Compounds GF4 (NAMPT IC_{50} = 2.15 ± 0.22 μM) and GF8 (NAMPT IC_{50} = 7.31 ± 1.59 μM) were identified as new urea-typed inhibitors of NAMPT which also displayed cytotoxic activities against human HepG2 hepatocellular carcinoma cell line with IC_{50} values of 15.20 ± 1.28 and 24.28 ± 6.74 μM, respectively.

1. Introduction

Nicotinamide adenine dinucleotide (NAD^+) is a critical redox co-factor in a wide range of cellular reactions and has emerged as an important regulator of many types of disease condition, most notably, cancers.[1] Poly(ADP-ribose) polymerases (PARPs), mono(ADP-ribose) transferases (ARTs), and sirtuins (SIRTs) use NAD^+ as substrate in their catalytic activity and recycle nicotinamide (NAM) produced during NAD^+ consumption.[2] In cancer cells, NAD^+ is rapidly consumed because of increased demand for ATP and high activity of NAD^+-consuming enzymes.[3] Therefore, malignant cells are more sensitive to NAD^+ as compared to normal cells and requires the constant resynthesis of NAD^+ in order to maintain sufficient levels for cell survival.[4]

Biochemically tryptophan, nicotinic acid (NA) and NAM are three major precursors for NAD^+ synthesis in mammalian cells[5] and among these salvage pathways, the pathway which recycles NAM back to NAD^+ is the main and efficient source of NAD^+.[6] This biosynthetic process is a 2-step conversion. The first step which is the rate-determining step relies on nicotinamide phosphoribosyltransferase (NAMPT) to facilitate the condensation reaction between NAM and 5-phosphoribosyl-1- pyrophosphate (PRPP) to generate nicotinamide mononucleotide (NMN). Subsequently NMN is converted into NAD^+ catalyzed by nicotinate/nicotinamide mononucleotide adenyltransferase (NMNAT).[7,8] Due to the high NAD^+ requirement for survival and proliferation, various cancer cells are highly dependent on NAMPT activity. Given that NAMPT is the rate-limiting enzyme in a key NAD^+ recycling pathway and observed overexpression of NAMPT across many cancers including colorectal, ovarian, breast, gastric, prostate, thyroid cancers, endometrial carcinomas, melanoma, gliomas and astrocytomas,[3,9] reduction of intracellular NAD^+ levels via inhibition of NAMPT activity may be an appropriate mechanism to target the

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Novel palladium(II) complexes of *N*-(5-nitro-salicylidene)-Schiff bases: Synthesis, spectroscopic characterization and cytotoxicity investigation

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ABSTRACT

A series of palladium(II) complexes (1e–3e) with the general formulae $[Pd(L)(H_2O)]\cdot xH_2O$ were newly synthesized by the interaction of palladium(II) chloride and the monosodium salts of *N*-(5-nitro-salicylidene)-Schiff base ligands (1a–3a) in aqueous DMF solution. The identities of all the complexes were proven by elemental analysis, FTIR, ^1H, ^{13}C NMR, LC–MS, UV–vis, XPS, powder XRD spectra, thermal analysis, conductivity and magnetic susceptibility measurements. The obtained analytical and physicochemical results exhibited a square-planar coordination of the palladium(II) ion having a double deprotonated ligand and a coordinated water molecule. *In vitro* cytotoxicity of these Pd(II) complexes was screened against tumor cell lines (HeLa and MCF-7), and a normal human cell line (HEK-293). The complexes 1e and 2e exhibited a moderate antitumor activity against HeLa cell lines, while 3e had better activity than standard anticancer drug, doxorubicin. All three complexes showed the best active cytotoxicity than doxorubicin against MCF-7 cancer lines. For HEK-293 lines, a decrease in concentration of the complexes significantly decreased their toxicity.

1. Introduction

Cancer is a group of diseases characterized by uncontrolled cell proliferation and disruption of vital tissues [1]. Platinum complexes cisplatin and its analogues such as lobaplatin, nedaplatin, oxaliplatin, carboplatin and heptaplatin have a unique place in the chemoterapeutic drugs [2]. Cisplatin (cis-diamminedichloroplatinum(II)) is effectively used in the chemotherapy of cancer types as ovarian, testicles, breast and melanoma [3]. Despite its high anticancer activity, cisplatin has exhibited several toxic side effects such as dose-limiting toxicity, neurotoxicity, nephrotoxicity, cardiotoxicity and ototoxicity [4]. These collateral effects and also the occurrence of cellular resistance limit the use of cisplatin in high dose [5]. In this direction, the development of new coordination compounds including different metal centers has become the main aim of research in medicinal chemistry.

Based on the significant similarities between thermodynamic parameters, complex geometry and coordination ability of platinum(II) and palladium(II) ions, Pd(II) seems to be a good alternative. Therefore, researchers have been focused on the synthesis of new palladium-based compounds. Many complexes of palladium with different bioligands such as amino acids [6,7], peptides [8], amino sugars [9] and drugs [10] have been reported in the literature. The pharmacological screening of these complexes has indicated that the model complex cispalladium (cis-$[PdCl_2(NH_3)_2]$) does not possess any antitumor properties as compared to cisplatin [11]. But, the complex $[Pd(phen)(Tyr)]^+$ bearing tryptophan as an amino acid has been shown to exhibit good anticancer activity against P388 lymphocytic leukaemia cells [12]. On the other hand, some palladium complexes of various Schiff bases containing biomolecules such as alkaloids [13], sulfa drugs [14] and chitosan [15,16] have been synthesized. As well, numerous papers on Pd(II) complexes of Schiff bases derived from amino acids or amino acid esters have been reported [17,18]. The Pd(II) complexes with o-vanillin and amino acids (where amino acids are L-glutamic acid and L-tyrosine) have been found to be no cytotoxic against

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EVALUATION OF CYTOTOXIC ACTIVITY OF NEW BENZIMIDAZOLE-PIPERAZINE HYBRIDS AGAINST HUMAN MCF-7 AND A549 CANCER CELLS

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A series of benzimidazole-piperazine hybrids (**14 – 37**) were designed, synthesized and evaluated for their cytotoxic activity against human lung (A549) and breast (MCF-7) cancer cell lines. Preliminary evaluation revealed that most of these hybrid molecules (i.e., **16 – 25**) exhibited noteworthy and preferential antiproliferative effect against human lung cancer (A549) with IC_{50} values of 2.8 – 7.8 μM. Among the synthesized molecules, compound **17** showed the most balanced cytotoxic effect against lung (A549) and breast (MCF-7) cancer cells with IC_{50} values of 5.4 and 4.2 μM, respectively. To explore the mechanistic aspects fundamental to the observed activity, further biological studies of compounds **16**, **17** and **22** were carried out. In addition, these compounds induced PARP-1 cleavage and caspase 7 activation, caused morphological changes such as bleb formation in the treated cells, and significantly increased the nuclear fragmentation. Taken all together, our findings indicate that cytotoxic activities of newly synthesized benzimidazole-piperazine hybrids are mediated through the apoptotic cell death induction. These benzimidazole derivatives have the potential for further development as anticancer agents.

Keywords: MCF-7, A549, benzimidazole, anticancer activity, apoptosis, cytotoxicity.

1. INTRODUCTION

Cancer is recognized as the second leading cause of deaths worldwide following heart diseases, and the global burden from cancer is anticipated to grow to about 22 million new cancer cases and 13 million deaths by 2030 [1]. Thus, an unending endeavour worldwide has been dedicated to the discovery of new chemotypes as small-molecule cancer therapeutics, which are prone to further development for intervening with this complex disease. In this context, benzimidazole ring is frequently encountered in contemporary medicinal chemistry as a privileged substructure for developing bioactive molecules including novel anticancer therapeutics [2 – 5]. Bendamustine, the well-known benzimidazole derivative with a unique mechanism of action to activate apoptosis and inhibit mitotic checkpoints, has recently been approved by the FDA for the treatment of chronic lymphocytic leukemia and non-Hodgkin's lymphoma [6, 7]. Further literature precedence also reveals that benzimidazole nucleus has been studied to develop tubulin polymerization inhibitors [8, 9], topoisomerase inhibitors [10, 11] and sirtuin inhibitors [12, 13] with potential antitumor activity.

Piperazine structure is another common structural motif in anticancer agents, and a large number of compounds with a piperazine fragments appeared in the literature as possessing antiproliferative activity against various cancer cells [14 – 17]. In particular, a series of piperazine analogs have also been developed by Samjin Pharmaceutical to inhibit microtubule synthesis, cell cycle progression, and angiogenesis with promising antiproliferative activities against colon, prostate, breast, lung and leukemia cell lines, as well as effectively suppressing experimental tumors in small animal models [18, 19]. Another recent study [20] showed that incorporation of an arylpiperazine moiety in purine nucleoside analogs produced compounds with senescence-induced cell death in liver cancer cells.

In the course of our longstanding commitment on developing bioactive heterocycles [5, 21 – 24], we have relied on the aforementioned data for the design, synthesis and biological evaluation of new benzimidazole derivatives amalgamated with an aryl piperazine residue through a methylene

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ARTICLE

Synthesis, molecular modelling and biological activity of some pyridazinone derivatives as selective human monoamine oxidase-B inhibitors

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Abstract

Background Since brain neurotransmitter levels are associated with the pathology of various neurodegenerative diseases like Parkinson and Alzheimer, monoamineoxidase (MAO) plays a critical role in balancing these neurotransmitters in the brain. MAO isoforms appear as promising drug targets for the development of central nervous system agents. Pyridazinones have a broad array of biological activities. Here, six pyridazinone derivatives were synthesized and their human monoamine oxidase inhibitory activities were evaluated by molecular docking studies, in silico ADME prediction and in vitro biological screening tests.

Methods The compounds were synthesized by the reaction of different piperazine derivatives with 3 (2*H*)-pyridazinone ring and MAO-inhibitory effects were investigated. Docking studies were conducted with Maestro11.8 software.

Results Most of the synthesized compounds inhibited hMAO-B selectively except compound **4f**. Compounds **4a–4e** inhibited hMAO-B selectively and reversibly in a competitive mode. Compound **4b** was found as the most potent ($k_i = 0.022 \pm 0.001$ µM) and selective (SI ($Ki_{hMAO\text{-}A}/Ki_{MAO\text{-}B}$) = 206.82) hMAO-B inhibitor in this series. The results of docking studies were found to be consistent with the results of the in vivo activity studies. Compounds **4a–4e** were found to be non-toxic to HepG2 cells at 25 µM concentration. In silico calculations of ADME properties indicated that the compounds have good pharmacokinetic profiles.

Conclusion It was concluded that 4b is possibly recommended as a promising nominee for the design and development of new pyridazinones which can be used in the treatment of neurological diseases.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s43440-020-00070-w) contains supplementary material, which is available to authorized users.

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BRIEF REPORT

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Synthesis and biological evaluation of new 3(2*H*)-pyridazinone derivatives as non-toxic anti-proliferative compounds against human colon carcinoma HCT116 cells

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ABSTRACT

Novel 3(2*H*)-pyridazinone derivatives were designed, synthesised in satisfactory yields and evaluated in different experimental assays to assess their preliminary toxicity *in vivo* and anti-proliferative effects against HCT116 cell lines *in vitro*. *Artemia salina* lethality test provided LC_{50} values >100 µg/mL for all compounds. Successive assays revealed that some compounds were endowed with a promising anti-proliferative effect against HCT116 cells, alone or stimulated by serotonin as a pro-inflammatory factor in order to mimick an inflamed model *in vivo* of cancer cell microenvironment. Moreover, the kinurenic acid level after treatment with these newly synthesised compounds was monitored as a marker of anti-proliferation in colon carcinoma models. The IC_{50} values obtained for the best-in-class compounds were comparable to that of daunorubicin as a reference drug. Conversely, these compounds were not able to counteract the spontaneous migration of human cancer HCT116 cell line in the wound healing paradigm.

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Serotonin; anti-proliferative agents; pyridazinone; kynurenic acid; HCT116; wound healing; *Artemia salina* lethality test

1. Introduction

Cancer consists of an uncontrolled proliferation of cells in different tissues and organs; it is a disease whose clinical appearance, treatment and approach are different from each other. Cancer is a major global health problem and it is currently the second leading cause of death in the world being expected to surpass cardiovascular diseases in the next few years[1,2]. Many factors, from bacteria to viruses, from radiation to heredity, from environmental factors to nutritional habits and chemicals, are accused of cancer formation. In the data announced by the World Health Organisation (WHO), approximately 18 million people were diagnosed with cancer in 2018, and around 10 million people died from cancer. According to data of Global Cancer Obervatory (GLOBOCAN), the most common types are lung (2.1 million), breast (2.09 million), colorectal (1.8 million), prostate (1.3 million), stomach (1 million) cancer. According to cancer-related deaths, lung (1.8 million), colorectal (881 thousand), stomach (783 thousand), liver (782 thousand) and breast (627 thousand) are listed. Colorectal carcinomas (CRC) are one of the most common types of cancer in the world that cause death. CRC metastases account for 40–50% of recently diagnosed cases and are correlated with high morbidity[3,4].

In medicinal chemistry pyridazinones have been the subject of intensive synthetic investigations, because they possess a wide spectrum of pharmacological activities and gained importance in recent years[5]. A number of compounds such as zardaverine/imidazole, bemoradan, indolindan, pimobendan are examples of pyridazinones that are biologically active. Literature survey revealed that substituted pyridazinones have reported to possess pharmacological activities, which can be rationalised in the SAR study reported in Figure 1 [6–12]. There are also compounds which were shown to have anti-cancer or cytostatic activity in the literature against HEP3B (liver cancer cells), HCT116 (colon cancer cells), SH-SY5Y (neuroblastoma cells) and promising selectivity index with respect to human fibroblasts[13–16]. These results suggest that pyridazinone compounds may be useful in cancer chemotherapy, depending on the type of cancer, and that derivatives bearing different substituents may exhibit varying degrees of cytotoxic effect.

Pursuing our efforts to discover novel anti-cancer compounds[17–19] and with the aim of enlarging the SAR knowledge within this chemical scaffold, we designed fifteen new 3(2*H*)-pyridazinones investigating the anti-proliferative effects against the human HCT116 cell line, their toxicity in the *Artemia salina* lethality assay *in vivo*, the HCT116 viability after serotonin challenging and compound treatment, the release of kynurenic acid after compound treatment and, lastly, the capability to limit the spontaneous migration of HCT116 cells in the wound healing paradigm.

2. Experimental protocols

The fine chemicals and all solvents used in this study were purchased locally from Merck (Darmstadt, Germany) and Aldrich Chemical Co. (Steinheim, Germany).

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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Inapropriate use of antibiotics effective against gram positive microorganisms despite restrictive antibiotic policies in ICUs: a prospective observational study

Hasan Selçuk Özger[1], Dolunay Merve Fakıoğlu[2], Kübra Erbay[1], Aslınur Albayrak[2*] and Kenan Hızel[1]

Abstract

Background: Gram-positive spectrum antibiotics such as vancomycin, teicoplanin, daptomycin, and linezolid are frequently used in empirical treatment combinations in critically ill patients. Such inappropriate and unnecessary widespread use, leads to sub-optimal utilisation. However they are covered by the antibiotics restriction programme. This prospective observational study, evaluates gram-positive anti-bacterial utilisations in intensive care units (ICUs) with various evaluation criteria, to determine the frequency of inappropriate usage and the intervention targets required to ensure optimum use.

Methods: This clinical study was conducted prospectively between 01.10.2018 and 01.10.2019 in the medical and surgical ICUs of Gazi University Faculty of Medicine Hospital, Turkey. The total bed capacity was 55. Patients older than 18 years and who were prescribed gram-positive spectrum antibiotics (vancomycin, teicoplanin, linezolid, and daptomycin) were included. Patients under this age or immunosuppressed patients (neutropenic,- HIV-infected patients with hematologic or solid organ malignancies) were not included in the study. During the study period, 200 treatments were evaluated in 169 patients. The demographic and clinical features of the patients were recorded. Besides observations by the clinical staff, the treatments were recorded and evaluated by two infectious diseases specialists and two clinical pharmacists at 24-h intervals from the first day to the last day of treatment.
SPSS software for Windows, (version 17, IBM, Armonk, NY) was used to analyse the data. Categorical variables were presented as number and percentage, and non-categorical variables were presented as mean ± standard deviation.

Results: It was found that inappropriate gram-positive antibiotic use in ICUs was as high as 83% in terms of non-compliance with the selected quality parameters. Multivariate analysis was performed to evaluate the factors associated with inappropriate antibiotic use, increased creatinine levels were found to increase the risk of such use.

Conclusions: In spite of the restricted antibiotics programme, inappropriate antibiotic use in ICUs is quite common. Thus, it is necessary to establish local guidelines in collaboration with different disciplines for the determination and follow-up of de-escalation of such use and optimal treatment doses.

Keywords: Antibiotic stewardship, Rational antibiotic use, Antibiotic resistance, Gram positive microorganisms, Inappropriate antibiotic use

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ELECTROANALYSIS

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Dual Responsive Disposable Electrode for the Enumeration of *Escherichia coli* in Whole Blood

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Abstract: In this report, we have designed a dual responsive disposable electrode for the enumeration of *Escherichia coli K12 (E. coli K12)*. The immunomagnetic separation strategy provided easily bacterial detection in the whole blood. Metal-organic frameworks magnetic (MOFs) modified, and citrate capped gold nanoparticles were used as capture probe and spectro-electrochemical labels, respectively. The cyclic voltammetry (CV) was employed to quantify *E. coli* with a ranging from 10^1 to 10^7 cfu/mL with a LOD of 1 cfu/mL. The Surface enhanced Raman spectroscopy (SERS) measurements were also performed with using disposable electrode.

Keywords: Disposable electrode · spectro-electrochemical labels · Cyclic Voltammetry · Pathogens bacteria · blood

1 Introduction

Pathogen bacteria remain an important cause of bloodstream infection and play a significant cause of morbidity and mortality in inpatients. The bloodstream infection also causes life-threatening conditions imposing to rapid medical care. Therefore, the rapid detection of pathogens from blood is essential. The bacterial load in blood samples from patients with the bacteremia is too low and under the LOD of the method for direct identification of pathogenic bacteria [1].

Pathogenic bacteria diseases have become challenging in developed and underdeveloped countries [2]. The rapid detection and monitoring of pathogenic bacteria are creating an interest by the researchers to control and prevent a human from pathogen diseases. The development of science and technology and economic progress have become incapable of controlling the spread of pathogenic bacteria diseases. It is happening due to the use of contaminated blood, food, and drinking water [3]. There are many types of pathogenic bacteria producing poisons and becoming causing pathogenic bacteria diseases like *Escherichia coli, Staphylococcus aureus, Bacillus cereus, and Vibrio cholera* are common [4]. *Escherichia coli* is a significant type of pathogenic bacteria that becomes an enteric extremely ineffective, blood, food water, and a waterborne pathogen that is a great challenge for public health. It usually causes serious diseases, for example, hemolytic uremic syndrome and hemorrhagic colitis illness, especially in children and old [5]. It is a rod-shaped microbial bacterium and a commensal microorganism of humans that lives in the digestive tract. Even, some of the *E. coli* stated as harmless to humans, some of the serotypes cause contamination arising from food poisonings such as urinary tract infection, sepsis, meningitis, and pneumonia [6,7].

Biosensing techniques such as mass-based, electronics, optical, and electrochemical methods applied for the identification of pathogenic bacteria [8]. The electrochemical biosensor worked as a standalone instrument and transferred the on-line data to monitor and control the water quality for the enhancement of water treatment dealing. The electrochemical method has more advantages due to its portability, simplicity, accuracy, low cost, and speedy response and dynamic range of detection. The electrochemical biosensor can be combined on a chip and a bacterium [9].

The amino-functionalized electrochemical biosensor was constructed for the identification of *E. coli* in a lower concentration of 10^1 cfu/mL and the maximum detection range of 10^5 cfu/mL from water [10]. The electrochemical biosensor can work as a standalone instrument and transmit data through wi-fi for remote monitoring and

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Article

Ortho versus Meta Chlorophenyl-2,3-Benzodiazepine Analogues: Synthesis, Molecular Modeling, and Biological Activity as AMPAR Antagonists

Mohammad Qneibi,* Nidal Jaradat, Mohammed Hawash, Abdurrahman Olgac, and Nour Emwas

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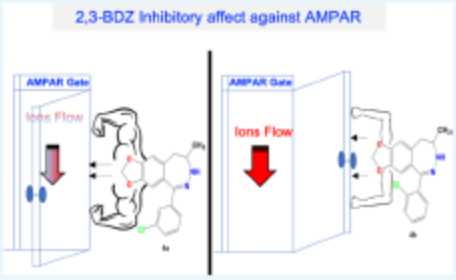
ABSTRACT: 2,3-Benzodiazepine compounds are an important family of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antagonists that act in a noncompetitive manner. Due to the critical role of AMPARs in the synapse and various neurological diseases, significant scientific interest in elucidating the molecular basis of the function of the receptors has spiked. The analogues were synthesized to assess the functional consequence of removing the amine group of the phenyl ring, the potency and efficacy of inhibition by substituting a halogen group at the meta vs ortho position of the phenyl ring, and layout the prediction of potential drug candidates for AMPAR hyperactivation. Using the whole-cell patch-clamp technique, we assessed the effect of the derivative on the amplitude of various AMPA-type glutamate receptors and calculated the desensitization and deactivation rates before and after treatment of HEK293 cells. We noticed that the amino group is not necessary for inhibition as long as an electron-withdrawing group is placed on the meta position of the phenyl ring of BDZ. Furthermore, compound 4a significantly inhibited and affected the desensitization rate of the tested AMPARs but showed no effect on the deactivation rate. The current study paves the way to a better understanding of AMPARs and provides possible drug candidates of 2,3-BDZ different from the conventional derivatives.



INTRODUCTION

2,3-Benzodiazepine (2,3-BDZ) derivatives, also known as GYKI, are a group of synthetic drug candidates that noncompetitively inhibit α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). In various acute neurological disorders such as cerebral ischemia and epilepsy as well as in chronic neurodegenerative pathologies such as Parkinson's disease, Alzheimer's disease (AD), Huntington's chorea, and amyotrophic lateral sclerosis (ALS), excessive stimulation of AMPARs has been implicated.[1−3] Consequently, chemotherapeutic applications provided strong motivation for the synthesis of 2,3-BDZ analogues due to their anticonvulsant and neuroprotective properties. Moreover, they have demonstrated higher potency and selectivity toward AMPA receptors than other compounds in animal and in vitro studies.[4] The prototypic compound of the 2,3-BDZ family, 7,8-methylenedioxy-5H-2,3-benzodiazepine (GYKI 52466; Figure 1) was first introduced in the 1980s and has been used as a template and standard in the synthesis and activity evaluations of new GYKI compounds.[5] While the 2,3-BDZs' structures (Figure 1) have different pharmacological activity besides their effect on the central nervous system, they also possess anti-inflammatory,[5] antimicrobial,[6] vasopressin antagonist,[7] endothelia antagonist,[8] cholecystokinin antagonist,[9] antithrombotic,[10]

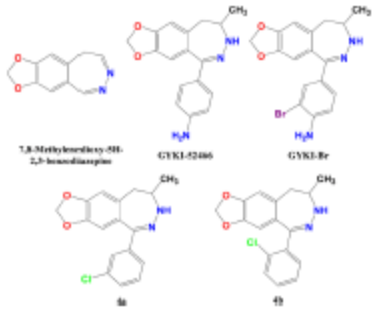


Figure 1. 2,3-BDZ prototype and GYKI 52466 structure.

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RESEARCH PAPER

Development of a nanoparticle-based gradient method for simple and fast quantification of bacteria-nanoparticle conjugates

Didem Rodoplu · Ismail Hakki Boyaci · Ugur Tamer · Zekiye Suludere

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Abstract Nanoparticles are widely used to separate and detect bacteria by immunoassay techniques. However, there is a great need to develop a new low cost, easy-handling, and fast bacteria quantification method in order to give fast response to patients, when there are limited time and instruments. This article describes a new nanoparticle-based quantification method by using only sucrose gradient centrifugation and an easy optical setup. First of all, spherical-shaped nanoparticles with different chemical components have been synthesized. Buoyancy tendencies of these nanoparticles and effects of different mediums were examined to obtain moving particle band which is necessary for rate-zonal centrifugation. Optimum gradient and process parameters were determined; then, moving bands of nanoparticle and bacteria-conjugated nanoparticle were analyzed by a software. Migration distance of bacteria-captured nanoparticle bands was found inversely proportional to bacterial concentration. Bacteria-nanoparticle conjugates were characterized by transmission electron microscopy images and zeta potential measurements. The developed method enables non-specific detection and quantification of *E. coli* K-12 within the range of 10^5–10^8 cfu/ml, by using chitosan-coated CdTe quantum dots. Chitosan-coated CdTe quantum dots were found advantageous for the easy and fast tracking of bacteria-particle conjugate bands in the developed gradient method with respect to their high bacterial capture, sedimentation rate, and light emission properties. According to our findings, the proposed gradient method was found to be an advantageous bacteria quantification method with limited instrument requirement and 50 min of total detection time in solution.

Keywords Density gradient centrifugation · Moving bands · Optical density · Nanoparticle · Bacteria · Buoyancy

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Combined Structure and Ligand-Based Design of Selective Acetylcholinesterase Inhibitors

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ABSTRACT: Acetylcholinesterase is a prime target for therapeutic intervention in Alzheimer's disease. Acetylcholinesterase inhibitors (AChEIs) are used to improve cognitive abilities, playing therefore an important role in disease management. Drug repurposing screening has been performed on a corporate chemical library containing 11 353 compounds using a target fishing approach comprising three-dimensional (3D) shape similarity and pharmacophore modeling against an approved drug database, Drugbank. This initial screening identified 108 hits. Among them, eight molecules showed structural similarity to the known AChEI drug, pyridostigmine. Further structure-based screening using a pharmacophore-guided rescoring method identifies one more potential hit. Experimental evaluations of the identified hits sieve out a highly selective AChEI scaffold. Further lead optimization using a substructure search approach identifies 24 new potential hits. Three of the 24 compounds (compounds 10b, 10h, and 10i) based on a 6-(2-(pyrrolidin-1-yl)pyrimidin-4-yl)-thiazolo[3,2-*a*]pyrimidine scaffold showed highly promising AChE inhibition ability with IC_{50} values of 13.10 ± 0.53, 16.02 ± 0.46, and 6.22 ± 0.54 μM, respectively. Moreover, these compounds are highly selective toward AChE. Compound 10i shows AChE inhibitory activity similar to a known Food and Drug Administration (FDA)-approved drug, galantamine, but with even better selectivity. Interaction analysis reveals that hydrophobic and hydrogen-bonding interactions are the primary driving forces responsible for the observed high affinity of the compound with AChE.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, primarily in elderly people.[1] The pathophysiological features of the disease involve slow obliteration of cognition abilities, logical thinking, and sensory processes, which eventually lead to death.[1,2] Once considered a rare disorder, it now emerges as the fifth leading cause of death worldwide. Not only the severe morbidity rate but also the disease imposes a huge financial burden on the public health care system, which makes AD a primary health-care concern worldwide.

The past two decades witnessed tremendous growth in research interest to uncover disease pathogenesis and identify a therapy that can target the disease pathogenesis. Although several risk factors have been identified, the definitive cause of the disease remains elusive.[3] Early-onset AD follows a Mendelian pattern of inheritance, and mutations in *APP*, *PSEN1*, and *PSEN2* genes are strongly correlated with the disease prevalence.[4] Genes responsible for the late-onset AD, the most prevalent form, are not clearly identified. However, several risk factors have been identified. APOE ε4 allele shows a high risk of association with the prevalence of late-onset AD.[5−7] Genome-wide association studies (GWASs) have identified a sortilin-related receptor (*SORL1*) gene as a high-risk factor for AD.[8] Also, several susceptibility loci have been identified, and among them, *CLU*, *PICALM*, *CR1*, and *BIN1* genes are most significant.[9] Molecular characterization of the disease reveals a complex nature of disease pathogenesis due to the induction of many detrimental signaling cascades. Several signaling pathways including amyloid cascades,[3,10,11] neurofibrillary tangle formation,[12−15] cholinergic systems,[16−20] and oxidative stress-mediated processes[21−23] are induced simultaneously, and their cross-talk makes the disease pathogenesis highly complex and yet to be understood completely.

Neurochemical and histopathological studies of the brains of AD patients revealed a strong correlation between the degeneration of the presynaptic cholinergic system and the behavioral and cognition deficits.[20,24] Damage of the cholinergic neurotransmission, particularly in the region of the nucleus basalis of Meynert and medial septum, strongly

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COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

Evaluation of the *status quo* of polyphenols analysis: Part II—Analysis methods and food processing effects

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Abbreviations: 2LC-ECD, two-channel liquid chromatography with electrochemical detection system; 5-CQA, 5-O-caffeoylquinic acid; APCI, atmospheric pressure chemical ionization; APPI, atmospheric pressure photoionization; ASE, accelerated solvent extraction; ATPS, aqueous two-phase system; CCC, counter-current chromatography; CEC, capillary electro chromatography; CPC, centrifugal partition chromatography; DAD, diode Array Detector; DLLME, dispersive liquid-liquid microextraction; EAE, enzyme-assisted Extraction; EAPPI-MS, extractive atmospheric pressure photoionization mass spectrometry; ECD, electron capture detection; ECCG, epigallocatechin gallate; ELISA, enzyme linked immunosorbent assay; ESI, electrospray ionization; EtOAc, ethyl acetate; EtOH, ethanol; FAB, fast-atom bombardment; FID, flame ionization detector; FRET, fluorescence resonance energy transfer; GC, gas chromatography; HHP, high hydrostatic pressure; HPCD, high-pressure carbon dioxide; HPLC, high-performance liquid chromatography; HP-TLC, high-performance-TLC; HT, hydrolyzable tannins; ITMS, ion trap mobility spectrometry; LLE, liquid-liquid extraction; LSIMS, liquid secondary ion MS; MAE, microwave assisted extraction; MALDI, matrix-assisted laser desorption/ionization; MEEKC, microemulsion electrokinetic chromatography; MeOH, methanol; MEPS, microextraction by packed sorbent; MHG, microwave hydro-diffusion and gravity; MPLC, medium pressure liquid chromatography; MS/MS, tandem mass spectrometry; MSPD, matrix solid-phase dispersion; MW, microwave processing; NMR, nuclear magnetic resonance; NPCE, negative pressure cavitation extraction; ODS, octadecylsilyl; OHP, Ohmic heat processing; PDA, photo diode array; PEF, pulse electric field; PHWE, pressurized hot water extraction; PLE, pressurized liquid extraction; PME, pectin methylesterase; PPO, polyphenol oxidase; PTLC, preparative thin layer chromatography; QqQ, triple-quadrupole; QToF, quadrupole time-of-flight; RP, reverse phase; RRLC, rapid resolution liquid chromatography; SALLE, assisted liquid–liquid extraction; SBSE, stir bar sorptive extraction; SFC, supercritical fluid chromatography; SFE, supercritical fluid extraction; SPE, solid-phase extraction; SPME, solid-phase microextraction; SSE, subcritical solvent extraction; STE, smashing tissue extraction; SWE, subcritical-water extraction; TLC, thin-layer chromatography; TOFMS, time-of-flight mass spectrometry; UAE, ultrasound-assisted extraction; UEH, UAE with healing; UHPLC, ultra-high performance liquid chromatography; US, ultrasound-assisted extraction procedure; UV, ultraviolet; UV/vis, ultraviolet-visible; VBE, vacuum-powered bubble-assisted solvent extraction.

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RESEARCH Open Access

Encapsulation of the dual FLAP/mPEGS-1 inhibitor BRP-187 into acetalated dextran and PLGA nanoparticles improves its cellular bioactivity

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Abstract

Background: Dual inhibitors of the 5-lipoxygenase-activating protein (FLAP) and the microsomal prostaglandin E_2 synthase-1 (mPGES-1) may exert better anti-inflammatory efficacy and lower risks of adverse effects versus non-steroidal anti-inflammatory drugs. Despite these advantages, many dual FLAP/mPGES-1 inhibitors are acidic lipophilic molecules with low solubility and strong tendency for plasma protein binding that limit their bioavailability and bioactivity. Here, we present the encapsulation of the dual FLAP/mPGES-1 inhibitor BRP-187 into the biocompatible polymers acetalated dextran (Acdex) and poly(lactic-*co*-glycolic acid) (PLGA) via nanoprecipitation.

Results: The nanoparticles containing BRP-187 were prepared by the nanoprecipitation method and analyzed by dynamic light scattering regarding their hydrodynamic diameter, by scanning electron microscopy for morphology properties, and by UV–VIS spectroscopy for determination of the encapsulation efficiency of the drug. Moreover, we designed fluorescent BRP-187 particles, which showed high cellular uptake by leukocytes, as analyzed by flow cytometry. Finally, BRP-187 nanoparticles were tested in human polymorphonuclear leukocytes and macrophages to determine drug uptake, cytotoxicity, and efficiency to inhibit FLAP and mPGES-1.

Conclusion: Our results demonstrate that encapsulation of BRP-187 into Acdex and PLGA is feasible, and both PLGA- and Acdex-based particles loaded with BRP-187 are more efficient in suppressing 5-lipoxygenase product formation and prostaglandin E_2 biosynthesis in intact cells as compared to the free compound, particularly after prolonged preincubation periods.

Keywords: Acetalated dextran, PLGA, Nanoparticles, Leukotriene biosynthesis, FLAP inhibitor, MPGES-1, Dual inhibitor, BRP-187

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Background

Inflammation is a physiological reaction of the body to fight harmful invaders and to restore damaged tissue. However, if inflammation persists and the body cannot return to homeostasis, chronic inflammatory diseases such as arthritis, Alzheimer´s disease or arteriosclerosis can evolve [1]. Inflammation is initialized and maintained

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COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

Evaluation of the *status quo* of polyphenols analysis: Part I—phytochemistry, bioactivity, interactions, and industrial uses

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Abbreviations: AChE, acetylcholinesterase; BPDE-2, (+)-7β-8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene; CAM, chorioallantoic membrane model; CEC, capillary electro chromatography; CNS, central nervous system; COX, cyclooxygenase; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; CT, non hydrolysable/condensed tannins; CYP, cytochrome P450; Cyt c, cytochrome c; DMAPP, dimethylallyl pyrophosphate; DMBA, 7,12-dimethylbenz[a]anthracene; ECCG, epigallocatechin gallate; ELISA, enzyme linked immunosorbent assay; ER, estrogen receptors; EtOAc, ethyl acetate; GRAS, generally regarded as safe; H-CM, hesperidin-treated astrocyte; HDL, high-density lipoprotein; HT, hydrolysable tannins; LDL, low-density lipoprotein; LOX, lipoxygenases; LPS, lipopolysaccharide; LTB4, leukotriene B4; MAPK, mitogen-activated protein kinase; MS/MS, tandem mass spectrometry; NDEA, N-nitrosodiethylamine; NFkB, nuclear factor kB; NK, natural killer; NNK, 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone; NOS, nitric oxide synthase; ODC, ornithine decarboxylase; *O*-Dma, *O*-desmethylangolensine; PAF, platelet activating factor; PDE, phosphodiesterase; PGE2, prostaglandin E2; RNOS, reactive oxygen and nitrogen species; RNS, reactive nitrogen species; TPA, 12–*O*-tetradecanoylphorbol-13-acetate; TXA2, thromboxane A2; UAE, ultrasound-assisted extraction; UV, ultraviolet; UV/vis, ultraviolet-visible.

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Article

Norditerpenoids with Selective Anti-Cholinesterase Activity from the Roots of *Perovskia atriplicifolia* Benth.

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Abstract: Inhibition of cholinesterases remains one of a few available treatment strategies for neurodegenerative dementias such as Alzheimer's disease and related conditions. The current study was inspired by previous data on anticholinesterase properties of diterpenoids from *Perovskia atriplicifolia* and other Lamiaceae species. The acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibition by the three new natural compounds—(1*R*,15*R*)-1-acetoxycryptotanshinone (**1**), (1*R*)-1-acetoxytanshinone IIA (**2**), and (15*R*)-1-oxoaegyptinone A (**3**)—as well as, new for this genus, isograndifoliol (**4**) were assessed. Three of these compounds exhibited profound inhibition of butyrylcholinesterase (BChE) and much weaker inhibition of acetylcholinesterase (AChE). All compounds (**1**–**4**) selectively inhibited BChE (IC_{50} = 2.4, 7.9, 50.8, and 0.9 µM, respectively), whereas only compounds **3** and **4** moderately inhibited AChE (IC_{50} 329.8 µM and 342.9 µM). Molecular docking and in silico toxicology prediction studies were also performed on the active compounds. Natural oxygenated norditerpenoids from the traditional Central Asian medicinal plant *P. atriplicifolia* are selective BChE inhibitors. Their high potential makes them useful candidate molecules for further investigation as lead compounds in the development of a natural drug against dementia caused by neurodegenerative diseases.

Keywords: tanshinones; cholinesterases; molecular docking; structure elucidation

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ORIGINAL ARTICLE

Lactobacillus plantarum improves lipogenesis and IRS-1/AKT/eNOS signalling pathway in the liver of high-fructose-fed rats

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ABSTRACT

In the present study, we investigated the influence of *Lactobacillus plantarum* and *Lactobacillus helveticus* supplementation on lipogenesis, insulin signalling and glucose transporters in liver of high-fructose-fed rats. Fructose was given to the rats as a 20% solution in drinking water for 15 weeks. *Lactobacillus plantarum* and *L. helveticus* supplementations were performed by gastric gavage once a day during final 6 weeks. Dietary high-fructose increased hepatic weight, lipid accumulation and FASN expression as well as caused a significant reduction in IRS-1 expression, pAKT/total AKT and peNOS/total eNOS ratios, but an elevation in GLUT2 and GLUT5 mRNAs in the liver. *Lactobacillus plantarum* supplementation decreased hepatic weight, triglyceride content and FASN expression as well as improved IRS-1/AKT/eNOS pathway and GLUT2 expression in the liver of high-fructose-fed rats. However, *L. helveticus* supplementation exerted a restoring effect on lipid accumulation by decreasing FASN expression, and regulating effect on IRS-1 and GLUT2 expressions.

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Dietary fructose; fatty liver; insulin signalling; *Lactobacillus plantarum*; *Lactobacillus helveticus*

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the hepatic manifestations of metabolic syndrome and closely associated with insulin resistance. Insulin plays an important role in the regulation of energy metabolism by inhibiting glucose production and promoting lipid synthesis in the liver (Brown and Goldstein 2008). In the insulin-resistant state, there is a paradoxical excessive hepatic lipogenesis even though hepatic glucose metabolism is disturbed (Brown and Goldstein 2008, Li *et al.* 2010). Insulin action is mediated by the hepatic insulin receptor and insulin receptor substrates (IRS-1 and IRS-2) which transmit insulin receptor signalling to intracellular effectors through the downstream kinase, protein kinase B (AKT) (Taniguchi *et al.* 2006, Kubota *et al.* 2008). The studies also point out the existence of an efficient interaction between insulin signalling and endothelial nitric oxide synthase (eNOS) (Montagnani *et al.* 2001, Tateya *et al.* 2011). In this context, we and others showed that dietary fructose intake leads to insulin resistance through downregulation of insulin signalling in liver and other insulin-sensitive organs such as skeletal muscle and vascular system in rodents (Zhao *et al.* 2009, Haas *et al.* 2012, Babacanoglu *et al.* 2013, Rebollo *et al.* 2014, Pektas *et al.* 2015, Sadi *et al.* 2015). The increased consumption of fructose in the diet may contribute to the high prevalence of fatty liver disease around the world (Jensen *et al.* 2018). Studies demonstrated that high consumption of fructose in rats caused hyperinsulinemia accompanied by hepatic triglyceride accumulation, microvesicular and macrovesicular fat deposition (Ackerman *et al.* 2005, Armutcu *et al.* 2005, Nomura and Yamanouchi 2012). Dietary fructose-induced fat accumulation in the liver of mice was linked to upregulation of lipogenic genes such as sterol regulatory element binding protein (SREBP)-1 and fatty acid synthase (FASN) (Kanuri *et al.* 2011, Spruss *et al.* 2011). In recent studies, we also showed that dietary high-fructose corn syrup (HFCS) caused mild microvesicular steatosis together with increased lipogenic gene expression (Sadi *et al.* 2015); moreover, high-fructose diet induced parenchymal degeneration and hyperaemia with induction of inflammatory mediators in liver of rats (Sadi *et al.* 2015, Pektas *et al.* 2017).

In last decades, it was shown that the modulation of intestinal microbiota by probiotics may improve some health parameters. In this context, supplementation with *Lactobacillus (L.)* species, which are one of the major components of the human microbiota, was reported to restrict hyperglycaemia, hyperinsulinemia, and dyslipidemia in high-fructose or high-fat-fed rats and genetic type 2 diabetic mice (Yadav *et al.* 2007, Honda *et al.* 2012, Huang *et al.* 2013, Wu *et al.* 2015, Choi *et al.* 2016). In the high-fructose-fed rats, treatment with a probiotic consisting of *L. curvatus* and *L. plantarum* or *L. reuteri* GMNL-263 reduced plasma insulin and triglyceride levels as well as hepatic expression of lipogenic genes SREBP-1 and FASN (Hsieh *et al.* 2013, Park 2013). *Lactobacillus rhamnosus* GG alleviated fructose-induced fat accumulation in liver of mice by regulating hepatic expression of genes involved in lipid metabolism (Ritze *et al.* 2014).

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Healing effects of *Cornus mas* L. in experimentally induced ulcerative colitis in rats: From ethnobotany to pharmacology

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ABSTRACT

Ethnopharmacological relevance: The ethnobotanical studies conducted in Turkey and other countries have revealed that *Cornus mas* L., from the family Cornaceae have been used against stomachache, diarrhea and colitis.

Aim of the study: The objective the present study is to determine the possible activity of *C. mas* in experimentally induced ulcerative colitis in rats and to identify its phytochemical feature.

Materials and methods: 2,4,6-Trinitrobenzene sulfonic acid-induced colitis model was induced in rats. The rats were orally treated with different doses (50, 100, 200 and 400 mg/kg) of *C. mas* 80% methanol extract for 14 days. Increase in body weight, consumed amount of feed, form of the stool, presence of rectal prolapse were followed every day. At the end of the experiment, colon tissues were removed and wet weights for each animal were measured and colon damages were scored. Total antioxidant and total oxidant status, cytokine (TNF-α and IL-1β) and protein levels of colon tissues were evaluated and histopathological analyses were carried out. After the detection of the effective dose as 400 mg/kg, the aqueous methanol extract was fractionated by using liquid-liquid fractionation technique and the sub-extracts were also tested for *in vivo* biological activities. High Performance Liquid Chromatography analyses were conducted to determine the phytochemical profile of the active crude extract and *n*-butanol sub-extract.

Results: Amount of feed consumed per day and increase in body weight were the lowest in the control group, while those values were determined to be the highest in 80% methanol extract (at 400 mg/kg dose), *n*-butanol sub-extract and reference groups. Following colitis induction, it was determined that the fecal form was yellow-slippery in all groups and returned to normal after the treatment with *C. mas* extracts. Rectal prolapse score was less in the extract (400 mg/kg) and *n*-butanol sub-extract treated groups. Total antioxidant, total oxidant status, cytokine and protein levels were found to be in parallel with macroscopic findings. 80% methanol extract (400 mg/kg) and *n*-butanol sub-extract provided the best healing according to the wet weight measurements and colon damage scoring performed on the removed colon tissues. These findings supported the results of histopathological analysis. According to the chromatographic analysis, ellagic acid was determined in both extracts and its amount was quantified.

Conclusions: The present study has verified the ethnomedical use of *C. mas* for the treatment of ulcerative colitis.

1. Introduction

Inflammatory bowel disease is a chronic disease of the gastrointestinal tract. It is a common disorder in the world which can cause morbidity and mortality. There are two different types of inflammatory bowel disease, *i.e.* Crohn's disease and ulcerative colitis. Because of the potential side effects of corticosteroids and salicylate derivatives including sulfasalazine, mesalazine as well as other synthetic drugs such

Abbreviations: ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid; BCA, Bicinchoninic acid; *n*-BuOH, *n*-Butanol; CM, *Cornus mas* L.; CMC, Carboxymethyl cellulose; CUPRAC, Cupric reducing antioxidant capacity; DAD, Diode array dedector; DCM, Dichloromethane; DPPH, 2,2-Diphenyl-1-picrylhydrazyl; EtOH, Ethanol; EtOAc, Ethyl acetate; FRAP, Ferric reducing ability of plasma; GUE, Herbarium of Faculty of Pharmacy Gazi University; G.Ü.ET, Gazi University Local Ethics Committee for Animal Experiments; *n*-Hex, n-Hexane; IL, Interleukin; i.p., Intraperitoneal; LOD, Limit of detection; LOQ, Limit of quantification; MeOH, Methanol; p.o., Per os; R–H_2O, Remaining water phase; RSD, Relative standard deviation; TAS, Total antioxidant status; TNBS, 2,4,6-Trinitrobenzene sulfonic acid; TNF, Tumor necrosis factor; TOS, Total oxidant status; HPLC, High performance liquid chromatography

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Conference paper

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Discovery of bioactive drug candidates from some Turkish medicinal plants-neuroprotective potential of *Iris pseudacorus* L.

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Abstract: Medicinal plants have an enormous potential for producing bioactive compounds of great benefit to mankind. There is a great scope for new drug candidates based on traditional medicinal plants throughout the world. The number of drugs derived from medicinal plants that are recently introduced into clinical use is increasing. Besides, numerous of standardized herbal extracts were also approved as phytomedicines by the health authorities to be used in phytotherapy. The drug discovery program from nature in our laboratory involves several steps from plant collection, extraction, HTS of the extracts by using *in vitro* enzyme inhibitory tests, bioassay-guided fractionation through the isolation and structure elucidation of bioactive compounds. Continuing our researches in the field of anticholinesterase activity, neuroprotective potential of *Iris pseudacorus* L. have presented in this article.

Keywords: anticholinesterase; biological activity; Eurasia 2018; *Iris pseudacorus*; isoflavonoid.

Introduction

Natural products have been recognized as an important tool in the drug discovery process throughout this century. Presently, over 100 natural product-derived pharmaceuticals are being used in modern medicine. Plants have been used as medicine by mankind to treat health-threatening diseases and still popular to obtain new drug candidates as it is the oldest medical practice for humans. It is worth saying that the number of drugs derived from medicinal plants that are recently introduced into clinical use is increasing. Additionally, several standardized herbal extracts were approved by the authorities to be used in therapy. These traditional medicines can serve as the source of potential new drugs and initial research focuses on the isolation of bioactive lead compounds for their ability to provide health benefits. Turkey is one of the rich countries in terms of bioresources depends on different climates, geographical location, ecological factors and aquatic environments as well as the passageway between Europe, Asia and Africa. Therefore, the floristic diversity provides a wide choice of species represented 12 000 taxa of which 3700 is endemic [1].

Among them, 1045 taxons belong to the class of geophytes having fleshy underground organs such as bulbs, corms, tubers, tuberous stems, tuberous roots, rhizomes and pseudobulbs [2]. Most of them require a "warm-cold-warm" sequence to complete their annual cycle. On the other hand, most of the geophytes contain beautiful and attractive flowers which also make them desired ornamental plants [3]. It is worth to mention that a good number of the geophytes species such as *Galanthus, Colchicum, Fritillaraia, Iris* etc. are considered

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Evaluation of collagenase, elastase and tyrosinase inhibitory activities of *Cotinus coggygria* Scop. through *in vitro* and *in silico* approaches

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ABSTRACT

Cotinus coggygria Scop. (Anacardiaceae, syn: *Rhus cotinus* L.) is known as "boyacı sumağı, sarı boya, duman ağacı" in Turkish and "smoke tree" in English. It is commonly grown in Southern Europe and Anatolia. The leaves have been used due to its antiseptic, hemostatic, antipyretic, and wound healing effects as a 5% infusion in traditional medicine. It has also been reported to be used against skin disorders in Russia. Based on this information, the ethanol extracts prepared from the pedicels and leaves of *C. coggygria* were investigated for their elastase, collagenase, and tyrosinase inhibitory effects, which are enzymes related to anti-aging, using ELISA microtiter assays. Based on our results, the ethanol extracts prepared from the leaves and pedicels of *C. coggygria* had low elastase (28.16% ± 2.91 and 25.76% ± 1.71, respectively), moderate collagenase (47.78% ± 4.90 and 46.51% ± 3.15, respectively), and tyrosinase (57.94% ± 0.67 and 46.20% ± 0.92, respectively) inhibition at final concentration (666 μg/mL). The ethanol extract prepared from the pedicels of *C. coggygria* was subjected to bioactivity-guided fractionation, which led to isolation of methyl gallate, astragalin, isoquercetin, and hyperoside from the active fractions. In addition to the enzyme assays, in order to understand the inhibition mechanisms of the compounds inside the ligand-binding domains, the interactions were simulated and the key amino acids contributing to the hydrogen bonds and non-polar interactions with the ligands were reported.

1. Introduction

Cotinus coggygria Scop. (Anacardiaceae, syn: *Rhus cotinus* L.) is known as "boyacı sumağı, pamuklu sumak, sarı boya, sarı can, sarı yaprak, tetre, tetra, tetere, duman ağacı" in Turkey, which can reach up to 5 m in length. The genus *Cotinus* has 5 species naturally growing in Asia, Europe, and North America, among which only *C. coggygria* (CC) grows in Turkey. The roots of this species have been used under the name of "yellow root or yellow wood" to dye the yarn, leather, and fabric in yellow. The leaves have been used as an internal infusion of 5% due to their antiseptic, constipation, blood-cutting, and antipyretic effects (Baytop, 1999, 2007; Davis, 1967; Kultur and Bitis, 2007). Previous studies revealed that different parts of the plant possess various pharmacological activities such as antimicrobial (Tunc et al., 2013), antioxidant (Niciforovic et al., 2010), anti-inflammatory (Marcetic et al., 2013), hepatoprotective (Matic et al., 2013), antiulcerogenic (Pavlov et al., 2013), immunostimulant (Bilen et al., 2013), and wound healing (Aksoy et al., 2016). Various bioactive secondary metabolites isolated from different parts of CC were reported as flavonoids (fisetin, fustin, quercetin, apigenin, myricetin, taxifolin), aurones (sulfuretin, disulfuretin, sulfurein), chalcones (butein, isoliquiritigenin), anthocyanins (delphinidin-3-galactoside, cyanidin-3-galactoside, petunidin-3-glucoside), catechins, and other phenolics, *e.g.* gallic acid and methyl gallate (Antal et al., 2010; Kultur and Bitis, 2007; Marcetic et al., 2013; Tanchev and Timberlake, 1969; Valianou et al., 2009; Westenburg et al., 2000).

Elastin and collagen, two important proteins being the main components of the connective tissue, are responsible for resistance and elasticity of the skin. Hydrolysis of them through elastase and collagenase triggered by free oxygen radicals cause wrinkle formation accompanied by skin aging (Mukherjee et al., 2011). Furthermore, production of elastase and collagenase also increases with inflammatory process. The findings showed that matrix metalloproteinases (MMPs) are active in inflamed skin such as photo-aged skin and breaking down proteins such as elastin and collagen, causing skin damage and wrinkle formation (Sin and Kim, 2005). The fact that cosmetic products containing synthetic

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Article

Potential Antioxidant and Enzyme Inhibitory Effects of Nanoliposomal Formulation Prepared from *Salvia aramiensis* Rech. f. Extract

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Abstract: *Salvia aramiensis* Rech. f. is a species that grows only in Hatay, Turkey and is used as a traditional stomachic tea. Neither the chemical composition nor the potential bioactivity of the plant has been investigated before. Antioxidant activity (1,1-Diphenyl-2-picrylhydrazyl Radical (DPPH•) and 2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid (ABTS$^{+\bullet}$) radical scavenging and β-carotene/linoleic acid co-oxidation) of 70% methanol, 70% ethanol extracts, and 2% infusion obtained from *S. aramiensis* aerial parts were determined. The effect of 70% methanol extract on collagenase and elastase enzyme inhibition and its chemical composition via chromatographic methods (LC-MS/MS and HPLC) were analyzed. Nanoliposomes were developed with 70% methanol extract, were characterized, and were evaluated. The key parameters for the most active 70% methanol extract included the following DPPH•EC_{50}: 28.4 µg/mL, Trolox equivalent antioxidant capacity (TEAC)/ABTS: 1.77 ± 0.09 mmol/L/Trolox. Furthermore 70% methanol extract showed more than 50% inhibition on collagenase and elastase enzymes at all the concentrations. The main component of the extract, rich in phenolic compounds, has been identified as rosmarinic acid; 83.7 µg/mL extract was released from the nanoliposomal formulation. The extract and its formulation are found to be nontoxic on the L929 fibroblast cell line. This study successfully developed a long-term antioxidant and enzyme inhibitory formulation containing *S. aramiensis*, which has been used safely among the public for years.

Keywords: *Salvia aramiensis*; Lamiaceae; antioxidant; enzyme; chromatography; nanoliposome

1. Introduction

The family Lamiaceae has 236 genera and about 6900 to 7200 species. *Salvia* (~900 species) is one of the largest genera of Lamiaceae [1]. The name derives from the Latin word "salveo", that means "to save, to heal" [2]. *Salvia* species have been used as tea since ancient times to prevent colds,

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Research Article

Development of Nanocrystal Ziprasidone Orally Disintegrating Tablets: Optimization by Using Design of Experiment and *In Vitro* Evaluation

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Abstract. The objective of the current study was to develop ziprasidone hydrochloride monohydrate (ZHM) nanocrystal–based orally dispersible tablet (ODT) formulations. Design of experiment approach was used to develop ODTs. The tablets were compressed using direct compression method and characterized with quality control tests. *In vitro* dissolution studies and Caco-2 cell permeability tests were executed. The hardness and friability values of nanocrystal-based ODTs were found 31.2 N and 1.05%, respectively. The disintegration time was below 10 s. Dissolution profile in pH 7.4 phosphate buffer showed that nanocrystal-based ODTs and commercial product were dissolved in 120 min 58.98% and 16%, respectively. In pH 7.4 phosphate buffer with SLS, sample groups dissolved above 85% at the end of the study. Permeability value and cumulative ZHM amount on the cells were improved with nanocrystals. In conclusion, the novel formulation of ZHM nanocrystal–based ODTs was successfully developed for alternative dosage form.

KEY WORDS: nanocrystal(s); oral drug delivery; factorial design; dissolution; physical characterization.

INTRODUCTION

Schizophrenia is a type of chronic mental disorder involving a breakdown in the relation between thought, emotion, and behavior, leading to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships by having fantasy and delusion, and a sense of mental fragmentation (1). It affects approximately 1% of population all over the world (2). It may arise at any age and affect women and men coequally (3,4). Patients who are schizophrenic have to use antipsychotic drug treatment. However, 40% of patients do not show compliance to treatment because of irreversible adverse effects of antipsychotics which are classified first and second generation (5–7). Moreover, long-term maintenance on the medication causes non-adherence of the drug treatment which is related with relapse and hospitalization (8). Besides, the conventional dosage forms, such as tablets and capsules, new formulation approaches of the schizophrenia treatment are needed to improve reliability of deliver medications (9). Orally disintegrating tablet (ODT) technology has gained success in recent years in pharmaceutical industry with its many advantages, such as easy swallowing and increasing patient compliance comparing with conventional tablet or liquid dosage forms (10). Intake of ODTs does not require the use of water and this is an advantage for especially old people, children, those who suffer from schizophrenia, dysphagia, or central nervous system diseases, and disabled people who may have difficulties in swallowing solid dosage forms (11–13). ODTs can improve the adherence of the antipsychotic drugs by increasing patient preference and providing easier drug application which brings benefits for both patients and health care providers (14). ODTs are also more cost-effective than the conventional medications as they reduce the relapse which is a major cost in the treatment of schizophrenia (15).

Ziprasidone is a second-generation antipsychotic drug and belongs to Biopharmaceutical Classification System Class II, which means it has low water solubility and high permeability (16). Ziprasidone has a high therapeutic effect and well tolerability profile for schizophrenia treatment (17). Besides, its oral bioavailability increases 2-fold when it is administered fed state (18,19). The poor solubility and the variation between fed and fasted state of ziprasidone limit the formulation approaches and patient compliance. To enhance patient compliance and bioavailability of the drug, many studies have been conducted with nanotechnological approaches, such as lipid-based drug delivery systems, self-emulsifying drug delivery systems, and nanocrystal containing solid pharmaceutical dosage forms (19,20). Nanotechnology in pharmaceutical development is really important to enhance oral bioavailability of the drug in schizophrenia treatment. Nanoparticular systems that comprise particulates between 10- and 1000-nm sizes increase saturated solubility and stability of low water soluble drugs as well as oral

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High-sensitive troponin T increase after hemodialysis is associated with left ventricular global longitudinal strain and ultrafiltration rate

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Abstract

Background: *Circulating troponin levels are both stable and higher in patients with end-stage renal disease, even in the absence of acute coronary syndrome. These patients commonly have underlying cardiac problems that frequently cause troponin elevation. The effect of hemodialysis (HD) on troponin levels has not been well elucidated. Thus, investigated herein is the relationship between the changes in troponin levels along with left ventricular deformation and volume depletion in patients with end-stage renal disease.*

Methods: *Patients included were between 18 and 85 years of age and were receiving hemodialysis for at least 6 months. High sensitive cardiac troponin T (hs-cTnT) levels were studied in blood samples taken at the beginning and end of HD. Two-dimensional speckle tracking strain imaging was used to evaluate myocardial contractility.*

Results: *Seventy patients (50.7 ± 16.9 years of age, 27 women) were included in study. The mean volume of ultrafiltration was 3260 ± 990 mL. A significant increase in circulating hs-cTnT levels was observed, as well as a prominent decrease in left ventricular global longitudinal strain (GLS) after HD (52.4 ± 40.2 ng/L vs. 66.8 ± 48.5 ng/L, $p < 0.001$ and 20.1 ± 3.6% vs. 16.8 ± 3.8% $p < 0.001$, respectively). Moreover, ultrafiltration rate and GLS were found as the strongest independent variables in relation to the relative increase in hs-cTnT.*

Conclusions: *Hemodialysis can cause a significant increase in hsTnT. This can jeopardize the accuracy of clinical diagnoses based on hs-TnT measurements. GLS may be used as a determinant of this hs-TnT increase. The influence of HD on the cardiovascular system should be kept in mind to prevent unnecessary interventions.* (Cardiol J 2020; 27, 4: 376–383)

Key words: dialysis, high-sensitive, load, speckle, troponin

Introduction

Troponins (Tn) are structural proteins involved in the regulation of skeletal and cardiac muscle contractility and cardiac troponins (cTn) are being used as sensitive and specific markers of cardiac injury [1]. Recently developed, new generation, high-sensitive cardiac troponin (hs-cTn)

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Benzimidazole derivatives as potent and isoform selective tumor-associated carbonic anhydrase IX/XII inhibitors

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ABSTRACT

We describe the synthesis of a series of 2-arylbenzimidazole derivatives bearing sulfonamide functionality (**4a–d**, **7a–c** and **10**) as well as hydroxamic acid (**15a–b**), carboxylic acid (**16a–b**), carboxamide (**17a–b**) and boronic acid (**22a–b** and **26**) functionalities, which act as human carbonic anhydrase (hCA, EC 4.2.1.1) inhibitors. The newly synthesized benzimidazole derivatives were evaluated against 4 physiologically relevant CA isoforms (hCA I, II, IX, and XII), and especially the sulfonamide-containing benzimidazoles demonstrated intriguing inhibitory activity against tumor associated CA IX and XII with K_I values in the range of 5.2–29.3 nM and 9.9–41.7 nM, respectively. Notably, compound **4c** was the most potent and selective CA IX (K_I = 6.6 nM) and XII (K_I = 9.9 nM) inhibitor with a significant selectivity ratio over cytosolic CA I and II isoforms in the range of 3.4–25.2. In addition, compounds having hydroxamic acid (**15a-b**) or carboxylic acid (**16a-b**) functionalities resulted in greater selectivity ratios for CA IX/XII over CAI/II in the range of 4.1–121.5 although with K_I values in lower micromolar potency (K_Is = 0.36–0.85 μM for CA IX/XII).

1. Introduction

The carbonic anhydrases (CAs) are ubiquitous metalloenzymes, which catalyze the reversible hydration of CO_2 into protons and bicarbonate [1]. CAs are involved in many physiological and pathological processes such as respiration and transport of CO_2 and bicarbonate between metabolizing tissues and lungs, homeostasis of pH and CO_2, secretion of electrolytes in various tissues and organs, biosynthetic reactions (i.e., gluconeogenesis, lipogenesis and ureagenesis), bone resorption, calcification and tumor growth [1]. Therefore, many CA isoforms participating these processes are crucial as therapeutic targets, and their inhibitors have great potential for pharmacological intervention with a wide range of ailments such as edema, glaucoma, obesity, osteoporosis, epilepsy and cancer [2,3]. To date, 16 distinct mammalian α-CA isoforms identified including human isoforms [4]. These CAs can be classified as cytosolic (CA I, CA II, CA III, CA VII and CA XIII), membrane bound (CA IV, CA IX, CA XII, CA XIV and CA XV), and mitochondrial (CA VA and CA VB), as well as one isozyme is secreted in saliva (CA VI). Among them cytosolic hCA I and II are ubiquitous isoforms, and inhibitors of these isoforms are mainly used as antiglaucoma drugs, diuretics, antiepileptic drugs, antiedema drugs, and also for the treatment of altitude sickness [1,4,5]. However, in recent years, hCA IX and XII isoforms have been the main focus of cancer research [6,7]. For instance, hCA IX is found to be overexpressed in hypoxic tumors whereas it is not abundant in normal tissues [8]. Hypoxic conditions regulate the expression of CA IX through the hypoxia inducible factor 1 (HIF1) cascade, which controls the external pH to support an acidic extracellular microenvironment suited for hypoxic tumor cell survival and proliferation, but detrimental to normal cells [9]. In a similar way, another tumor-associated isozyme hCA XII decreases the extracellular pH cooperating with hCA IX [10]. Since hCA IX/XII are reported to play an important role in the progression of tumor growth and metastasis, they have been anticipated as potential targets for the development of novel antineoplastic agents. However, the main obstacle for developing new cancer therapeutics by targeting hCA IX/XII occurred as a result of the nonselective inhibition of hCA I/II isoforms, which was envisaged as the main reason for the unwanted side effects observed with these nonselective inhibitors [1,5]. The one and only sulfonamide derivative SLC-0111 (Fig. 1) with high selectivity against CA IX isoform has entered to clinical trials alone for solid tumors [11] or as a combination therapy for pancreatic ductal cancer [12].

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A disposable gold-cellulose nanofibril platform for SERS mapping†

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In this study, we present a disposable and inexpensive paper-like gold nanoparticle-embedded cellulose nanofibril substrate for the rapid enumeration of *Escherichia coli* (*E. coli*) using surface-enhanced Raman scattering (SERS) mapping. A disposable SERS substrate was simply constructed by mixing CNF and gold chloride solution at 120 °C in a water bath. The application of the resulting substrate was carried out by enrichment and SERS detection of *E. coli*. To this end, the spherical gold nanoparticle-embedded cellulose nanofibril substrate was used as a scavenger for *E. coli*. After the target bacteria *E. coli* were separated from the matrix *via* oriented antibodies, the sandwich assay procedure was carried out using 5,5-dithiobis-(2-nitrobenzoic acid) (DTNB)-coated Au nanorod particles that acted as SERS mapping probes. The distribution density of DTNB was demonstrated visually using SERS mapping, and the assay was completed in one hour. The correlation between the *E. coli* and SERS mapping signals was found to be linear within the range of 15 cfu mL^{-1} to 1.5 × 10^5 cfu mL^{-1}. The limit of detection for the SERS mapping assay was determined to be 2 cfu mL^{-1}. The selectivity of the developed method was examined with *Micrococcus luteus* (*M. luteus*), *Bacillus subtilis* (*B. subtilis*), and *Enterobacter aerogenes* (*E. aerogenes*), which did not produce any significant response. Furthermore, the developed method was evaluated for detecting *E. coli* in artificially contaminated samples, and the results were compared with those of the plate-counting method.

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1. Introduction

Bacteria are the key to the protection of ecological balance. Some bacteria are found in human body systems and play roles in the digestion of nutrients, secretion of growth factors, and protection of the body against pathogenic microorganisms. These bacteria are normally harmless and even useful in the body parts they colonize. However, they have the potential to cause infection when they spread to different areas from their natural environment, and some species cause serious diseases in humans, such as pestis (*Yersinia pestis*), tuberculosis (*Mycobacterium tuberculosis*), cholera (*Vibrio cholerae*), anthrax (*Bacillus anthracis*) and food poisoning (specific types of *Escherichia coli* (*E. coli*) and *Salmonella*).[1–3]

There are several methods to detect bacteria in water and food sources in order to protect human health. Traditional methods of bacteria detection are slow and require more manual skills compared to rapid analysis methods. Because rapid and sensitive diagnosis is critical for patient life, many rapid analysis methods, such as fluorescence spectroscopy,[4–6] surface plasmon resonance (SPR),[7,8] enzyme-linked immunosorbent assay (ELISA),[9] immunosensor-based methods,[10,11] polymerase chain reaction (PCR),[12,13] quartz crystal microbalance (QCM),[14,15] electrochemical methods[16] and surface enhanced Raman spectrometry (SERS)[17–19] have gained more importance in recent years.

SERS is a powerful analytical method for biological analyte detection. The analyte is determined at lower detection limits with high spectral identification. The fabrication of SERS substrates is essential for detecting analytes in a fast and effective way. The substrate should be uniform and reproducible in order to maintain the enhancement effect over the whole surface.[20] A rough conductive material surface is required for the observation of SERS signals. Due to its chemical stability, gold (Au) is a frequently chosen material for SERS substrate fabrication. Nanoparticle-based SERS substrates have also been developed using different kinds of nanoparticles, such as magnetic, Au, silver and graphene, to detect pathogenic bacteria.[21–23] Although SERS can be used for label-free detection,

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The effect of a new wound dressing on wound healing: Biochemical and histopathological evaluation

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ABSTRACT

Electrospinning process has gained importance in the production of wound dressings in recent years. The wound dressings prepared by electrospinning method provide many advantages over conventional wound dressings. The aim of this study was to assess the histological, biochemical, and immunohistochemical evaluation of collagen/doxycycline loaded nanofiber wound dressing in both acute and chronic wound healing. Full-thickness wound model was created on rats and rats were divided in two main groups: normoglycemic (acute) and hyperglycemic (chronic) groups. Each group was divided into three sub groups: not treated (control) group, treated with nanofiber wound dressing group and treated with commercial product group. Wound closure rates were measured. Oxidative events were investigated by biochemical analyses. In addition to histological studies, matrix metalloproteinase, tissue inhibitor of metalloproteinase, vascular endothelial growth factor, basic-fibroblast growth factor, and von Willebrand factor levels were investigated with immunohistochemical studies. According to the biochemical analyses, it was concluded that the nanofiber wound dressing helps to increase antioxidant capacity and decrease lipid peroxidation. Immunohistochemical studies showed that nanofiber wound dressing enhanced angiogenesis and shortened the inflammatory phase. It was concluded that an effective and safe prototype nanofiber wound dressing, which has similar wound healing effect to the commercial product, has been developed to be used in acute or chronic wound treatment.

1. Introduction

Wound healing is the development of damaged tissue or organs due to various factors through hemostasis, inflammation, proliferation and remodeling phases [1]. Wound healing is a dynamic and complex process [2]. An immune response is initiated to repair the damaged tissue after any tissue damage or disease. If a wound occurs, the body is very reactive to close the wound and protect it against infections. Following an injury, clotting begins to rapidly stop bleeding (hemostasis) in the wound area. During hemostasis, blood flow in the blood

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ORIGINAL ARTICLE

Effects of UV Exposure Time on Nanofiber Wound Dressing Properties During Sterilization

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Abstract

Purpose Electrospinning and nanofiber-based products have become popular in many areas in recent years. The increase in product range has brought various necessities such as sterilization. Conventional sterilization methods can be applied to nanofiber-based products. However, their effects on different properties of nanofibers must be carefully evaluated.

Methods In this study, the effects of ultraviolet (UV) exposure time on the average fiber diameter, contact angle, mechanical and bioadhesion properties, and drug content of the nanofiber wound dressing were investigated.

Results The duration of exposure time for 1 and 2 h did not cause any significant changes in the properties of the nanofibers. However, the 3-h UV exposure time significantly reduced the contact angle and tensile strength values ($p < 0.05$). The sterilization efficiency on both the fluid thioglycolate medium and the soybean casein digest medium was determined to be sufficient for 2 and 3 h of sterilized samples.

Conclusion This study showed that UV sterilization can be used for the sterilization of nanofiber products without damaging the membrane properties. On the other hand, the UV exposure time must be carefully determined.

Keywords Nanofibers · Electrospinning · UV exposure · Sterilization

Introduction

Electrospinning, which gained importance recently, is a novel nano/microfiber production technique. Nanofiber membranes can be produced with this technique from natural and synthetic polymers or their mixtures. Membranes and nanofiber-based materials are suitable for use in many different areas such as filtration, textile engineering, or biomedical applications due to their unique properties [1–3]. Some of the nanofiber-based final products especially wound dressings, tissue engineering, or implantable biomedical products which are applied directly onto the wound or into the body must be sterile [4]. Although standard sterilization procedures are available for many materials today, there is no standard procedure for materials prepared from nanofibers. Therefore, sterilization method should be selected carefully, because the sterilization process may affect the product performance.

Nanofibers can be sterilized using different sterilization methods. The common sterilization techniques such as steam, gamma, ethylene oxide (EtO), or ultraviolet (UV) sterilization can be also used for the sterilization of the nanofiber-based products [5, 6]. In addition to these methods, ozone gas treatment, which did not change the mechanical and physicochemical properties of nanofiber scaffolds, can be used for sterilization [7]. Each method has its own advantages and disadvantages. Steam sterilization is a simple and effective process, and the material is in direct contact with saturated steam under pressure. Although this process kills all microorganisms, high temperatures (121 to 134 °C) and moisture can be a problem for heat- or water-sensitive materials. These high temperatures can also affect the mechanical properties of nanofibers. It was shown that the elongation at break values of polyethylene terephthalate nanofibers reduced significantly at the end of steam sterilization at 121 °C for 15 min [5].

Gamma sterilization process can be applied for different products [8]. This sterilization method is generally used for sterilizing disposable medical devices. Gamma radiation may pass the packaging material and kill microorganisms by

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Self-inflating floating nanofiber membranes for controlled drug delivery

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ABSTRACT

Floating gastro-retentive delivery systems can prolong the gastric residence providing sustained drug release. In this study, we report on self-inflating effervescence-based electrospun nanofiber membranes embedding polyethylene oxide/sodium bicarbonate cast films. In this system, sodium bicarbonate results in an effervescence effect by creating carbon dioxide gas upon contacting an acidic gastric fluid, with the resulting gas bubbles being entrapped within the swollen network of nanofibers. Eudragit RL and RS polymers are utilized as a host material to manipulate release kinetics of incorporated drugs. Pramipexole, a common medication for chronic Parkinson's disease (PD), is used as a model drug. Uniform and bead-free nanofibers with diameters of ~300 nm were obtained. Although floating nanofibers initially exhibited high water contact angles (WCA), water droplets were quickly absorbed into the surface and the WCA decreased to ~0° within 60 s. Floating lag time, total floating time, swelling properties and drug release profiles were investigated both in a simulated gastric fluid (pH 1.2 buffer solution) and in a simulated intestinal fluid (pH 6.8 buffer solution) at 37 °C. All floating nanofiber formulations began to float instantly with nearly zero floating lag time and did not sink into the solution even after 24 h. By comparison, the same formulations without sodium bicarbonate cast films could not maintain continuous floating beyond 15 min. The floating nanofiber pouches presented lower initial release of between 20 and 57 %, compared to that of non-floating nanofiber pouches (40–82% within 2 h). Clearly, floating nanofibers reduced the initial burst release and provided sustained drug release. This demonstrates the potential to result in 'once-a-day' oral introduction of drugs that normally must be taken frequently. Effervescence-based floating nanofibers present a novel and promising prototype delivery system for the drug delivery in the upper gastrointestinal (GI) tract.

1. Introduction

Oral drug delivery is the preferred route of drug administration because of its noninvasive nature, ease of use, higher patient compliance and cost-effectiveness (Viswanathan et al., 2017). Oral drug delivery with controlled release kinetics is effective for chronic diseases with frequent dosage consumption. To reduce the drug concentration below the toxic level in plasma, controlled drug delivery systems can be approximated by multiple administrations of immediate release formulations (Moodley et al., 2011). An important controlled drug delivery system in oral formulations is the gastro-retentive delivery system (GRDS) (Malik et al., 2015a; Singh, 2000; Streubel et al., 2006). The use of GRDS can resist contractions and peristaltic waves in the stomach and show the sustained release of drugs in the gastric environment (Awasthi and Kulkarni, 2016). Therefore, increasing the gastric residence time of some drugs that are stable at the acidic pH in the stomach or upper GI tract could increase their bioavailability. For some drugs, such as baclofen and metformin HCl, their main principal sites of drug absorption are either the stomach itself or the upper part of small intestine and these drugs are significantly degraded in the colon. Therefore, the gastric retention property is highly beneficial to deliver those drugs for an extended time period (Mandal et al., 2016). Approaches for GRDS development include the floating drug delivery system (FDDS) or the non-floating system (mucoadhesive, swelling, or high-density systems). FDDS can be developed (Reddy et al., 2013) either by an effervescent or a non-effervescent system (hydrodynamical system, alginate beads or matrix layered tablets). While the non-effervescent FDDS uses a swelling system, the effervescent FDDS is formulated such that when in contact with the acidic gastric fluid (pH of ~1.5–3), CO_2 gas is generated and becomes entrapped in swollen hydrocolloids, providing buoyancy to the dosage form (Singh, 2000).

Fibers with homogenous or complex structures formed by the electrospinning method have been reported to provide excellent controlled release of drugs and other functional molecules (Han et al.,

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ORIGINAL ARTICLE

In vitro and *in vivo* evaluation of microneedles coated with electrosprayed micro/nanoparticles for medical skin treatments

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ABSTRACT

Aim: Microneedles (MNs) create micropunctures and deliver drugs or nutrients deep into skin layer. We demonstrated that MNs, coated with electrosprayed nanoparticles loaded with functional molecules, are useful for transdermal delivery.

Methods: Electrospraying was utilised to generate drug-loaded nanoparticles and to create uniform coating on MNs. Process parameters and release kinetics were evaluated *in vitro*. The *in vivo* efficacy of insulin-coated MNs was investigated using diabetic rats.

Results: Electrosprayed micro/nanoparticles loaded with dye or insulin were coated on MNs with particle size of 515 ± 286 and 522 ± 261 nm, respectively. Optimally coated MNs resulted in >70% transfer rate into porcine skins. Insulin-coated MNs were applied to diabetic rats resulting in reduction of blood glucose levels fluctuations, compared to subcutaneous injections.

Conclusions: Electrospraying is shown to be an effective method to coat MNs with drug-loaded nanoparticles. Coated MNs provide a promising platform for cosmetic, drug and protein delivery applications.

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KEYWORDS
Electrospraying; electrohydrodynamic atomisation; microneedle; dermaroller; skin; drug delivery

1. Introduction

Microneedles (MNs) are one of the best options for painless drug delivery via skin penetration because they have several advantages over conventional hypodermic needles (Gill and Prausnitz 2007), such as minimal invasiveness, reduced infection risk, ease of administration, reduced skin irritation at and near the injection site. Another skin-based delivery approach is the transdermal drug delivery (TDD) wherein drugs loaded in patches placed on the skin diffuse through the top skin surface (stratum corneum) to introduce the drug molecules into the blood stream. The patches are non-invasive approach and quite easy to use (Nejad *et al.* 2018). However, because TDD uses diffusion through the skin layers, it requires a relatively large dose to be effective and it is very challenging to deliver advanced large drug molecules.

Microneedles do present some potential issues, such as local inflammation on sensitive and allergic skin, and the possibility of broken MN tips that may be left under the skin. Broken MN tip issue can be avoided by using stainless steel MNs instead of silicon MNs, and local inflammation can be minimised by using smaller MNs (Escobar-Chávez *et al.* 2011). The height of the MNs affects the level of pain stimulation, related to the penetration depth into the stratum corneum (10–20 μm), the epidermis (~100–200 μm) and the dermis (~1–2 mm). MNs with height of 1.5–2 mm are routinely used for treating acne and scars, while shorter MNs with height of 0.5–1.0 mm are used for treating aging skin and wrinkles (Singh and Yadav 2016, Iriarte *et al.* 2017). If epidermal cells are targeted, relatively short MNs (200–300 μm) are suitable. For other medical treatments, longer MNs are appropriate. Usually the treatment process is painless with MNs up to 0.5 mm height, but it is also a function of the epidermis thickness of the individual receiving treatments (Singh and Yadav 2016). A simple but limited approach is to use an array of solid MNs to create small holes on stratum corneum of the skin through which drugs from a topical formulation can diffuse into the skin more efficiently than from a transdermal patch. More complex approaches, such as using hollow MNs for drug injection and dissolvable MNs for the patient's convenience as an easy one-step process, have been reported to deliver insulin, heparin, anticancer agents, gene therapy vectors and vaccines

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RESEARCH ARTICLE

Electrospun metronidazole-loaded nanofibers for vaginal drug delivery

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ABSTRACT

Objective: To develop and characterize innovative vaginal dosage forms for the treatment of bacterial vaginosis (BV).

Significance: This study is the first comparative evaluation of the metronidazole (MET)-loaded polyvinylpyrrolidone (PVP) nanofiber formulations on BV treatment. Vaginal nanofibers are one of the potential innovative dosage forms for BV treatment because of their flexible, mucoadhesive, and easy application in vaginal application which can be applied by the mucosal route.

Methods: Blank and MET-loaded PVP solutions were prepared at three different concentrations (10, 12.5, 15%) for produce nanofiber. The suitability of the viscosities, surface tensions, and conductivity values of the solutions used to produce nanofibers for the electrospinning process has been evaluated. Scanning electron microscopy, mucoadhesion, permeability, Fourier transform infrared spectroscopy, differential scanning calorimetry, and drug release tests were performed to reveal the physical, chemical, and pharmaceutical properties of the nanofibers. Mechanical properties, and contact angle of the fibers were also determined. Gel and solution formulations containing MET were prepared for comparative studies.

Results: All polymer solutions were found to be suitable for electrospinning process. PVP concentration directly affected nanofiber diameter, mechanical, and mucoadhesion properties of nanofibers. The release profiles of the drug from the nanofibers were similar for all concentration of PVP and release from the fibers was rapid. The permeability coefficient of MET from nanofibers was increased more than gel and solution formulations.

Conclusions: Vaginal use of MET-loaded nanofibers has been shown to be a potential drug delivery system for the treatment of BV.

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Electrospinning; vaginal nanofibers; mucoadhesion; metronidazole; bacterial vaginosis

Introduction

Bacterial vaginosis (BV) is one of the common genital situations have seen in females of childbirth age [1,2]. BV is associated with preterm labor, pelvic inflammatory disease, chorioamnionitis, and bacteremia and is the most common reason for vaginitis and vaginal discharge [3]. BV can be treated by using nitroimidazole-derived antibiotic metronidazole (MET), which exhibits broad-spectrum activity against various protozoans, most gram-negative, and gram-positive anaerobic bacteria [4]. MET is an internationally wide-usage drug with antibacterial and antiprotozoal properties with appropriate pharmacokinetic properties and minor side effects [5]. Local MET concentration in the vagina may be useful in cases of refractory infection with susceptible protozoa and bacteria [6]. Local application of MET is more preferred than the oral route, specially due to adverse effects during pregnancy and lactation [7]. There are clinical studies on various dosage forms such as gel containing MET for vaginal administration. Gel [8], vaginal mucoadhesive tablet [9], ovule [10], mucoadhesive film [11], tablet [12], and suspensions [13] have been used for the vaginal administration of MET. Sobel et al. showed that vaginal MET provides a significant reduction in the recurrence rate of bacterial vaginosis (BV) [14]. In a study comparing vaginal gel and oral formulations containing MET for the treatment of BV, it has been found to be nearly close treatment rate [15]. It was observed that MET containing Pluronic F127 and Pluronic 68 thermosensitive gel formulations did not affect the viability of the cells and did not change the morphology of the vaginal tissues [16]. MET was found to be more effective than placebo in a study comparing locally vaginal tablet, gel formulation, or oral use [17]. Fewer gastrointestinal side effects were observed in the vaginal regimen, although the effectiveness of MET vaginal and oral regimens is similar [17]. In another study, administration of MET (0.75%) vaginal gel twice a week for 4 months decreased significantly the clinical recurrence rate during the treatment period [14]. Vaginal film formulations containing MET for the treatment of BV are designed to prevent problems, such as low bioavailability, leakage observed in conventional therapy [18].

Nanospheres, nanovesicles, nanotubes, and nanofibers are some of the nanostructures that can be loaded with antimicrobial agents [19]. Nanofibers can be produced using various techniques such as solution blowing, centrifugal spinning, pressurized gyration, phase separation and electrospinning [20]. Pressurized gyration and centrifugal spinning methods have advantages such as large-scale production, simplicity, low cost, and high efficiency and prevents the use of high voltage [21,22]. The electrospinning method is the most common method for nanofiber production under atmospheric conditions and room temperature from many natural and synthetic polymers [23,24]. Electrospinning is an inexpensive method to produce nanofibers which were ranged from nanometers to micrometers [25]. This method can be used alternatively to achieve a lower fiber diameter [26]. In addition, like

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Antitumor activity of gemcitabine hydrochloride loaded lipid polymer hybrid nanoparticles (LPHNs): In vitro and in vivo

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ARTICLE INFO

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ABSTRACT

The present study demonstrated the application of gemcitabine hydrochloride (GEM) loaded lipid polymer hybrid nanoparticles (LPHNs) for the enhancement the chemotherapeutic response. GEM, which is an anti-tumor drug, is frequently utilized for the treatment of non-small cell lung cancer, breast cancer and pancreatic cancer. GEM loaded LPHNs were formed and examined for pharmacokinetic profile and in vivo anticancer activity. Modified double emulsion solvent evaporation method was employed in the preparation of the LPHNs. Cytotoxicities of the GEM loaded LPHNs formulation were evaluated on MCF-7 and MDA-MB-231 cells by MTT assays. Pharmacokinetics and in vivo anticancer efficacy studies were conducted following intraperitoneal administration in female Sprague-Dawley rats.

In vivo pharmacokinetic studies in rats exhibited the advantage of the GEM loaded LPHNs over commercial product Gemko® and the GEM loaded LPHNs had longer circulation time. The half-life of GEM in LPHNs formulation was notable advanced (4.2 folds) comparing to commercial product of GEM (native). These findings indicated that GEM loaded LPHNs can be used for enhancing antitumor efficacy for breast cancer treatment.

1. Introduction

Cancer is a complicated and highly heterogeneous disease characterized by the uncontrolled growth of abnormal cells in the body. Among the types of cancer, breast cancer is the most commonly diagnosed type of cancer and ranks second for cancer-related mortality in females (Eloy et al., 2017; He et al., 2017). Although chemotherapy is generally used in breast cancer treatment, it often causes drug resistance, which decreases the efficacy of chemotherapy. Despite terrific advances, breast cancer treatment still remains as a considerable challenge due to metastasis and development of drug resistance (Ahmad, 2013; Kovalchuk et al., 2008). Therefore, development of more effective nano-sized drug delivery systems is important to enhance the clinical outcome of breast cancer treatment.

Nanoparticulate drug delivery systems make an outstanding contribution to the advancement of drug delivery in breast cancer (Shavi et al., 2016; Shen et al., 2015; Xu et al., 2015). The nanoparticulate drug delivery system can efficaciously save drugs from enzymatic degradation, alter their blood circulation and also decrease side effects of drugs (Elzoghby et al., 2012; Narvekar et al., 2014). Polymeric nanoparticles and liposomes are two major drug delivery approaches of nano-carriers, which have been employed for anticancer drugs (Date et al., 2018; Yalcin et al., 2018a). Both polymeric nanoparticles and liposomes have their own exclusive advantages. For example, liposomes are highly biocompatible and biodegradable nano-carriers (Hardiansyah et al., 2014; Sercombe et al., 2015) while polymeric nanoparticles exhibit high structural integrity, stability during storage, and controlled release capability (Hadinoto et al., 2013). However, polymeric nanoparticles and liposomes also have their own limitations. Low drug encapsulation efficiency for hydrophilic active ingredients and polymer cytotoxicity are among the limitations of polymeric nanoparticles (Date et al., 2018; Mandal et al., 2013). In comparison with polymeric nanoparticles, liposomes have low structural integrity and low stability during storage (Cheow and Hadinoto, 2011; Yalcin et al., 2018a). However, both liposomes and polymeric nanoparticles have some common limitations in terms of rapid drug diffusion and leakage (Tahir et al., 2017). Nowadays, lipid polymer hybrid nanoparticles (LPHNs), a new category of therapeutic nanocarriers, have arrived as a promising drug delivery system to overcome the possible drawbacks and to integrate the effective features of liposomes and polymeric nanoparticles (Wakaskar, 2018; Zhang et al., 2015). In comparison with liposomes and polymeric nanoparticles, LPHNs display advanced drug encapsulation, modulated drug release, and enhanced cellular uptake (Liu et al., 2017) LPHNs are core–shell nanoparticle structures consisting of polymer cores and lipid/lipid–PEG shells, which have biomimetic advantages of phospholipid shell and architectural advantage

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Immunomagnetic separation and *Listeria monocytogenes* detection with surface-enhanced Raman scattering

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Background/aim: We aimed to develop a rapid method to enumerate *Listeria monocytogenes* (*L. monocytogenes*) utilizing magnetic nanoparticle based preconcentration and surface-enhanced Raman spectroscopy measurements.

Materials and methods: Biological activities of magnetic Au-nanoparticles have been observed to have the high biocompatibility, and a sample immunosensor model has been designed to use avidin attached Au-nanoparticles for *L. monocytogenes* detection. *Staphylococcus aureus* (*S. aureus*) and *Salmonella typhimurium* (*S. typhimurium*) bacteria cultures were chosen for control studies. Antimicrobial activity studies have been done to identify bio-compatibility and bio-characterization of the Au-nanoparticles in our previous study and capturing efficiencies to bacterial surfaces have been also investigated.

Results: We constructed the calibration graphs in various population density of *L. monocytogenes* as 2.2×10^1 to 2.2×10^6 cfu/mL and the capture efficiency was found to be 75%. After the optimization procedures, population density of *L. monocytogenes* and Raman signal intensity showed a good linear correlation ($R^2 = 0.991$) between 10^2 to 10^6 cfu/mL *L. monocytogenes*. The presented sandwich assay provides low detection limits and limit of quantification as 12 cfu/mL and 37 cfu/mL, respectively. We also compared the experimental results with reference plate-counting methods and the practical utility of the proposed assay is demonstrated using milk samples.

Conclusion: It is focused on the enumeration of *L. monocytogenes* in milk samples and the comparision of results of milk analysis obtained by the proposed SERS method and by plate counting method stay in food agreement. In the present study, all parameters were optimized to select SERS-based immunoassay method for *L. monocytogenes* bacteria to ensure LOD, selectivity, precision and repeatablity.

Key words: Immunomagnetic separation (IMS), surface-enhanced Raman scattering (SERS), *Listeria monocytogenes* (*L. monocytogenes*)

1. Introduction

Listeria monocytogenes (*L. monocytogenes*) is a crucial foodborne pathogenentailing disease. *L. monocytogenes* can grow and develop even at refrigerator temperatures and is a major problem, especially in ready-to-eat foods. Listeriosis illness is caused by contaminated foods with *L. monocytogenes* [1]. Raw milk is known as an important source of *L. monocytogenes*. In 1986, Hayes et al. isolated this bacterium from 12 samples from 100 raw milk samples in USA [2].

Rapid pathogenic bacterial diagnosis has been applied to conduct measurements in biological and food matrix [3]. Up to date, different method has been applied by several research group for enumeration of pathogenic bacteriaespecially *L. monocytogenes* using polymerase chain reaction immunoassay [4,5], electrochemical sensors [6–8], bioluminescence [9,10], DNA-based sensors [11,12], ELISA [13,14], surface plasmon resonance [15,16], fluorescence [17,18], surface-enhanced Raman scattering (SERS) [19–21]. It was indicated that the reported methods were optimized to select proper system usage to obtain selectivity and precision, there were some problems such as poor sensitivity and long experimental procedures. Also, the enumeration of pathogenin food matrix is problematic [22]. Therefore, new analytical methods are required for the detecting of pathogens and other biomolecules in food matrix. Recently, immunomagnetic separation (IMS) overcomes the matrix

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A new steroidal alkaloid from *Fritillaria michailovskyi* Fomin

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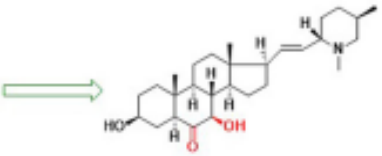
ABSTRACT

A new steroidal alkaloid, michainine (**1**), was isolated from *Fritillaria michailovskyi* Fomin, along with nine known compounds **2–10** of different classes, including ribonucleoside, steroids, and fatty acids, which were isolated for the first time from this plant. Their structures were elucidated through extensive spectroscopic techniques, as well as by comparing the data in the literature. Furthermore, the dichloromethane fraction of *F. michailovskyi* showed a positive butyrylcholinesterase inhibitory activity, along with non-cytotoxicity against 3T3 cell line.

Fritillaria michailovskyi Fomin



Michainine (1)

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KEYWORDS
Fritillaria michailovskyi; steroidal alkaloid; michainine; butyrylcholinesterase inhibitory activity

1. Introduction

Fritillaria is a large genus of the family Liliaceae, which consists of approximately 100 species (Akhtar et al. 2003). The species of this genus mainly distribute in temporal regions of the northern hemisphere from the Middle East, through Europe, and North America to Central Asia. 41 species of *Fritillaria* genus are natural habitants of Turkey

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ARAŞTIRMA MAKALELERİ
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2. Keser, M., Gürbüz, İ. 2020. Piyasadan Temin Edilen Bazı Çemen Tohumu Örneklerinin Avrupa Farmakopesi Ölçütleri Açısından Değerlendirilmesi. Lokman Hekim Dergisi 10, 327-335.

3. Mutlu Agardan, N.B. Studies on the formulation optimization and controlled ionic gelation of chitosan nanoparticles using TPP-HP-β-CD inclusion complex. Istanbul Journal of Pharmacy. 50(1) (2020) 54-59.

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Research Article/Araştırma Makalesi

The effect of turmeric on microbial quality in meatballs

Köftelerde zerdeçalın mikrobiyal kalite üzerine etkisi

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ABSTRACT

Investigation of the effects of turmeric on the pH and microbiological quality of the meatballs was aimed in this study. 2% and 4% turmeric was added to the meatballs, and these samples stored at refrigerator temperature. pH values, total aerobic bacteria, total coliform bacteria, lactic acid bacteria and *Staphylococcus aureus* counts of the samples were followed at daily intervals for five days. As a result of the analysis, it was shown that Total Aerobic Bacteria counts of the turmeric containing groups were lower compared to the control group. pH value of the 4% turmeric group was found lower than the control group. It was found that the Total Coliform Bacteria counts of the 4% turmeric group were lower when compared to the control group. As a result, the addition of 4% turmeric to the meatballs is effective on the microbiological quality of the meatballs.

Key Words: Food safety, Meatball, Microbiological quality, Turmeric

ÖZ

Bu çalışmada, zerdeçalın köftelerin pH'sı ve mikrobiyolojik kalitesi üzerindeki etkileri incelenmesi amaçlanmıştır. Köftelere %2 ve %4 oranında zerdeçal ilave edilmiştir ve örnekler buzdolabı sıcaklığında muhafaza edilmiştir. Örnekler pH, toplam aerob mezofil bakteri, toplam koliform bakteri, laktik asit bakteri ve *Staphylococcus aureus* sayıları açısından beş gün süresince analiz edilmiştir. Analizler sonucunda zerdeçal kullanılan grupların Toplam Aerob Mezofil Bakteri sayısının kontrol grubuna kıyasla daha düşük düzeyde olduğu görülmüştür. %4 Zerdeçal içeren grubun pH değeri kontrol grubundan daha düşük olduğu bulunmuştur. Köftelerden %4 zerdeçal içeren grubun Toplam Koliform Bakteri sayısının kontrol grubuna kıyasla daha düşük değere sahip olduğu belirlenmiştir. Sonuç olarak, köftelere %4 konsantrasyonda zerdeçal ilave edilmesinin köftelerin mikrobiyolojik kalitesinde etkili olduğu görülmüştür.

Anahtar Kelimeler: Gıda güvenliği, Köfte, Mikrobiyolojik kalite, Zerdeçal

Introduction

Foodstuffs could be contaminated by microorganisms such as bacteria and fungi. These microorganisms may cause undesirable changes in the taste, smell, color, sensory and structural properties of food (Lucera et al., 2012; Ünver and Çelik, 2017; Yaralı, 2019). Various preservation methods such as fermentation, drying, heat treatment, organic acid application, UV ionizing radiation, non-thermal applications such as high hydrostatic pressure are used in the food industry to prevent the development of spoilage and pathogenic microorganisms in foods (Davidson and Taylor, 2007; Farkas, 2007; Ünver and Çelik, 2017; Belibağlı and Ersan, 2018). In recent years, there has been a significant increase in the preservation of food with natural additives due to consumer concern about synthetic chemicals used in foods (Lucera et al., 2012).

Araştırma Makalesi – Original Article

Piyasadan Temin Edilen Bazı Çemen Tohumu Örneklerinin Avrupa Farmakopesi Ölçütleri Açısından Değerlendirilmesi*

Evaluation of Some Fenugreek Seed Samples Obtained from the Market in Terms of European Pharmacopoeia Criteria

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ÖZ

Giriş: Çemen (*Trigonella foenum-graecum* L.) tohumu baharat ve gıda olarak tüketilmektedir. Ayrıca Avrupa Farmakopesi (9,6) ve Türk Farmakopesi'nde (2017) de yer alan önemli droglardan biridir. Ancak ülkemizde farmakope standartlarına uygun çemen tohumu bulmak pek mümkün değildir. Dolayısıyla droğu tıbbi amaçla kullanmak isteyenler çoğunlukla aktardan temin etmektedir. Aktardan alınan çemen tohumlarının farmakope standartlarında olması beklenmemekle birlikte, bu konuda herhangi bir araştırmaya da rastlanılmamıştır. Bu nedenle Türkiye'deki 12 farklı aktardan çemen tohumu temin edilmiş ve farmakope uygunluğunun araştırılması amaçlanmıştır.

Yöntem: Analizlerde Avrupa Farmakopesi (9.6) içerisindeki "Çemen Tohumu (Trigonella foenugraeci semen)" monografı referans alınmıştır. Çemen tohumu monografında yer alan tüm analizler mongrafta tarif edildiği gibi yapılmıştır.

Bulgular: Mikroskobik analiz, ince tabaka kromatografisi, kurutmada kayıp, toplam kül miktarı deney sonuçları farmakopeye uygun bulunup, morfolojik analiz sonuçlarının bir kısmı ve şişme indisinin uygun olmadığı tespit edilmiştir.

Sonuç: 12 farklı aktardan temin edilen çemen tohumu örnekleri üzerinde yapılan analizlerin sonucuna göre, örneklerin Avrupa Farmakopesi (9,6) açısından uygun olmadığı tespit edilmiştir. Dolayısıyla bu örneklerin terapötik amaçlarla kullanılması doğru olmayacaktır. Çalışılan örnek sayısı geneli temsil etmemekle birlikte, aktarlarda satılan droglar hakkında bir fikir edinilmesi açısından önemlidir.

Anahtar Kelimeler: Çemen tohumu, *Trigonella foenum-graecum L.*, Fabaceae, Farmakope analizi.

ABSTRACT

Introduction: Fenugreek (*Trigonella foenum-graecum* L.) seeds are consumed as spices and food. In addition, it is one of the important drogs in the European Pharmacopoeia (9.6) and the Turkish Pharmacopoeia (2017). However, it is not possible to find fenugreek seeds in our country that comply with pharmacopoeia standards. For this reason, those who want to use the fenugreek seed for medicinal purposes mostly obtain it from herbalist. Although fenugreek seeds obtained from herbalist are not expected to be in pharmacopoeia standards, no research has been encountered on this subject. Therefore, fenugreek seeds were obtained from 12 different herbalists in Turkey and it was aimed to investigate their suitability for pharmacopeia.

Methods: In the analyzes, the "Fenugreek Seed (Trigonella foenugraeci semen)" monograph in the European Pharmacopoeia (9.6) was taken as reference. All analyzes in fenugreek seed monograph were done as described in the monograph.

Results: Microscopic analysis, thin layer chromatography, loss of drying, total ash amount were found suitable for pharmacopoeia, some of the morphological analysis results and swelling index was not appropriate.

Conclusion: According to the results of the analysis on fenugreek seed samples obtained from 12 different herbalists, it was determined that the samples were not suitable for the European Pharmacopoeia (9,6). Therefore, it will not be appropriate to use these samples for therapeutic purposes. Although the number of samples studied does not represent the general, it is important in terms of forming an idea about drugs that are sold in herbalist.

Key words: Fenugreek, *Trigonella foenum-graecum L.*, Fabaceae, Pharmacopeia analysis.

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Original Article

Studies on the formulation optimization and controlled ionic gelation of chitosan nanoparticles using TPP-HP-β-CD inclusion complex

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ABSTRACT

Background and Aims: Ionic gelation strategy is the most common method used for the preparation of chitosan nanoparticles to obtain controlled drug delivery. Although it is a convenient and easy method, it is highly related with particle aggregation, high polidispersity index and insufficient physical/chemical stability. The aim of this study was the development of chitosan nanoparticles using tripolyphosphate-hydroxy propyl β-cyclodextrin or tripolyphosphate-sulfobutyl ether β-cyclodextrin inclusion complex as an alternative to TPP, and hence to increase physical stability, reduce polidispersity index and develop a stable nanocarrier for drug delivery purposes.

Methods: The nanoparticles were prepared with the ionic gelation technique. The effects of chitosan percent, pH, and chitosan/tripolyphosphate ratio were investigated to find out the optimum nanoparticles in terms of particle size, polidispersity index and zeta potential. After determining the conditions for the tripoly phosphate-chitosan nanoparticles, the nanoparticles were prepared using tripolyphosphate-hydroxypropyl β-cyclodextrin or tripolyphosphate-sulfobutyl ether β-cyclodextrin to make a comparison with the nanoparticles which were prepared using tripolyphosphate.

Results: The chitosan/tripolyphosphate-hydroxypropyl β-cyclodextrin nanoparticles were successfully formulated with 178 ±84.1 nm particle size, 0.310±0.0134 PDI, 31.2±4.68 mV zeta potential. The interday changes in the measured characteristics were minimized for chitosan/tripolyphosphate-hydroxypropyl β-cyclodextrin nanoparticles as intended.

Conclusion: CS/TPP-HP-β-CD nanoparticle formulation with particle size below 200 nm, high zeta potential and increased physical stability nanoparticles would offer a promising approach especially for hydrophobic drugs to improve their stability, solubility, encapsulation efficiency and in vivo bioavailability.

Keywords: Chitosan nanoparticles, controlled ionic gelation, cyclodextrins

INTRODUCTION

In past decades, many efforts have been made to obtain a controlled and targeted release of drugs with micro and nano sized drug delivery systems. Due to their small size and large surface area, drug nanoparticles are superior to conventional drugs, with the ability to increase solubility, and hence improve bioavailability, providing a controlled release and reduced side effects. No doubt, advances in polymer science also promoted the advancement of drug-delivery technology. Among all nanoparticulate drug delivery approaches, polymeric nanoparticles have attracted significant attention since they are biodegradable, biocompatible, relatively easy to prepare and suitable for a variety of chemical drug classes and dosage forms (Crucho & Barros, 2017; Kumari, Yadav & Yadav, 2010; Rizvi & Saleh, 2018).

Polymeric nanoparticles are mainly prepared with biodegradable polymers, either synthetic or natural ones. Poly (lactide) (PLA), poly (lactide-co-glycolide) copolymers (PLGA), poly (ε-caprolactone) (PCL) and poly(amino acids) are the most common synthetic

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Antioxidant and Cytotoxic Activity Studies in Series of Higher Amino Acid Schiff Bases

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Highlights

- DPPH scavenging ability of the higher amino acid Schiff bases was investigated.
- *In vitro* cytotoxicity of these Schiff bases was tested against cancer and human normal cells.
- Schiff base 2b killed 90 percent of MCF-7 cells at concentration of 100 μM.

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Keywords

Amino Acid Schiff bases
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Abstract

In this work, the antioxidant activity of the higher amino acid Schiff bases, which were prepared as the monosodium salts (**1a–3a**) and the neutral forms (**1b–3b**) was determined by DPPH scavenging assay. In pure MeOH solution, the scavenging ability of Schiff bases **1a-3a** were higher than **1b-3b**, but lower than ascorbic acid. The activity followed the order 3 (a,b) > 2 (a,b) > 1 (a,b). On the other hand, Schiff bases **2a** and **3a** behaved as the most effective scavengers of the DPPH radical in methanol-water mixture (v:v, 1:3). And, they were found to be have lower SC50 values in this mixture compared to pure methanol. In vitro cytotoxicity of these Schiff bases was studied against human cervical cancer cells (HeLa), human breast adenocarcinoma cells (MCF-7), and human normal embryonic kidney cells (HEK293). For HeLa cell line, Schiff bases **1a-3a** exhibited a litttle high activity than **1b**, but very low activity than doxorubicin. Schiff bases **2b** and **3b** had no cytotoxicity against HeLa cell. For MCF-7 cell line, Schiff bases **1a**, **3a**, **1b** and **3b** nearly were inactive at 100 μM, whereas **2a** increased cell proliferation in the all tested concentration range. Differently, Schiff base **2b** showed the highest cytotoxicity and killed 90 percent of MCF-7 cells at concentration of 100 μM. For HEK-293, doxorubicin was strongly cytotoxic. Despite this, Schiff bases **1a**, **3a** and **3b** were inactive, whereas the others showed little weak toxicity.

1. INTRODUCTION

Endogenous reactive oxygen species (ROS: O·,OH·, O_2^{-} and H_2O_2) are naturally formed in the life of aerobic organism. Exogenous species occur as a result of toxic agents, drugs or different lifestyle choices like as smoking and burnt food, etc. [1]. The excess ROS production becomes toxic, and this damages structure and function of biological molecules like as lipids, carbohydrates, proteins, DNA and nucleic acids in body metabolism, and causes degenerative diseases such as aging, diabetes, inflammatory, cardiovascular, autoimmune and cancer [2-4]. Also, neurodegenerative diseases as Alzheimer's and Parkinson's have been found to be related to an increase in quantity of ROS inside the human body [5]. Antioxidants react with these free radicals, terminate their chain reactions and minimize their harmful effects in metabolism [6]. They also protect the quality of food stuffs [7]. Natural antioxidants isolated from aromatic plants are flavonoids, tannins, phenolic acids, alkaloids, chlorophyll derivatives, carotenoids and tocopherols. There are also some synthetic phenolic antioxidants as butylated hydroxy-toluene, butylated hydroxy-anisole and tert-butylhydroquinone [8].

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Studies on Anticholinesterase and Antioxidant Effects of Samples from *Iris* L. Genus of Turkish Origin

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Abstract: The genus *Iris* L. (Iridaceae) is a member of geophytes with attractive flowers. There are about 56 *Iris* taxa growing in Turkey, 24 of which are endemic. A survey of the literature indicates that the research carried out on *Iris* species are focused on the flavonoid and volatile compounds of the plant.

In present study, the dichloromethane and methanol extracts prepared from the rhizomes of 47 *Iris* taxa growing in Turkey were investigated for their *in vitro* cholinesterase inhibitory effects against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) which the enzymes linked to Alzheimer's diseases and antioxidant capacities using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging test as well.

The *Iris* extracts studied have been found more active against BChE than AChE. compared with 100 µg/ml galanthamine (89.29 ± 0.96 %) as reference, *Iris kørneriana* (coded as Y122) and *Iris pseudacorus* (coded as Y131) methanol extracts had significant BChE inhibition effect (respectively, 80.22 ± 1.04 % and 53.06 ± 1.13 %) at concentration of 200 µg/ml. Among tested samples, methanol extracts of *I. kørneriana*, *I. lazica*, *I. pseudacorus* and *I. suaveolens* have shown remarkable antioxidant activity at concentration of 2 mg/ml for DPPH compared with gallic acid.

Keywords: *Iris*, Anticholinesterase, Antioxidant, Activity

1. Introduction

Turkey is an important gen centers for biodiversity and it is known that Turkey possesses approximately 1045 geophyte taxons are economically important such as *Colchicum*, *Fritillaria*,*Hyacinthus*, *Lilium*, *Nectaroscordum*, *Polygonatum*, *Tulipa* and *Iris* species (Kaya, 2014). Among them, genus *Iris* (family *Iridaceae*) is represented by 56 species in Turkey, of which 24 are endemic (Güner, 2012). *Iris* species have gained great popularity in the perfume and cosmetic industries due to their sweet fragrance alongwith their ornamental purposes (Orhan et al. 2002; Atta-ur-Rahman et al. 2004; Sevim, 2018). *Iris* species have been previously recognized as rich sources of secondary metabolites and used in the treatments of cancer, inflammation and bacterial and viral infections (Wang et al. 2010; Singab et al. 2016). Previous phytochemical investigations on the *Iris* species have resulted in the isolation of a variety of compounds including flavonoids, isoflavonoids, isoflavonoid glycosides, benzoquinones, triterpenoids and stilbene glycosides and essential oils (Orhan et al. 2002; 2003, Atta-ur-Rahman et al. 2002; 2003; 2004).

The aim of the present study was to investigate the antioxidant capacities and anticholinesterase activities of 47 *Iris L.* species growing in Turkey in order to evaluate their medicinal value and to point to an easily accessible source of natural antioxidants that could be used as a possible food supplement in addition to cosmetic, and perfume industries.

2. Materials and Method

2.1. Plant material

The rhizomes of *Iris* L. species were collected from different locations in Turkey given in Table 1. Their identification was confirmed by Prof. Dr. Neriman Ozhatay and Prof. Dr. Adil Güner and preserved as *ex-situ* at Atatürk Horticultural Central Research Institute, Department of Ornamental Plant Breeding and Agronomy in Yalova, Turkey.

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Isolation and Identification of Cholinesterase Inhibitors from the Bulbs of *Iris pseudacorus* L.

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Abstract: Most of the bulbous plants are known for their medicinal purposes in addition to their ornamental value. Turkey is one of the home country of many beautiful bulbous plants. In continuation of our extensive studies on finding new natural cholinesterase inhibitors from Turkish medicinal plants, *Iris* L. species were investigated for their *in vitro* cholinesterase inhibitory effects designed to assess cholinesterase inhibitor activities on both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) and antioxidant capacities with respect to their neuroprotective potential in this study.

The dichloromethane and methanol extracts prepared from the bulbs of 47 *Iris* taxa were screened by using modified Ellmann method and the highest butyrylcholinesterase inhibitory effect was found in the methanol extract of the bulbs of *Iris pseudacorus* L. (Sevim, 2018). The dichloromethane sub-extract, which is obtained bioactivity-guided fractionation of methanol extract of *I. pseudacorus* L., was exhibited significant butyrylcholinesterase inhibitory activity (73.65 ± 2.06 %). These active sub-extract was subjected to fractionation on column chromatography and obtained six fractions. Among the fractions, coded as N5 was shown the significant butyrylcholinesterase inhibitory activity (93.78 ± 1.49 %) compared with galanthamine (80.02 ± 0.12 %). Fractionation of N5 on flash chromatography the highest butyrylcholinesterase inhibitory activity of sub-fraction coded as DS-5 was determined as 94.00 ± 1.03 %. The responsible compound from the activity of this sub-fraction was detected as irisolidone glucopyranoside based on its mass data by using LC-ESI-Q/TOF-MS-MS technique.

Keywords: *Iris pseudacorus* L., Iridaceae, Activity, Anticholinesterase

1. Introduction

The genus *Iris* L. (Iridaceae) is a member of geophytes with attractive flowers. There are about 56 *Iris* taxa growing in Turkey, 24 of which are endemic (Güner, 2012). *Iris* species are an important plants as an ornamental due to their different colours and attractive flowers (Orhan et al., 2002, Atta-ur-Rahman et al., 2004, Wang et al., 2010); they have also evaluated in the preparation of products as an violet odour from their rhizomes in perfumery and cosmetic industries (Atta-ur-Rahman et al., 2004). Besides, *Iris* species were reported to be utilized for the treatment of different ailments in traditional medicine as an anticholinesterase, antioxidant, antimicrobial, antidiabetic, antiinflammatory, hepatoprotective, molluscisidal and cytotoxic effects depends on variety of secondary metabolites (Wang et al., 2010, Singab et al., 2016). Alzheimer's disease (AD) is one of the neurodegenerative disorder affecting the elder people (Howes et al., 2003). One of the main approaches has been for the control of AD is the inhibition of acetylcholinesterase and butrylcholinesterase for the elevation of acetylcholine level secreted from synaptic region in brain to restrain the cholinergic function related with memory loss. Currently, clinically available drugs are used for the treatment of AD. Continuing our researches in the field of anticholinesterase activity, we herein aimed to determine butyrylcholinesterase inhibitory activity of *Iris pseudacorus* L. showed the highest inhibitory activity *Iris* L. species (Sevim, 2018).

2. Materials and Method

2.1. Plant material

The rhizomes of *Iris pseudacorus* L. were collected from Hatay province and identified by Prof. Dr. Neriman Ozhatay and Prof. Dr. Adil Güner and preserved as *ex-situ* at Atatürk Horticultural Central Research Institute, Department of Ornamental Plant Breeding and Agronomy in Yalova, Turkey (population no. 3108) (Mathew, 1984, Güner, 2012).

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Evaluation of phenolic compounds and protective effects of olive (*Olea europaea* L.) leaf extracts on endothelial cells against hydrogen peroxide-induced toxicity

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ABSTRACT: *Olea europaea* L. (Oleaceae) leaves have been used for centuries in folk medicine to treat many degenerative and inflammatory diseases including hypertension, atherosclerosis and cardiovascular disorders. The present study was aimed to quantify the phenolic compounds present in three different extracts of *O. europaea* leaves, and to demonstrate their protective effects on human umbilical vein endothelial cells against oxidative injury induced by H_2O_2. Oleuropein, hydroxytyrosol, quercetin, luteolin and rutin in the olive leaf extracts were quantified by using a validated HPLC-UV method. Total phenolic content was determined using the Folin-Ciocalteau assay. The MTT and dichlorofluorescein assays were conducted to measure cytotoxicity and intracellular reactive oxygen species generation, respectively. Oleuropein was the major phenolic component. Each phenolic compound (1.0 and 10.0 µM) and each extract (10.0 µg/mL) significantly ($p<0.05$) preserved human umbilical vein endothelial cells against H_2O_2-induced toxicity, but olive leaf extract-1 and luteolin seemed to be more effective in studied concentrations even in the inhibition of cellular reactive oxygen species generation ($p<0.05$). In addition, a positive correlation was found between reactive oxygen species inhibitory activity and total phenol content versus viability protecting capacity of each olive leaf extracts. These results supply a new validated HPLC method for the effective characterization of olive leaf polyphenolic compounds and support the notion that the polyphenolic components of olive leaves are the efficient cytoprotective agents against H_2O_2-induced oxidative stress and toxicity in human umbilical vein endothelial cells.

KEYWORDS: *Olea europaea*; cytoprotection; HPLC; oleuropein; hydroxytyrosol; quercetin; luteolin; rutin.

1. INTRODUCTION

Olive tree, *Olea europaea* L. (Oleaceae), is one of the most important fruit trees in Mediterranean region. Olive leaf extracts contain oleuropein as the major phenolic compound together with other phenolic glycosides or esters such as secoiridoids derived from tyrosol structure, i.e. hydroxytyrosol, several flavonoids and hydroxycinnamic acid derivatives, i.e. verbascoside [1,2]. Several studies have reported that olive leaf extracts (OLExts) exert many biological activities including antihyperglycemic [3], antihypertensive [4,5], and antiatherosclerotic activities [6]. Accordingly, we demonstrated that ethanolic extracts from olive leaves have cytoprotective against H_2O_2-, cytokines- or carbonyl(4-HNE)-induced toxicity and apoptosis in insulin releasing cells [7,8] and cardiomyocytes [9]. These potential health benefits of olive leaves are mostly related to polyphenols such as oleuropein, hydroxytyrosol, tyrosol, tocopherol, verbascoside, elenolic acid derivatives, caffeic, *p*-coumaric and vanillic acids as well as flavonoids (luteolin, diosmetin, rutin, luteolin-7-glucoside, apigenin-7-glucoside, and diosmetin-7-glucoside) [9]. Oleuropein, which is an advanced glycation end-product inhibitor [10], has been shown to decrease intracellular ROS levels, reducing amount of oxidized proteins [11] and preventing doxorubicin-induced cardiomyopathy [12].

The aim of this study was (i) to develop and apply an alternative HPLC-UV method for the simultaneous quantification of oleuropein (O), hydroxytyrosol (H), quercetin (Q), luteolin (L) and rutin (R) in the olive leaf extracts and (ii) to investigate the effects of the extracts and reference phytochemicals, O, H, Q, L and R on H_2O_2-induced toxicity in human umbilical vein endothelial cells (HUVECs).

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Annals of Clinical and Analytical Medicine
Original Research

Homocysteine thiolactonase activity in coronary atherosclerosis

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Abstract

Aim: Discovery of paraoxonase natural substrate, homocysteine thiolactone, shed more light on the protective role of paraoxonase and toxicity of homocysteine. Since homocysteine thiolactone and paraoxon were hydrolyzed at different sites in the PON protein, the aim of this study was to investigate the Hcy-thiolactonase (HTase). This study was undertaken to ascertain whether low the Hcy-thiolactonase activity is associated with paraoxonase activity and to clarify its relation with ox-LDL and total plasma homocysteine levels in coronary artery diseasase.

Material and Methods: Forty-six subjects undergoing coronary angiography for suspected coronary artery disease were included. Depending on angiography results, 14 subjects with normal coronary arteries according to Gensini scoring were selected as a control group. Serum homocysteine thiolactonase and paraoxonase activities were measured spectrophotometrically. Homocysteine, ox-LDL levels were measured with ELISA methods.

Results: A significant decrease in HTase activity and a significant increase in ox-LDL levels were observed in patients compared with controls (p=0.040, p=0.037, respectively). Homocysteine levels and paraoxonase activity did not show any statistically significant difference between groups. Positive correlations between HTase and paraoxonase activities were observed in study groups (rs=0.742, p=0.004 for control, rs=0.494, p=0.01 for patient).

Discussion: HTase activity decreased in coronary artery disease in spite of unchanged paraoxonase activity and is associated with a higher level of ox-LDL. N-homocysteinylation of HDL changes the properties of apolipoprotein, which could affect the enzymatic activities. When considering a relationship between HTase activity and HDL levels, correlation observed in our study confirms a possible consequence of low PONs homocysteine thiolactonase activity.

Keywords

Homocysteine; Homocysteine Thiolactone; Paraoxonase; Oxide LDL; Censini score

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Original Article

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Correlation Between Gamma-Glutamyl Transferase Activity and Glutathione Levels in Molecular Subgroups of Breast Cancer

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ABSTRACT

Objective: The gamma-glutamyl cycle catalyzed by gamma-glutamyl transferase (GGT) plays an important role in glutathione (GSH) homeostasis in the cell. In cells continuously exposed to the drug, the main phase of the enzymatic detoxification is the conjugation of the drug with GSH catalyzed by glutathione-S-transferase (GST). Conjugation of drugs with GSH is the first step in the development of chemotherapeutic drug resistance. In this study, we aimed to investigate the relationship between GGT and GSH in molecular subgroups of breast cancer patients.

Materials and Methods: Serum GGT activity and GSH levels for patients diagnosed with breast cancer (n=58) and healthy controls (n=8) were measured by a spectrophotometric method and a colorimetric kit, respectively.

Results: GGT activity was significantly higher in the total patient group and in the molecular subgroups than those in the control groups ($p<0.05$). Serum GSH levels were higher in the patient groups compared to controls without reaching statistical significance ($p>0.05$). GGT activity was positively correlated with GSH levels in the total patients and healthy controls ($p<0.001$ and $p<0.05$, respectively). There was also a positive correlation between GGT activity and GSH levels in Luminal A, HER2-positive (Human epidermal growth factor receptor 2), and Triple-negative groups ($p<0.05$).

Conclusion: This is the first study showing the relationship between GGT and GSH in molecular subgroups of breast cancer. An increase in GGT activity may affect intracellular GSH synthesis. Therefore, having a correlation between GGT and GSH in some molecular subgroups may affect the course of treatment in these patients.

Keywords: Gamma-glutamyltransferase, glutathione, molecular subgroups of breast cancer

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Introduction

Gamma-glutamyl transferase (GGT) (GGT, EC 2.3.2.2) is an enzyme known as (5-L-glutamyl) -peptide: amino acid 5-glutamyl transferase in systematic nomenclature. GGT is located on the outer surface of plasma membranes of cells which has ecto-enzyme activity. The enzyme is a dimeric glycoprotein composed of a heavy chain and a light subunit bound by a non-covalent bond, processed from a single chain precursor with an autocatalytic cleavage in prokaryotes and eukaryotes (1, 2). GGT is located in the plasma membrane of almost all cells, but mainly involved in epithelial tissues with secretory or absorbing functions (1). Although the enzyme is shown in many organs, the highest GGT activity is present in the kidney, then in the duodenum, small intestine and gallbladder, respectively (3). GGT is present in the biliary pole of hepatocytes and cholangiocytes in adult liver and thus secreted into bile. It is known that the main source of plasma GGT is the liver (1).

Glutathione (GSH) (GSH, L-glutamyl-L-cysteinylglycine) is a tripeptide which has a thiol group and it is present in 1-10 mM concentration in all mammalian tissues (4). It is the most abundant antioxidant molecule in cells and is involved in various critical cellular functions such as detoxification of xenobiotics and/or their metabolites, cell proliferation, apoptosis, and modulation of fibrogenesis (4). GSH is also an important determinant of sulfur assimilation, protection of cells against oxidative stress and storage and transport of nitric oxide and cysteine. The gamma-glutamyl cycle catalyzed by GGT uses GSH as a continuous source of cysteine for cells (5). GSH is synthesized in the cytosol and then transferred out of the cell. The extracellular GSH metabolism is initiated by GGT, which is the first enzyme of the GSH destruction pathway, and is then finished with membrane dipeptidases (6). The γ-glutamyl moiety released by the breakdown of GSH by

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Evaluation of Alcohol Content of Cologne Products in the Turkish Market Amid the COVID-19 Pandemic

COVID-19 Salgını Sürecinde Türkiye Pazarındaki Kolonyaların Alkol İçeriğinin Değerlendirilmesi

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ABSTRACT

The World Health Organization and Turkish National Health Authorities advise the public to use an alcohol-based hand sanitizer or wash with soap and water for cleaning against the COVID-19 outbreak whilst Turkey was ready for this new situation from the beginning because of the widespread use of colognes. While the pandemic resulted in stockpiling and absence of related products, the industry responded fast by making fast production, but it has raised concerns about the safety and efficacy of these new products. Alcohol content of the cologne samples purchased from various daily supermarket stores in Turkish market were evaluated with Headspace - Gas Chromatography - Flame Ionization Detector (HS-GC-FID) to check and verify their safety for consumers during the COVID-19 pandemic. The headspace oven, loop, and transfer line temperatures were 130 °C, 135 °C, and 140 °C, respectively. The GC oven temperature program was hold at 30 °C for 10 min, increased at 10 °C/min to 220 °C for 5 min. Helium flow rate was 1 mL/min. Injection and detector temperature were 140 °C, and 250 °C, respectively. Injection volume was 1 µL with the split ratio of 50:1. The ethanol content of the colognes is in a range of 37.9 – 98.9 % (w/w). The alcohol content of some of the products was observed as below the limit of Turkish Guideline for Cosmetic Products to be labelled as cologne. Therefore, the regulatory bodies should check the products more intensively or the regulations on cologne in pandemic can be revisited.

Key Words: Cologne, Turkish market, ethanol content, COVID-19 pandemic, safety, regulation

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ÖZET

Dünya Sağlık Örgütü ve Türk Ulusal Sağlık Otoriteleri, COVID-19 salgınına karşı halka temizlik için ellerin alkol bazlı el temizleyicileri veya sabun ve su ile yıkama yapılmasını tavsiye ederken, Türkiye bu yeni duruma kolonya kullanımının yaygın olması nedeniyle en baştan beri hazır durumdaydı. Pandemi, ilgili ürünlerin stoklanması ve yokluğuna yol açarken, endüstri hızlı bir şekilde üretim yaparak duruma cevap vermiştir, lakin bu yeni ürünlerin güvenliği ve etkinliği konusunda endişeler ortaya çıkmasına sebep olmuştur. COVID-19 salgını sırasında tüketicilerin güvenliğini kontrol etmek ve doğrulamak için Türkiye pazarındaki çeşitli süpermarket mağazalarından satın alınan kolonya örneklerinin alkol içeriği, Tepe Boşluk- Gaz Kromatografi – Alev İyonlaşma Dedektörü (GC-FID) ile değerlendirilmiştir. Tepe boşluk fırın, döngü ve transfer hattı sıcaklıkları sırasıyla 130 °C, 135 °C ve 140 °C seçildi. GC fırın sıcaklık programı; 30 °C'de 10 dk ısıtılıp, 10 °C/dak artışla 220 °C'ye arttırılarak 5 dak ısıtıldı. Helyum akış hızı 1 mL/dak, enjeksiyon ve dedektör sıcaklığı sırasıyla 140 °C ve 250 °C, enjeksiyon hacmi 50:1 bölme oranıyla 1 µL seçildi. Test edilen kolonyaların etanol içeriği %37.9 ila %98.9 (a/a) aralığındadır. Bazı ürünlerin alkol içeriği, Kozmetik Yönetmeliği'nde kolonya olarak etiketlenebilecek limitin altında olduğu görülmüş olup, düzenleyici kurumların ürünleri daha yoğun bir şekilde kontrol edilmesi tavsiye edilebilir veya pandemi döneminde kolonya ile ilgili düzenlemeler yeniden gözden geçirilebilir.

Anahtar Sözcükler: Kolonya, Türkiye pazarı, etanol içeriği, COVID-19 salgını, güvenlik, düzenleme

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Characterization of Thermosensitive Gels for the Sustained Delivery of Dexketoprofen Trometamol for Dermal Applications

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Poloxamer, sustained release, viscosity, dexketoprofen trometamol, propylene glycol

Abstract

In this report, the release properties of dexketoprofen (DEX) from propylene glycol (PG) and poloxamer gel systems were investigated. After formulation of gel systems composed of poloxamer 338 and PG, rheological experiment was conducted to investigate effects of PG on temperature-dependent viscoelasticity of poloxamer 338-based gels. It appeared that PG and poloxamer 338 could form gel systems with good thermosensitive properties, the gel system containing 2.5% and 5% PG showed similar thermosensitive properties. In vitro release studies were performed at two different temperatures, room temperature (25 °C ± 0.1 °C) and skin temperature (32 °C ± 0.1 °C), using Franz diffusion cells and showed decreased the release rate of DEX at skin temperature (32 °C) according the thermosensitive properties of poloxamer 338. Also released amount of DEX were decreased due to the use of high poloxamer concentration. At both temperatures, the highest release (39.35% at 32 °C and 31.78% at 25 °C in 8 hours) was obtained with 20%poloxamer + 5%PG, the lowest release (29.46% at 32 °C and 26.23% at 25 °C in 8 hours) was obtained with 25% poloxamer + 5% PG. After the drug release amount was examined, kinetic models (zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas) were investigated. In both temperatures (25 °C and 32 °C), the in vitro drug release profiles of poloxamer based formulations were fit to the Korsmeyer-Peppas kinetic model.

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RESEARCH ARTICLE

Chemical and antimicrobial characterization of essential oils obtained from aerial part, root and fruit of *Ferulago longistylis* Boiss., an endemic species

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Abstract

The aerial part, root and fruits of *Ferulago longistylis* Boiss. an endemic species, were subjected to the evaluation of essential oil compositions and antimicrobial activity. The essential oils were analyzed by gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS). The main components of the aerial part were identified as α-pinene (18.7%), bornyl acetate (11.8%), 2,3,6-trimethyl benzaldehyde (9.3%), *p*-cymene (7.7%), for the roots, α-pinene (91.7%); and for the fruits, 2,3,6-trimethyl benzaldehyde (26.5%), α-pinene (14.9%), *(Z)*-β-ocimene (14.1%), myrcene (7.5%), sabinene (7.3%), respectively. The essential oils were evaluated for their *in vitro* antimicrobial activity against a panel of some human pathogens using a broth microdilution technique resulting in relatively weak antimicrobial and antifungal activity (MIC 1.25-10 mg/mL).

Keywords: *Ferulago longistylis*, Apiaceae, essential oil chemistry, antimicrobial activity.

Introduction

Apiaceae, which is one of the largest plant families in the world, is represented by about 160 endemic species in Turkey (Şenol et al., 2018). New species of Apiaceae family in Turkey are still being discovered (Şenol et al., 2018; Menemen et al., 2018). The *Ferulago* W. Koch genus is a member of Apiaceae family and 35 taxa grow naturally in Turkey (Güner et al., 2012). The genus *Ferulago* is an Anatolian-based genus that is very similar to *Ferula* L. (Özhatay & Akalın, 2000). One of the 19 endemic *Ferulago* species in Turkey, *F. longistylis* Boiss., is among the rare endemics (Güner et al., 2012; Gençler Özkan et al., 2007; Başer & Kırımer, 2014). *Ferulago* species are used in Turkish folk medicine for treatment of intestinal worms, hemorrhoids and also used as a tonic, sedative, digestive, however, one of its most significant traditional usage is due to its aphrodisiac activity (Baytop, 1999; Demetzos et al., 2000). Various phytochemical studies revealed that *Ferulago* species contain mainly coumarins such as bergapten, 8-(1,1-dimethylallyl)bergaptol, bergamotin, isoimperatorin, oxypeucedanin, (−)-prantschimgin and (−)-*iso*valerylmarmesin (Jimenez et al., 2000), essential oil (major components 2,3,6-trimethylbenzaldehyde, α-pinene, (*Z*)-β-ocimene, myrcene, *p*-cymene) (Erdurak et al., 2006; Kılıç et al., 2010; Başer & Kırımer, 2014), flavonoids such as quercetin and rutin (Khanahmadi et al., 2011) and quinone (1-acetylhydroquinone 4-galactoside) (Doğanca et al., 1991). Additionally, essential oils of different *Ferulago* species showed antimicrobial activity on various pathogens (Taran et al 2010; Khalighi-Sigarodi et al., 2005; Demirci et al., 2000).

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mRNA Expressions of Specific Gamma-Glutamyl Transferases in Molecular Subtypes of Breast Cancer

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An increased risk of breast cancer has been reported in individuals with elevated levels of gamma-glutamyl transferase (GGT). GGT1 was the only enzyme used for diagnosis in clinic and human genome contains additional related genes or sequences besides GGT1. From the perspective of amino acid sequences, genes showing substantial similarity (GGT5, GGT6, and GGT7) to GGT1 have been identified. The aim of this study was to investigate the mRNA expressions of GGT1, GGT5, GGT6, and GGT7 in 58 breast cancer patients' tissue samples by qRT-PCR method. In total, mRNA expressions of GGT5 and GGT7 increased and GGT6 decreased in tumor tissues than those in normal tissues of the same patients ($p<0.145$, $p<0.003$ and $p<0.05$, respectively). Among molecular subtypes, GGT7 expressions were significantly higher in tumor tissues than those in normal tissues of the patients in Luminal A group ($p<0.009$). Over-expression of GGT7 was observed in almost half of the patients. The research showed mRNA expressions of GGT1, GGT5, GGT6, and GGT7 in breast cancer. Among the four genes, we obtained surprising results for GGT7 and we believe that the activity of this gene should be examined in breast cancer.

Keywords: *GGT1, GGT5, GGT6, GGT7, breast cancer, mRNA expressions*

Introduction

Among the most common cancers in women, breast cancer is seen in one out of every four females. A total of 17,571 Turkish women with breast cancer, which is the first-line cancer type in women all around the world, was diagnosed in 2013. Breast cancer incidence in Turkish women was observed as 45% between 50–69 years of age and 40% between 25–49 years of age (Türkyilmaz et al. 2018).

Breast carcinomas are highly heterogeneous tumors with clinical signs/ symptoms/treatment responses as well as biological behaviors. According to recent research, immunophenotypic and molecular classification have been shown to be much more prognostic and predictive than classification based on basic clinicopathological parameters such as morphology, tumor histological subtype, and histologic grade applied for many years (Banerji et al. 2012, Carey et al. 2006, Rouzier et al. 2005, Tran and Bedard 2011).

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Original Article

Vertical and Horizontal Transmission of Streptococcus Mutans and Effective Factors: An In Vivo Study

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Abstract

Aim: The degree of vertical (intrafamilial) and horizontal (extrafamilial) transfer of *Streptococcus mutans* (*S. mutans*) to a child shows differences according to cultures. The wrong care habits may result in transfer of *S. mutans*. The aim of this study was to determine the vertical and horizontal transmission of *S. mutans* to a child and effective factors.

Materials and Methods: Mothers and kindergarten staff of 37 children aged between 4 and 5 years who initially started in two kindergartens (Group 1, $n = 19$; Group 2, $n = 18$) were included in this in vivo study according to 95% reliability and 80% theoretical power. Intraoral examination of mothers and children made according to the World Health Organization criteria (dmf-t/DMF-T) was done, following which mothers were asked to fill questionnaire forms including knowledge and attitudes of them about oral/dental health care. 1 mL saliva samples received from children/mothers/staff were examined microbiologically in order to isolate and quantify *S. mutans*. Arbitrarily primed polymerase chain reaction analysis was done to determine the genetic characteristics of *S. mutans*. All examinations were repeated to evaluate the horizontal transmission in the fifth month. Parametric tests (t-test and two-way analysis of variance) were employed for comparison of the variables that meet the normality assumption and nonparametric tests (Mann–Whitney) were also used.

Results: It was observed that there is a statistically significant correlation between mother DMF-T values and mother–child *S. mutans* similarity level ($P < .05$). There is a statistically positive correlation between the habits of using a common fork, spoon, glass, and mother–child similarity level.

Conclusion: Vertical and horizontal transfers occurred in Turkish families in order to prevent the transfer of *S. mutans*; wrong baby care habits that may lead to the transfer of *S. mutans*, which is the main factor in case of tooth decay, should be avoided.

Keywords

AP-PCR, Horizontal transmission, *Streptococcus mutans*, Vertical transmission

Introduction

Tooth decay is a destruction of the hard tissues of the teeth caused by bacteria as a result of fermentation of carbohydrates.[1] According to the studies conducted in this area, the pathogens associated with caries are acquired in the mouth earlier than expected.[2–5] *S. mutans* is the microorganism commonly associated with the development of caries.[6,7] Having *S. mutans* at early ages is decisive for future caries experiences.[8,9] *S. mutans* can maintain its vitality in very limited surfaces other than mouth, and saliva transfer is seen as the most important factor for transmission of this microorganism.[3] The transfer of these bacteria to the children and their acquisition, depending on the amount of bacteria in the mouth is mostly from the mother, father, or the caregiver.[10–12]

Vertical transmission refers to the interfamilial transfers of *S. mutans*.[13,14] Comparing the species obtained from infant with the father, it has been accepted that the vertical transfer of these bacteria are mostly from the mother

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RESEARCH ARTICLE

Development and Validation of a Fast and Simple LC-ESI MS/MS Method for Quantitative Analysis 8-Hydroxyl-2′-Deoxyguanosine (8-OHdG) in Human Urine

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Development and Validation of a Fast and Simple LC-ESI MS/MS Method for Quantitative Analysis 8-Hydroxyl-2′-Deoxyguanosine (8-OHdG) in Human Urine

SUMMARY

8-Hydroxyl-2′-Deoxyguanosine (8-OHdG) is an extensively used biomarker of oxidative DNA damage, which is formed by oxidative stress factors such as chemical carcinogens, cigarette smoke. The main aim of this study was to develop a fast, sensitive and easy method for the quantitative determination of 8-OHdG in human urine samples. In this study, we developed and validated an accurate, fast, sensitive, and robust liquid chromatography–tandem mass spectrometry (LC–MS/MS) method for determination of 8-OHdG concentrations in human urine samples. The levels of the 8-OHdG in urine samples were determined quantitatively with LC-MS/MS by using positive electrospray ionization (ESI) in the multiple reaction monitoring (MRM) mode and a Hilic Plus column. 8-Hydroxy-2′-Deoxyguanosine [15N5, 98%] was used as an internal standard in this study. Our validated method was successfully applied to the analysis of spot urine samples collected from randomly selected healthy human cigarette smoker and non-smoker subjects. With the help of this validated LC-ESI MS/MS method we can determine the presence of 8-OHdG at very low concentrations in human urine samples.

Key Words: *Urine, LC-MS/MS, 8-Hydroxyl-2′-Deoxyguanosine, DNA damage, Biomarker, Tobacco smoke*

İnsan İdrarında 8-Hidroksil-2′-Deoksiguanozin (8-OHdG) Kantitatif Analizi için Hızlı ve Basit LC-ESI MS/MS Yöntemi Geliştirilmesi ve Doğrulanması

ÖZ

8-Hidroksil-2′-Deoksiguanozin (8-OHdG), oksidatif DNA hasarının yaygın olarak kullanılan bir biyolojik belirleyicisi olup, kimyasal kanserojenler, sigara dumanı gibi oksidatif stres faktörlerine bağlı olarak oluşur. Bu çalışmanın amacı, insan idrarında 8-OHdG'nin kantitatif analizi için hızlı, hassas ve basit bir prosedür geliştirmektir. Bu çalışmada, insan idrarında 8-OHdG konsantrasyonlarını ölçmek için doğru, hızlı, hassas ve sağlam bir sıvı kromatografisi-tandem kütle spektrometresi (LC-MS/MS) metodu geliştirilmiş ve valide edilmiştir. İdrar numunelerindeki 8-OHdG seviyeleri, MRM modunda ve bir Hilic Plus kolonunda pozitif elektrosprey iyonizasyonu kullanılarak LC / ESI-MS / MS ile kantitatif olarak belirlendi. Bu çalışmada iç standart olarak 8-Hidroksi-2′-Deoksiguanozin [15N5,% 98] kullanılmıştır. Doğrulanmış yöntem, rastgele seçilen sağlıklı sigara içen ve sigara içmeyen deneklerden toplanan spot idrar örneklerinin analizine başarıyla uygulanmıştır. Valide edilmiş bu LC-ESI MS / MS metodu yardımıyla insan idrar numunelerinde 8-OHdG varlığı çok düşük seviyelerde tespit edilebilmektedir.

Anahtar Kelimeler: *İdrar, LC-MS/MS, 8-Hidroksi-2′-Deoksiguanosin, DNA hasarı, Biyobelirteç, Sigara içme*

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A comparative evaluation of *Juniperus* species with antimicrobial magistrals

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Abstract: The objective of this study was to evaluate the *in vitro* bioactivity of the active ingredient in selected antimicrobial magistral drug formulations and plant extracts used in folk medicine, comparatively. The active ingredients of magistrals such as; boric acid, balsam of Peru, zinc oxide, *Calendula* tincture, thymol, resorcinol, crystal violet were used as well as fruit or leaf extracts of *Juniperus excelsa* (*Je*), *J. sabina* (*Js*), *J. foetidissima* (*Jf*), *J. communis ssp. nana* (*Jcsn*), *and J. oxycedrus* spp. *oxycedrus* ripe (*Joso*) to determine the antimicrobial activity against gram positive bacteria (*S. pyogenes*, *S. aureus*, *S. epidermidis*, *E. faecalis*), gram negative bacteria (*K. pneumoniae*, *H. influenza*, *P. aeruginosa*, *A. baumannii*, *E. coli)*, and fungi (*Candida. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*) by using microdilution method. The inhibition end point of the minimum inhibition concentrations (MICs) were determined as µg mL^{-1}. The active ingredient and plant extracts have shown antibacterial and antifungal activities with a MIC values of 1->128µgmL^{-1}. The active ingredient crystal violet (MIC; 1 µg mL^{-1}) as well as *Je*- fruit ethanol, *Jf*-leaf and fruit ethanol, *Joso*-leaf and fruit ethanol extracts (MIC; 16µg mL^{-1}) have exhibited the highest antimicrobial activities (MIC; 16µg mL^{-1}). Although ingredients of magistrals seem to exert similar antifungal activity against *C. albicans, C. tropicalis, and C. parapsilosis* (MIC; 32µgmL^{-1}), thymol and resorcinol were observed to be more active against *C. krusei* (MIC; 16µg mL^{-1}). Extracts were more pronounced against *P. aeruginosa, A. baumannii,* and *S. epidermidis* (MIC ranging from 16 to 32). In the mine time, the extracts showed equal antifungal activity against *C. albicans and C. parapsilosis* (MIC; 16µg mL^{-1}). In our study, antimicrobial activity of the natural compounds and ingredients of selected magistrals have found to be promising with MIC values of 16-32µg mL^{-1}. According to the results of our antimicrobial activity studies, utilization of *Juniperus* extracts in antimicrobial magistral formulations can be suggested.

Keywords: Medicinal plant, antibacterial, antifungal, magistrals, *Juniperus*.

INTRODUCTION

Magistral drugs are the preparations, mixed, assembled, packed and labeled drugs prepared by a licensed pharmacist to meet the unique needs of an individual patient when commercially available drugs do not meet those needs. They can also contain and provide compounds that are not available and involved in commercial medicinal formulations. Pharmaceutical formulations as magistral drugs can play a vital or important role to find an appropriate treatment for a patient. Despite the large role of technology and manufacturers play in the development and production of pharmaceuticals from natural or synthetic compounds, many pharmacists continue to work with researchers to come up with improved or entirely new medicinal compounds (Allen, 2012).

Plants are also well-known to be rich sources of bioactive compounds. Traditional healers have long used plants to prevent or cure infectious diseases. Many of these agents appear to have structures and modes of action that distinct from those of the antibiotics in current use. So, it is worthwhile to study plants and plant products for their activities against microorganisms. One approach that has been used for the discovery of antimicrobial agents from plants based on the evaluation of traditional medicinal plant extracts. Throughout history books arranged for drugs and pharmacopeia, which includes the magistral drugs were discovered (Allen, 2012).

The active substances that are used in antimicrobial magistrals in Turkey are boric acid, balsam of Peru, zinc oxide, *Calendula* tincture, thymol, resorcinol, and crystal violet etc. Boric acid is odorless, slight pearl sheen colorless crystals or white powder that is soluble in water, ethanol and glycerin. It has a weak topical bacteriostatic and fungistatic activity (Prutting and Cerveny, 1998). Balsam of Peru is a dark brown, viscous liquid that is non-drying. It is practically insoluble in water but freely soluble in dehydrated alcohol. It is used for topical treatment of superficial skin lesions because of its high cinnamic and benzoic acid contents which have antiseptic activity (Ph. Eur., 2009). Zinc oxide is a white powder that is insoluble in water. It exhibits antimicrobial activity through different mechanisms and used as preservative in topical pharmaceutical formulations (Pasquet *et al*., 2014). *Calendula officinalis* is a medicinal plant belonging to the family Asteracea. It is used in phytotherapy because of its antibacterial, anti-

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ORIGINAL ARTICLE / ÖZGÜN MAKALE

DEVELOPMENT AND CHARACTERIZATION OF MUCOADHESIVE-*THERMOSENSITIVE BUCCAL* GEL CONTAINING METRONIDAZOLE FOR THE TREATMENT OF ORAL MUCOSITIS

ORAL MUKOZİT TEDAVİSİ İÇİN METRONİDAZOL İÇEREN MUKOADEZİF-ISIYA DUYARLI BUKKAL JELİN GELİŞTİRİLMESİ VE KARAKTERİZASYONU

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ABSTRACT

Objective: *This study was aimed to develop and characterize, mucoadhesive-thermosensitive gel formulation containing metronidazole that can quickly gel at the buccal mucosa temperature for treatment of oral mucositis.*

Material and Method: *In this study, the combinations Poloxamer 407 (P407), Poloxamer 188 (P188) and Hydroxypropyl methylcellulose (HPMC) were used in certain concentrations to form a gel in buccal mucosa. Optimum formulations were selected by measuring the gelling time and gelling temperature of the formulations prepared. The hardness, adhesiveness, cohesiveness, resilience, sprayability, mucoadhesion and release properties of selected formulations were evaluated.*

Result and Discussion: *The results showed that F1 and F3 formulations, which quickly turn into gel form at 33 °C, could be the optimum formulations. These two formulations showed controlled release for 8 hours. Texture profile analysis (TPA), mucoadhesion studies and sprayability studies have shown that F1 formulation which the mixture of P407 (15%), P188 (20%) and HPMC (5%) is the optimum formulation for the buccal mucosa. In conclusion, mucoadhesive-thermosensitive gels containing metronidazole may be a good alternative in the treatment of oral mucositis.*

Keywords: *Metronidazole, mucoadhesive-thermosensitive gel, oral mucositis, poloxamer*

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ORIGINAL ARTICLE

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In vitro Enzyme Inhibitory Properties, Antioxidant Activities and Phytochemical Profiles of *Moltkia aurea* and *Moltkia coerulea*

Moltkia aurea ve *Moltkia coerulea*'nın *In vitro* Enzim İnhibitör Özellikleri, Antioksidan Aktiviteleri ve Fitokimyasal Profilleri

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Abstract
Objectives: The genus *Moltkia* Lehm., is represented by two species; *Moltkia aurea* Boiss., and *M. coerulea* (Willd.) Lehm. in Turkey. They are used both as food and for medicinal purposes. The current study aimed to investigate the antidiabetic and antioxidant potential, and the phytochemical profile of the leaf, flower and root extracts of *Moltkia* species.
Materials and Methods: α-Glucosidase and α-amylase enzyme inhibitory activities of the extracts were studied. Also, antioxidant effects, total phenol and flavonoid contents of the extracts were evaluated. High performance liquid chromatography (HPLC) method was applied for the identification and quantification of the phenolic compounds which could be liable for the observed various activities of the extracts.
Results: Among the investigated phenolic compounds, caffeic and rosmarinic acids and rutin were determined and quantified in the methanol extracts. Rutin was found as the major compound in *M. aurea* flower extract, also it was determined as one of the major compounds of the leaf extract together with rosmarinic acid. *M. coerulea* flowers, leaves and roots were found to be rich in rosmarinic acid. The antioxidant and antidiabetic potentials of the extracts may be thought to be due to their rutin and rosmarinic acid content.
Conclusion: These results propose that tested *Moltkia* species could be used as potential natural antioxidant sources. On the other hand, especially *M. aurea* extracts could be evaluated in the development of herbal products with antidiabetic potential.
Keywords: *Moltkia*, Boraginaceae, antidiabetic, antioxidant, HPLC, phenolic compounds
ÖZET
Amaç: *Moltkia* Lehm. genusu Türkiye'de iki tür ile temsil edilmektedir: *Moltkia aurea* Boiss. ve *M. coerulea* (Willd.) Lehm. Her iki bitki de hem besin olarak hem de tıbbi amaçla kullanılmaktadır. Bu çalışma, *Moltkia* türlerinden elde edilen yaprak, çiçek ve kök

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Preclinical Study on Hepatoprotective Effect of Pollen Extract of *Pinus brutia* Ten. (Red Pine) in Mice and Phenolic Acid Analysis

Pinus brutia Ten. (Kızılçam) Polen Ekstresinin Karaciğer Koruyucu Etkisinin Preklinik Olarak Araştırılması ve Fenolik Asit Analizleri

Hepatoprotective Effect of Pollen Extract of *Pinus brutia* Ten

***Pinus brutia* (Kızılçam) Polen Ekstresinin Hepatoprotektif Etkisi**

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Abbreviations: ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; ApoE: Apolipoprotein E; AST: Aspartate transaminase; b.w.: Body weight; CAT: Catalase; CCl_4: Carbon tetrachloride; ConA: Concanavalin A; GSH-Px: Glutathione peroxidase; HDL: High density lipoprotein; HPLC: High performance column chromatography; LC: Liquid chromatography; LDH: Lactic dehydrogenase; LDL: Low density lipoprotein; MDA: Malondialdehyde; MO: Missouri; USA; RBC: Red blood cell count; SD: Standard deviation; SOD: Superoxide dismutase; United States of America; WBC: White blood cell count.

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ORIGINAL ARTICLE

Cholinesterase and Tyrosinase Inhibitory Potential and Antioxidant Capacity of *Lysimachia verticillaris* L. and Isolation of the Major Compounds

Lysimachia verticillaris L.'nin Kolinesteraz ve Tirozinaz İnhibitör Etki Potansiyeli ve Antioksidan Kapasitesi ile Ana Bileşiklerinin İzolasyonu

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ABSTRACT

Objectives: The scope of the present study was to specify the therapeutic potential for neurodegenerative diseases through evaluating cholinesterase and tyrosinase (TYR) inhibitory and antioxidant activity of *Lysimachia verticillaris* (LV), and to isolate the major compounds considering the most active fraction.

Materials and Methods: The methanol extract (ME) of LV and the chloroform, ethyl acetate (EtOAC), and aqueous fractions obtained from it were used for biological activity and isolation studies. The ME and all fractions were tested for their acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and TYR inhibitory and antioxidant potentials using ELISA microtiter assays. Seven major compounds were isolated from the active EtOAC fraction by semi-preparative high performance liquid chromatography. The structures of the compounds were elucidated by several spectroscopic methods.

Results: Marked AChE inhibitory activity was observed in the EtOAC fraction (6337±1.74%), BChE inhibitory activity in the ME and EtOAC fraction (85.84±3.01% and 83.62±3.93%), total phenol content in the EtOAC fraction (261.59±3.95 mg equivalent of gallic acid/1 g of extract) and total flavonoid contents in the EtOAC fraction (515.54±2.60 mg equivalent of quercetin/1 g of extract), and 2,2-diphenyl-1-picrylhydrazyl radical scavenging activity and ferric-reducing antioxidant power values in the aqueous and EtOAC fractions (92.54±0.67%, 92.11±0.30%; 2.318±0.054, 2.224±0.091, respectively). Accordingly, the isolation studies were carried out on the EtOAC fractions. Compounds 1-7 (gallic acid, (+)-catechin, myricetin 3-O-arabinofuranoside, myricetin 3-O-α-rhamnopyranoside, quercetin 3-O-β-glucopyranoside, quercetin 3-O-arabinofuranoside, and quercetin 3-O-α-rhamnopyranoside, respectively) were isolated from the active EtOAC fraction.

Conclusion: LV may be a potential herbal source for treatment of neurodegenerative diseases based on its strong antioxidant activity and significant cholinesterase inhibition similar to that of the reference.

Key words: Anticholinesterase, HPLC, isolation, *Lysimachia*, tyrosinase

ÖZ

Amaç: Bu çalışmanın amacı, *Lysimachia verticillaris*'in (LV) kolinesteraz, tirozinaz inhibitör etkisini ve antioksidan aktivitesini değerlendirerek nörodejeneratif hastalıklar için terapötik potansiyelini belirlemek ve en etkili fraksiyondan hareketle ana bileşiklerini izole etmektir.

Gereç ve Yöntemler: Biyolojik aktivite ve izolasyon çalışmaları için LV'nin metanol ekstresinden hareketle kloroform, EtOAC ve sulu fraksiyonları elde edilmiştir. Etkili EtOAC fraksiyonundan, yarı preparatif yüksek performanslı sıvı kromatografisi (YBSK) yöntemi ile 7 ana bileşik izole edilmiştir. İzole edilen bileşiklerin yapıları çeşitli spektroskopik yöntemler kullanılarak aydınlatılmıştır. Metanol ekstresi (ME) ve tüm fraksiyonların asetilkolinesteraz (AChE), butirilkolinesteraz (BChE), tirozinaz inhibitor etkileri ve antioksidan potansiyelleri ELISA yöntemleri kullanılarak belirlenmiştir.

Bulgular: En yüksek AChE inhibitor etki EtOAc fraksiyonunda (%63,37±1,74), en yüksek BChE inhibitör etki ME'de ve etil asetat fraksiyonunda

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Original Investigation / Özgün Araştırma

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Tort and Acartürk

Investigation of Propolis and Boron Containing Disinfectants and Comparison with WHO-Recommended Formulation against COVID-19

Propolis ve Bor İçeren Dezenfektanların İncelenmesi ve DSÖ Tarafından COVID-19'a Karşı Kullanılması Önerilen Formülasyon ile Karşılaştırılması

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ABSTRACT

Objective: The need for disinfectants has increased worldwide due to the developing pandemic COVID-19. If access to water is limited, the use of alcohol-based disinfectant formulations recommended by the WHO. In this study, disinfectant gel formulations containing propolis and boric acid with lower alcohol levels than the WHO-recommended formulation were developed.

Materials and Methods: Four different gels formulations containing propolis and boric acid were developed. A gelling agent was added to the developed formulations to make it remain longer on the skin than liquid solution formulations. Texture profile analyses, spreadability, and bioadhesion tests of the formulations were evaluated. After the characterization studies, bactericidal and fungicidal activity assays were performed with final and the WHO-recommended formulations.

Results: The results showed that increasing of gelling agent increased the viscosity, bioadhesion and textural values. The final formulation containing propolis and boric acid had acceptable gel properties. Propolis and boric acid containing disinfectant gel formulation included lower alcohol level than the WHO-recommended formulation showed a similar bactericidal and fungicidal activity with WHO-recommended formulation.

Conclusions: Propolis and boric acid-containing disinfectant gel formulations were successfully produced. Final formulation with a lower alcohol level might be an alternative for the WHO-recommended formulation with similar effectiveness.

Key Words: Disinfectant, propolis, boric acid, COVID-19, hydroalcoholic gel, carbomer

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ÖZET

Amaç: COVID-19 salgını nedeniyle dünya genelinde dezenfektanlara olan ihtiyaç artmıştır. Eğer suya erişim kısıtlı ise, DSÖ tarafından alkol bazlı dezenfektanların kullanılması önerilmektedir. Bu çalışmada, DSÖ tarafından önerilen formülasyondan daha düşük alkol oranına sahip propolis ve borik asit içeren dezenfektan jel formülasyonları geliştirilmiştir.

Yöntemler: Propolis ve borik asit içeren dört farklı jel formülasyonu geliştirilmiştir. Geliştirilen fomülasyonlara, cilt üzerinde sıvı çözelti formülasyonlarından daha uzun süre kalmasını sağlamak için jelleştirici madde ilave edilmiştir. Formülasyonların tekstür profili analizleri, sürülebilirlik ve yapışma testleri değerlendirilmiştir. Karakterizasyon çalışmalarından sonra, bakterisidal ve fungisidal aktivite çalışmaları, son ve DSÖ tarafından önerilen formülasyonlar ile gerçekleştirilmiştir.

Bulgular: Jelleştirici madde oranının artırılmasının viskozite, yapışma ve tekstür değerlerini artırdığı gösterilmiştir. Propolis ve borik asit içeren son formülasyon kabul edilebilir jel özelliklerine sahiptir. Propolis ve borik asit içeren daha düşük alkol oranına sahip dezenfektan jel formülasyonu, DSÖ tarafından önerilen formülasyon ile benzer bakterisidal ve fungisidal aktivite göstermiştir.

Sonuçlar: Propolis ve borik asit içeren dezenfektan jel formülasyonları başarıyla üretilmiştir. Geliştirilen son formülasyon, DSÖ tarafından önerilen formülasyondan daha düşük alkol seviyesine ve benzer etkinliğe sahip bir alternatif olabilir.

Anahtar Sözcükler: Dezenfektan, propolis, borik asit, COVID-19, hidroalkolik jel, karbomer

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INVESTIGATION OF HISTAMINE LEVELS IN PASTEURIZED, HIGH HEAT-TREATED MILK AND TYPES OF CHEESE

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ABSTRACT

Histamine is the most common and toxic biogenic amine in foods. The presence of histamine in some foods is considered as an indicator of microbiological quality and hygiene. In this study, it was aimed to investigate the amount of histamine in some milk and cheese consumed in Ankara. A total of 116 samples of 20 different pasteurized milk, 20 high heat-treated milk and 76 cheese samples (tulum cheese, white cheese, fresh kashar cheese, and labne cheese) were analyzed by enzyme-linked immunosorbent assay (ELISA) technique. As a result, In 29 (72.5%) of 40 milk samples, the presence of histamine was detected in concentrations ranging between 0.10 and 0.32 mg/L. The mean levels (±S.E) of histamine of milk samples were found to be 0.18±0.01 mg/L. In 58 (76.3 %) of 76 cheese samples, the presence of histamine was detected in concentrations ranging between 2.52 and 189.79 mg/kg. Regarding the tulum cheese, white cheese, fresh kashar cheese, and labne cheese samples, mean levels (±SE) of histamine in were found to be 56.60±12.56 mg/kg, 3.68±0.29 mg/kg; 4.88±0.35 mg/kg and 4.48±0.39 mg/kg, respectively. The mean levels of histamine of cheeses were higher than mean levels of histamine of milk. The differences between mean levels of histamine in milk samples and the mean levels of histamine in cheese samples were statistically significant (P<0.001). At present, there are no established limits on Turkish Food Codex for histamine concentrations in milk and cheeses.

Keywords: Cheese, ELISA, Histamine, Milk

INTRODUCTION

Milk has special importance in the nutrition of people and especially children due to its rich nutritional content including protein and calcium (**Er *et al.*, 2010; Er Demirhan *et al.*, 2015**). Milk products should be safe in health as they are included in the diet and its consumption is required in all age groups. (**Erkan *et al.*, 2018**). Pathogenic microorganisms that may arise from raw milk pose a risk in cheese production (**Duckova *et al.*, 2020**). Starter cultures used in cheese production are mixed cultures of different microorganisms, and functions of starter cultures are lactic acid production, the formation of sensory active compounds and antimicrobial effect (**Květoslava *et al.*, 2020**). Food safety and quality are a major concern of consumer and health care organizations around the world (**Ruiz-Capillas and Herrer, 2019**). Foodborne diseases caused by microorganisms, biotoxins and chemical pollutants pose a serious risk to human health (**Samandoulougou *et al.*, 2015**). The occurrence of toxic compounds has a negative impact on the safety and nutritional value of foods (**Er Demirhan *et al.*, 2015**).

Histamine that is the causative agent of scombroid poisoning, is biogenic amine and is produced by microorganisms (**Er *et al.*, 2014**). Histamine is formed by microbial decarboxylation of histidine amino acid by the histidine decarboxylase enzyme. Generally, fresh foods do not contain histamine. (**Stratton *et al.*, 1991; Ede, 2017**). During the food processing steps, the microbial activity could cause the production of histamine (**Er *et al.*, 2014**).

Histamine could cause foodborne intoxication. Alcoholic beverages such as red wine and beer, and various foods such as milk, fish, cheese, fruits, vegetables, sausages, and salami are considered as histamine-rich foods (**Worm *et al.*, 2009; Švarc-Gajic and Stojanovic, 2011; Er *et al.*, 2014; Diaz *et al.*, 2015; Diaz *et al.*, 2018**). The histamine content increases in the improper food processing of milk and milk products. Normally, fresh milk contains very low levels of histamine, while commercially sold pasteurized or ultra-high temperature (UHT) milk is reported to have a higher histamine content. A significant increase in histamine content is observed with the fermentation of milk (**Bodmer *et al.*, 1999**). In particular, cheese is one of the most ideal mediums in the formation of biogenic amine (**Vale and Gloria, 1998; Budak *et al.*, 2008; Spizzirri *et al.*, 2013**). Many factors are effective in the formation of histamine in cheese. These factors could be specified as starter culture used in cheese making, pH of cheese, salt concentration, contamination during production, storage temperature and ripening time. The highest histamine production occurs during the ripening of the cheeses. This is explained by the degradation of proteins into free amino acids (**Madejska *et al.*, 2018**).

Although histamine has important physiological functions in humans, consuming food or beverages containing high amounts of histamine can lead to histamine poisoning, which causes symptoms such as headache, diarrhea, asthma, hypotension, pruritus, urticaria, and dizziness (**Joosten and Nunez, 1996; Leszczyńska *et al.*, 2004; Er *et al.*, 2014; Diaz *et al.*, 2018**). Generally, in case of a low level of histamine exposure, histamine could not be absorbed by the gastrointestinal (GI) tract. Otherwise, histamine is absorbed by the GI tract and histamine intoxication occurs due to the high level of histamine intake and the increase of the blood histamine levels (**Taylor, 1986; Er *et al.*, 2014**). Healthy people are able to rapidly detoxify dietary histamine by amine oxidases, but histamine detoxification capacity can be exceeded by the accumulation of histamine, thereby histamine toxicity could occur (**Maintz and Novak, 2007; Cheng *et al.*, 2011; Akan and Demiraş, 2018**). In this case, people with low diamine oxidase (DAO) enzyme activity are at risk for histamine toxicity (**Maintz and Novak, 2007**). However, toxicological reactions may also occur after food intake containing relatively high amounts of histamine. Histamine intolerance is due to the accumulation of histamine in the human system (**Rai *et al.*, 2014**). Consumption of histamine-rich food or drugs that histamine release or block the DAO can cause diarrhea, headache, rhinoconjunctival symptoms, asthma, hypotension, arrhythmia, urticaria, pruritus, redness and other disorders in patients with histamine intolerance. In this instance, symptoms can be reduced with a histamine-free diet or eliminated by antihistamines (**Maintz and Novak, 2007**). The presence of histamine has no positive effect on foodstuffs and reduces the quality of food. Thus, the determination of histamine levels in food is necessary to indicate deterioration and quality. Fresh and suitably stored or processed foods and beverages have low histamine content. However, products with lower histamine content in the same type of food are of better quality (**Bodmer *et al.*, 1999**).

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PHARMACOGNOSIE

Protective Effect of Boswellic Resin Against Memory Loss and Alzheimer's Induced by Aluminum Tetrachloride and D-Galactose (Experimental study in Mice)

Effet protecteur de la résine boswellique sur la perte de mémoire et la maladie d'Alzheimer induite par le tétrachlorure d'aluminium et le D-galactose (étude expérimentale chez la souris)

K. Zerrouki · N. Djebli · L. Gadouche · I. Erdogan Orhan · F. SezerSenol Deniz · S. Aslan Erdem

Abstract Nowadays, because of the industrialization, a lot of contaminant were available ; the consequences of this availability are apparition of diseases including neurodegeneration. Neurodegenerative diseases of the human brain comprise a variety of disorders that affect an increasing percentage of the population. This study is based on the effect of the Boswellic resin, which is from a medicinal plant and known for its antioxidant effects on nerve cell damage. The objective of this work was to evaluate the in vitro and in vivo effects of the Boswellic resin on anticholinesterase activity and Alzheimer's disease (AD) induced by D-galactose and aluminum tetrachloride in Swiss mice. Chemical composition of the resin essential oil was identified by the CG-MS analysis. The antioxidant activity was also assessed by the DMPD and metal chelation methods. In order to understand the mechanism of memory improvement, the acetylcholinesterase, AChE, and butyrylcholinesterase, BChE, inhibitory assays were performed. In vivo part of the study was achieved on Swiss mice divided into four groups: control, AD model, treated AD, and treated control group. The identification of chemical composition by CG-MS reach the 89.67% of the total extract compounds presented some very important molecules (*p*-Cymene, *n*-Octyl acetate, α-Pinene…). The present study proves that Boswellic resin improves memory and learning in treated Alzheimer's group, modulates the oxidative stress and be involved in the protective effect against amyloid deposition and neurodegeneration, and stimulates the immune system in mice's brain.

Keywords Neurotoxicity · Alzheimer's · Memory · Neuroprotection · Boswellic resin

Résumé Les maladies neurodégénératives du cerveau comprennent divers troubles qui touchent un pourcentage croissant de la population. Cette étude est fondée sur l'effet de la résine boswellique, une plante médicinale reconnue pour ses effets antioxydants sur les lésions des cellules nerveuses. L'objectif de ce travail était d'évaluer les effets in vitro et in vivo de la résine boswellique sur l'activité anticholinestérasique et la maladie d'Alzheimer (AD) induites par le D-galactose et le tétrachlorure d'aluminium chez la souris (Swiss). La composition chimique de l'huile essentielle de la résine a été identifiée par l'analyse CG-MS. L'activité antioxydante a également été évaluée par les méthodes DMPD et de chélation des métaux. Afin de comprendre le mécanisme d'amélioration de la mémoire, les tests d'inhibition d'AChEet de BChE ont été réalisés. La partie in vivo de l'étude a été réalisée sur des souris Swiss divisées en quatre groups : Témoin, modèle Alzheimer AD, Alzheimer traité et un groupe témoin traité. L'identification de la composition chimique par CG-MS atteint les 89,67 % du total des composés extraits, présentait une molécule très importante (p-Cymène, acétate de n-Octyle, α-pinène…). La présente étude prouve que la résine boswellique a amélioré la mémoire et l'apprentissage des souris model Alzheimer traité, module le stress oxydatif et est impliquée dans l'effet protecteur sur le

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Review

Anticancer Potential of Furanocoumarins: Mechanistic and Therapeutic Aspects

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Abstract: Cancer is one of the most extreme medical conditions in both developing and developed countries around the world, causing millions of deaths each year. Chemotherapy and/or radiotherapy are key for treatment approaches, but both have numerous adverse health effects. Furthermore, the resistance of cancerous cells to anticancer medication leads to treatment failure. The rising burden of cancer overall requires novel efficacious treatment modalities. Natural medications offer feasible alternative options against malignancy in contrast to western medication. Furanocoumarins' defensive and restorative impacts have been observed in leukemia, glioma, breast, lung, renal, liver, colon, cervical, ovarian, and prostate malignancies. Experimental findings have shown that furanocoumarins activate multiple signaling pathways, leading to apoptosis, autophagy, antioxidant, antimetastatic, and cell cycle arrest in malignant cells. Additionally, furanocoumarins have been shown to have chemo preventive and chemotherapeutic synergistic potential when used in combination with other anticancer drugs. Here, we address different pathways which are activated by furanocoumarins and their therapeutic efficacy in various tumors. Ideally, this review will trigger interest in furanocoumarins and their potential efficacy and safety as a cancer lessening agents.

Keywords: furanocoumarin; apoptosis; autophagy; metastasis; cell cycle arrest

1. Introduction

Cancer exacts one of the greatest medical tolls on humankind, requiring a proactive procedure for prevention and treatment. An enormous number of patients succumb to cancer every year. It is one of the chief reasons for mortality around the world, and the number of cases is continually expanding and estimated to reach 21 million by 2030. The lack of efficient anticancer treatments remains a clinical problem [1,2]. Chemotherapy and/or radiotherapy are the main clinical approaches to cancer treatment, yet both have documented adverse effects [3–6]. Cancer treatment affects not only rapidly multiplying cancerous cells but also normal body cells (bone marrow, gastrointestinal tract (GIT), and hair follicles); therefore, these treatments may give rise to severe adverse symptoms. Moreover, quick disposal and

Drug Discovery Today • Volume 25, Number 12 • December 2020 REVIEWS

ELSEVIER

Teaser We review recent advances in the field of preparation and synthesis of indispensable anticoagulant drugs, heparin, and related products.

Reviews • KEYNOTE REVIEW

Advances in the preparation and synthesis of heparin and related products

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Heparin is a naturally occurring glycosaminoglycan from livestock, principally porcine intestine, and is clinically used as an anticoagulant drug. A limitation to heparin production is that it depends on a single animal species and potential problems have been associated with animal-derived heparin. The contamination crisis in 2008 led to a search for new animal sources and the investigation of non-animal sources of heparin. Over the past 5 years, new animal sources, chemical, and chemoenzymatic methods have been introduced to prepare heparin-based drugs. In this review, we describe advances in the preparation and synthesis of heparin and related products.

Introduction

Heparin is a natural polysaccharide derived from animal tissues and has been widely used in clinics as an anticoagulant for over 80 years [1,2]. Similar to many other natural products, such as hormones or neurotransmitters, heparin was discovered accidentally [3]. The heparin story started around a century ago. By the end of the 19th century, an enzyme inhibitor, called antithrombin (AT), was suggested to exhibit anticoagulant activity [4]. Heparin, isolated from dog liver, was discovered by Jay McLean in 1916 [5]. By the late 1930s, heparin was shown to be an effective anticoagulant in the presence of a plasma component called 'heparin-cofactor' [6]. The presence of a relationship between heparin-cofactor and AT was understood during the 1950s and it was suggested that AT activity was catalyzed by heparin [7,8]. Pure AT was isolated for the first time in 1968 by Abildgaard [9] and, finally, during the early 1980s following extensive research, a unique pentasaccharide, corresponding to the AT-binding site in heparin, was characterized [10,11].

Heparin, the most negatively charged biological molecule, is a highly sulfated member of the glycosaminoglycan (GAG) family. The GAG family comprises heparin, heparan sulfate (HS),

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Sultan N. Baytas received her PhD in medicinal chemistry from Gazi University in 2002, did her postdoctoral studies at Rensselaer Polytechnic Institute, and is currently a professor of pharmaceutical chemistry at Gazi University, Faculty of Pharmacy. Her research activities include the design, discovery, and development of new molecules for pathologies associated with infections, thrombosis, cancer development, and inflammation. She is currently on sabbatical leave, working with Robert J. Linhardt's group at Rensselaer Polytechnic Institute focusing on the chemoenzymatic synthesis of glycosaminoglycans.

Robert J. Linhardt received his PhD in chemistry from Johns Hopkins University in 1979 and did his postdoctoral studies at Massachusetts Institute of Technology. He is currently the Anne and John Broadbent, Jr. '59 Senior Constellation Chair in Biocatalysis and Metabolic Engineering at Rensselaer Polytechnic Institute. His research focuses on glycoscience, and he is an expert on glycosaminoglycans and their synthesis, biology, and analysis. He has received multiple honors, including the National Academy of Inventors (NAI) Fellow, American Chemical Society Horace S. Isbell, Claude S. Hudson, and Melville L. Wolfrom Awards, the AACP Volwiler Research Achievement Award, the Society of Glycobiology Karl Meyer Award, and the Scientific American 10.

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nutrients

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Review

Almonds (*Prunus Dulcis* Mill. D. A. Webb): A Source of Nutrients and Health-Promoting Compounds

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Abstract: Almonds (*Prunus dulcis* Miller D. A. Webb (the almond or sweet almond)), from the Rosaceae family, have long been known as a source of essential nutrients; nowadays, they are in demand as a healthy food with increasing popularity for the general population and producers. Studies on the composition and characterization of almond macro- and micronutrients have shown that the nut has many nutritious ingredients such as fatty acids, lipids, amino acids, proteins, carbohydrates, vitamins and minerals, as well as secondary metabolites. However, several factors affect the nutritional quality of almonds, including genetic and environmental factors. Therefore, investigations evaluating the effects of different factors on the quality of almonds were also included. In epidemiological studies, the consumption of almonds has been associated with several therapeutically and protective health benefits. Clinical studies have verified the modulatory effects on serum glucose, lipid and uric acid levels, the regulatory role on body weight, and protective effects against diabetes, obesity, metabolic syndrome and cardiovascular diseases. Moreover, recent researchers have also confirmed the prebiotic potential of almonds. The present review was carried out to emphasize the importance of almonds as a healthy food and source of beneficial constituents for human health, and to assess the factors affecting the quality of the almond kernel. Electronic databases including PubMed, Scopus, Web of Science and SciFinder were used to investigate previously published articles on almonds in terms of components and bioactivity potentials with a particular focus on clinical trials.

Keywords: almonds; secondary metabolites; health-promoting properties; almond composition; clinical trials

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The effect of environmental Bisphenol A exposure on breast cancer associated with obesity

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ARTICLE INFO

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Telomerase activity
Telomere length
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ABSTRACT

Bisphenol A (BPA) is a widely used endocrine disrupter. Its environmental exposure is a causative factor of cell aging via decreasing telomerase activity, thus leading to shortening of telomere length. Epidemiological studies confirm positive associations between BPA exposure and the incidence of obesity and type 2 diabetes (T2DM). Increased urinary BPA levels in obese females are both significantly correlated with shorter relative telomere length and T2DM. BPA is a critically effective endocrine disrupter leading to poor prognosis via the obesity-inflammation-aromatase axis in breast cancer. Environmental BPA exposure contributes to the progression of both estrogen dependent and triple negative breast cancers. BPA is a positive regulator of human telomerase reverse transcriptase (hTERT) and it increases the expression of hTERT mRNA in breast cancer cells. BPA exposure can lead to tamoxifen resistance. Among patients treated with chemotherapy, those with persistent high telomerase activity due to BPA are at higher risk of death.

1. Introduction

Bisphenol A (BPA) is an industrial chemical that acts as an environmental endocrine disrupter with estrogenic activity. It is widely used to make consumer products, including certain plastics; like polycarbonate, epoxy resin, as well as thermal paper, and additionally BPA can leach from dental sealants (Arenholt-Bindslev et al., 1999; Legeay and Faure, 2017; Sajiki and Yonekubo, 2003; Sonavane and Gassman, 2019). Chronic BPA exposure has been shown to be connected with an increased rate of various age-related diseases. Growing evidences indicate that the induction of reactive oxygen species (ROS) by BPA is the main driving factor of its toxicity and carcinogenic potential. Furthermore, as the consequence of BPA exposure, oxidative stress is induced and this leads to the expedition of the aging process (Rochester, 2013; Seachrist et al., 2016; Tan et al., 2015). Numerous clinical studies revealed that shorter telomere length and decreased telomerase activity are associated with age-related disorders and premature death. The environmental exposures like BPA appear to be causative factors that promote cell aging mechanisms, mainly by decreasing telomerase activity and leading to telomere length shortening and cell senescence. Since telomerase activity is a dynamic process, it is thought to be an essential alterable determinant in mediating environmental and lifestyle factors (Epel, 2009; Lin et al., 2010). Thus, without a functional telomerase, a cell undergoing cell division will have progressive telomere shortening. This leads to the telomere-dependent replicative senescence and disruption of the division capacity of the cell so that mitosis halts when a "critically" short telomere length is reached (Hallows et al., 2012). Telomere linked cellular senescence can further be a contributing factor in age-related diseases. Thus, proliferative senescence occurs with the accompanying evidence of telomere shortening as a hallmark of oxidative stress and related diseases. It is thought that slowing down the rate of telomere shortening could slow down the human aging process. (Babizhayev et al., 2014). BPA suppresses the activity of telomerase, while increasing DNA damage frequency. Indeed, epidemiological studies put forward the link between BPA exposure and the risks of obesity, type 2 diabetes mellitus (T2DM) and breast cancer (Herz et al., 2017; Hwang et al., 2018; Kim et al., 2017; Legeay and Faure, 2017). This review discusses the body of literature that highlights the adverse effects of environmental BPA exposure and telomere shortening on breast cancer patients, who suffer from obesity and type 2 diabetes.

2. BPA and obesity

Accumulating data have demonstrated that increased BPA exposure

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Review

The effect of environmental pollution on immune evasion checkpoints of SARS-CoV-2

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ABSTRACT

Many diverse strategies allow and facilitate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to evade antiviral innate immune mechanisms. Although the type I interferon (IFN) system has a critical role in restricting the dissemination of viral infection, suppression of IFN receptor signals by SARS-CoV-2 constitutes a checkpoint that plays an important role in the immune escape of the virus. Environmental pollution not only facilitates SARS-CoV-2 infection but also increases infection-associated fatality risk, which arises due to Systemic Aryl hydrocarbon Receptor (AhR) Activation Syndrome. The intracellular accumulation of endogenous kynurenic acid due to overexpression of the indoleamine 2,3-dioxygenase (IDO) by AhR activation induces AhR-interleukin-6 (IL-6)-signal transducers and activators of the transcription 3 (STAT3) signaling pathway. The AhR-IDO1-Kynurenine pathway is an important checkpoint, which leads to fatal consequences in SARS-CoV-2 infection and immune evasion in the context of Treg/Th17 imbalance and cytokine storm.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was firstly identified in Wuhan, China in December 2019, rapidly spread all over the world. Whilst the number of cases to date exceeds 37 million worldwide, more than one million people have died due to this virus infection (Coronavirus Update (Live), 2020). Although the pathogenesis of SARS-CoV-2 infection is still not completely clarified, a four-stage classification is proposed for the course of disease (From the American Association of Neurological Surgeons (AANS), American Society of Neuroradiology (ASNR), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), Canadian Interventional Radiology Association (CIRA), Congress of Neurological Surgeons (CNS), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), European Stroke Organization (ESO), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), and World Stroke Organization (WSO) et al., 2018; Rizk et al., 2020; Rodríguez et al., 2020; Siddiqi and Mehra, 2020).

SARS-CoV-2 enters cells via angiotensin-converting enzyme 2 (ACE2) by activating viral spike glycoproteins (SARS-2-S) through transmembrane protease serine 2 (TMPRSS2) (Engin et al., 2020a; Lei et al., 2020; Letko et al., 2020). However, the crosstalk between the SARS-CoV-2 and host innate immunity is poorly understood (Lei et al., 2020). Upregulation of ACE2 or higher ACE2 gene expression may increase susceptibility to infection by SARS-CoV-2 (Brake et al., 2020). Unfortunately, SARS-CoV-2 not only effectively uses a critical and unique system which is ACE2, to enter and multiply in the host (Ghebrawi et al., 2020), but also its binding to ACE2 allows it to evade immune surveillance. The engulfment of ACE2 provides the virus access to the host cells system, thereby viral proliferation and immune evasion are strongly linked with a successful and potentially devastating infection (Brake et al., 2020). Thus, despite all the preventive measures, the rate of COVID-19 began to rise again, over second half of 2020. Most probably, one of the important contributing factors for the continuation of the pandemic is that environmental pollution negatively modulates the host's immune response.

In this context, epidemiological data regarding COVID-19 from 110 Italian provinces confirmed that environmental pollution facilitates SARS-CoV-2 infection and increases the infection-associated fatality risk (Borro et al., 2020). Specifically, the adverse health effects of traffic-related daily ambient particulate matter pollution result from their chemical components like polycyclic aromatic hydrocarbons

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Review or Mini-review

Dual function of sialic acid in gastrointestinal SARS-CoV-2 infection

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ARTICLE INFO

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SARS-CoV-2
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Chloroquine
ACE2
Faecal-oral route

ABSTRACT

Recent analysis concerning the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)- angiotensin converting enzyme (ACE) receptor interaction in enterocytes, the definition of gut-lung axis, as well as the molecular basis of sialic acid-related dual recognition concept in gastrointestinal SARS-CoV-2 infection, have brought a new perspective to potential therapeutic targets. In this review evolving research and clinical data on gastrointestinal SARS-CoV-2 infection are discussed in the context of viral fusion and entry mechanisms, focusing on the different triggers used by coronaviruses. Furthermore, it is emphasized that the viral spike protein is prevented from binding gangliosides, which are composed of a glycosphingolipid with one or more sialic acids, in the presence of chloroquine or hydroxychloroquine. In gastrointestinal SARS-CoV-2 infection the efficiency of these repositioned drugs is debated.

1. Introduction

Human coronaviruses (hCoVs) are a large family of pathogenic enveloped viruses that carry a single strand of RNA. Infection with these viruses generally results in mild to moderate respiratory system disorders, which can also be fatal in some vulnerable individuals. (Graham et al., 2013). To date, six hCoV strains have been identified and classified into four groups. Among these, one of the group B β-CoVs, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the microorganism responsible for the 2019 pandemic coronavirus disease (COVID-19) (Huang et al., 2015). Although the transmission via respiratory tract is the principal exposure route for this disease, the faecal-oral route of transmission should not be ignored. Many hypotheses have been proposed regarding why COVID-19 causes significant gastrointestinal symptoms. Firstly, recent analysis revealed that angiotensin-converting enzyme-2 (ACE2) despite being highly expressed in alveolar cells in the lung, it is also expressed on a large scale in the glandular epithelial cells of gastrointestinal system. Thus, it is accepted that interaction between SARS-CoV-2 and ACE2 may mediate gastrointestinal symptoms (Liang et al., 2020; Zhang et al., 2020a). Secondly, SARS-CoV-2 indirectly damages the gastrointestinal epithelial cells via initiating a cascade of inflammatory reactions. The bacterial abundance of the gastrointestinal system reciprocally influences the respiratory tract through the "gut-lung axis" (Budden et al., 2017; Pan et al., 2020). The third option is that dual recognition of gangliosides and ACE2 by the spike (S) protein of SARS-CoV-2 leads to malabsorption, unstable gut secretion and hyperactive enteric motility (Matrosovich et al., 2015; Zhang et al., 2020a). Recently, the presence of mutual recognition systems by the use of sialic acid (SIA) and sugar chains, between viruses and their host cells has focused interest on this research area leading to the accumulation of knowledge in the field of "sialoglycovirology." (Sriwilaijaroen and Suzuki, 2020). In this context, receptor-related approaches for determination of the binding sites on host and virus proteins will clarify the perspective in potentially drug repurposing and developing new drug candidates for COVID-19.

2. Gastrointestinal SARS-CoV-2 infection

In a meta-analysis reviewing 60 different investigations, a total of 4243 cases had digestive system symptoms and this distribution calculated as 17.6 % in average. In this series of patients, 48 % of the stool specimens were RNA virus positive, although 70 % of them were taken after the disappearance of virus from respiratory tract (Cheung et al., 2020; Grassia et al., 2020). Nationwide data from China showed that 8.7 % of 1099 SARS-CoV-2 confirmed patients had gastrointestinal symptoms (Guan et al., 2020). In another study, among the 651 cases with COVID-19, the proportion of patients with gastrointestinal symptoms was found to be 11.4 %. Increased tendency to suffer from gastrointestinal symptoms among the patients with COVID-19 enhances the risk of contamination in healthcare workers who treat the suspected

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Review or Mini-review

Two important controversial risk factors in SARS-CoV-2 infection: Obesity and smoking

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ABSTRACT

The effects of obesity and smoking in the coronavirus disease 2019 (COVID-19) pandemic remain controversial. Angiotensin converting enzyme 2 (ACE2), a component of the renin-angiotensin system (RAS), is the human cell receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19. ACE2 expression increases on lung alveolar epithelial cells and adipose tissue due to obesity, smoking and air pollution. A significant relationship exists between air pollution and SARS-CoV-2 infection, as more severe COVID-19 symptoms occur in smokers; comorbid conditions due to obesity or excess ectopic fat accumulation as underlying risk factors for severe COVID-19 strongly encourage the virus/ACE2 receptor-ligand interaction concept. Indeed, obesity, air pollution and smoking associated risk factors share underlying pathophysiologies that are related to the Renin-Angiotensin-System in SARS-CoV-2 infection. The aim of this review is to emphasize the mechanism of receptor-ligand interaction and its impact on the enhanced risk of death due to SARS-CoV-2 infection.

1. Introduction

Viral infection aggression is linked to both environmental and genetic factors. Although the mortality in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is highly age dependent, the etiology of the coronavirus disease 2019 (COVID-19)-specific mortality in these patients is largely unknown (Lyons-Weiler, 2020). SARS-CoV-2 has a size of 60−140 nm. Nasal or saliva droplet aerosols from infected individuals provide an efficient means of transport for the viral particles, as well as attachment to suspended fine particles in air (Woon Fong Leung and Sun, 2020). Positive correlations of PM2.5, PM10, nitrogen dioxide (NO_2) and ozone (O_3) levels with cases confirmed with new COVID-19 underlines the how air pollution is assisting in the propagation of SARS-CoV-2 infection (Zhu et al., 2020). Angiotensin-converting enzyme-2 (ACE2) protein provides the host cellular entry point for SARS-CoV-2 (Battistoni and Volpe, 2020). Thus, the relationship between ACE2 and SARS-CoV-2 is pivotal in the infection process (Ge et al., 2013; Gheblawi et al., 2020; Qin et al., 2020). If these receptors are inhibited by the angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin II type-I receptor blockers (ARBs), a concomitant fall in inflammation might occur via diminished viral invasion of tissues such as the lungs and the heart (Rico-Mesa et al., 2020). Conversely, upregulation of ACE2 or higher ACE2 gene expression may increase susceptibility to infection by SARS-CoV-2, and COVID-19 disease severity (Brake et al., 2020). Tobacco smokers have a greater predisposition (1.4 fold) to developing severe symptoms of COVID-19. This often necessitates their entry into intensive care units (ICU), alongside concomitant mechanical ventilation; moreover, their death rate is approximately 2.4 times that of non-smokers (Guan et al., 2020; Vardavas and Nikitara, 2020). Among adults aged more than 65 years approximately 89 % suffer from one or more underlying comorbidities, including obesity (48 %), cardiovascular disease (28 %), hypertension (50 %) and diabetes mellitus (28 %) as well as chronic lung disease (35 %) (Garg et al., 2020). These comorbidities show a trend towards increased disposition to COVID-19 severe disease, but no specific significant association could be shown with active smoking and obesity and severity particularly in Chinese patients (Lippi and Henry, 2020; W. Liu et al., 2020). However, among the patients admitted to ICU for SARS-CoV-2, requiring invasive mechanical ventilation (IMV), the proportion of obese patients is high. This increase in the rate of patients who need IMV is significantly linked with being male and possessing a high body mass index (BMI) (Simonnet et al., 2020).

Recently, the low mortality rate in patients with acute respiratory distress syndrome (ARDS) with obesity and morbid obesity is defined as

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Review

Oxidative Stress and Marine Carotenoids: Application by Using Nanoformulations

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Abstract: Carotenoids are natural fat-soluble pigments synthesized by plants, algae, fungi and microorganisms. They are responsible for the coloration of different photosynthetic organisms. Although they play a role in photosynthesis, they are also present in non-photosynthetic plant tissues, fungi, and bacteria. These metabolites have mainly been used in food, cosmetics, and the pharmaceutical industry. In addition to their utilization as pigmentation, they have significant therapeutically applications, such as improving immune system and preventing neurodegenerative diseases. Primarily, they have attracted attention due to their antioxidant activity. Several statistical investigations indicated an association between the use of carotenoids in diets and a decreased incidence of cancer types, suggesting the antioxidant properties of these compounds as an important factor in the scope of the studies against oxidative stress. Unusual marine environments are associated with a great chemical diversity, resulting in novel bioactive molecules. Thus, marine organisms may represent an important source of novel biologically active substances for the development of therapeutics. Marine carotenoids (astaxanthin, fucoxanthin, β-carotene, lutein but also the rare siphonaxanthin, sioxanthin, and myxol) have recently shown antioxidant properties in reducing oxidative stress markers. Numerous of bioactive compounds such as marine carotenoids have low stability, are poorly absorbed, and own very limited bioavailability. The new technique is nanoencapsulation, which can be used to preserve marine carotenoids and their original properties during processing, storage, improve their physiochemical properties and increase their health-promoting effects. This review aims to describe the role of marine carotenoids, their potential applications and different types of advanced nanoformulations preventing and treating oxidative stress related disorders.

Keywords: bioavailability; carotenoids; marine; nanoformulation; oxidative stress; reactive oxygen species

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REVIEW ARTICLE

The Main Targets Involved in Neuroprotection for the Treatment of Alzheimer's Disease and Parkinson Disease

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Abstract: With respect to the total cure failure of current drugs used in the treatment of neurodegenerative diseases, alternative strategies are followed. Particularly, neuroprotection approaches are questioned. Metal chelation, antioxidant towards oxidative stress, modulation of the amyloidogenic pathway, MAO-B inhibition, and NMDA receptor antagonism is more or less typical examples. Some of the representative drug candidates with promising neuroprotective features are assessed in clinical trials. Although initial attempts were found hopeful, none of the candidates have been found successful in each required clinical trials, particularly depending on the failures in terms of cognitive enhancement and slowing the progressive characteristics of neurodegenerative diseases. Today, neuroprotection is evaluated using multi-target ligand-based drug design studies. Within this study, the clinical outcomes of these studies, the rationale behind the design of the molecules are reviewed concomitant to the representative drug candidates of each group.

Keywords: Neurodegeneration, neuroprotection, amyloidogenic pathway, monoamine oxidase, iron chelator, antioxidant, cholinesterase, NMDA receptor, nitric oxide.

1. INTRODUCTION

Some severe central nervous system (CNS) disorders, generated through the development of neurodegeneration, are characterized by neuronal cell loss. These disease states mainly include Alzheimer's disease (AD) and Parkinson's disease (PD) as well as the rare CNS diseases such as Huntington's disease (HD) and multiple sclerosis (MS) [1-5] , in which various pathophysiological cascades are involved throughout their development [6-7]. The common point about them is their progressive neurodegenerative characteristics ending up with the death of neuronal cells [8] . Unfortunately, the majority of the current drugs employed for the current treatment of neurodegenerative disorders mainly target the relief of the symptoms associated with each disease state. In other words, the drugs used for their treatment generally lack the feature of preventing neurodegeneration and their progressive character and only available for symptomatic treatment. This is partially related to the deficiency of the information on the pathology leading to the formation of these CNS disorders [9] .

Indeed, currently, the clinical outcomes of the neurodegenerative disorders are well-described including the developmental stages [10-13] . Therefore, the majority of the efforts performed so far in relevant drug design studies have been provided to limit the symptoms of each disease state depending on the phase. However, these drugs, as aforementioned, are generally not capable of providing features to prevent the progress, which leads to the comment that they lack the total cure of neurodegenerative disease states [14-17] .

Regarding the incidence of both AD and PD, particularly in the elderly, numerous studies have been conducted within the last half-century both to understand the pathophysiological cascades involved and to design novel drug molecules for their treatment [18] . AD is well-characterized with the development of progressive cognitive failures (*i.e.*, it is the most common form of dementia). The clinical studies indicate the significance of acetylcholine acting on cholinergic receptors to continue regular cognitive functions [19-20] . Rivastigmine, galantamine, and donepezil are the three cholinesterase inhibitory molecules used for the symptomatic treatment of AD (Fig. 1). Since cholinesterase (ChE) enzymes (*i.e.*, acetylcholinesterase and butyrylcholinesterase) are responsible for the metabolic degradation of acetylcholine, the inhibition of ChE enzymes in CNS increases both the available amounts of acetylcholine and the number of cholinergic receptors agonized by acetylcholine [21-22] . Besides, another strategy is followed through the employment of memantine, a partial N-methyl-D-aspartate (NMDA) receptor antagonist. NMDA receptors are activated by excitatory amino acids (*e.g.*, particularly with glutamate) and it is believed that excessive stimulation of these receptors triggers both neuronal excitotoxicity and cognition problems (Fig. 1) [23] . However, none of these treatments (*i.e.*, neither cholinesterase inhibition nor NMDA receptor antagonism) have been shown to possess disease-modifying characteristics [24] . Moreover, cholinergic dysfunction is not the only system affected within the development of AD, since serotoninergic, adrenergic, and dopaminergic systems have also been shown to be deregulated [25] .

PD, on the other hand, has been related to dopaminergic dysfunction. From this point of view, the current drugs used for the treatment of PD are, in one way or another, associated with the therapeutic approaches utilizing the mechanisms for the elevation of dopaminergic function such as the Levodopa, a dopaminergic receptor agonist, monoamine oxidase B (MAO-B) inhibitor, catechol-O-methyltransferase (COMT) inhibitor, or dopamine agonist employment. Similar to the clinical perspectives behind the AD treatment, none of these strategies followed for the PD treatment offers a radical treatment, since the pathophysiological cascades

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Review

Neuroprotective Effects of Quercetin in Alzheimer's Disease

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Abstract: Quercetin is a flavonoid with notable pharmacological effects and promising therapeutic potential. It is widely distributed among plants and found commonly in daily diets predominantly in fruits and vegetables. Neuroprotection by quercetin has been reported in several in vitro studies. It has been shown to protect neurons from oxidative damage while reducing lipid peroxidation. In addition to its antioxidant properties, it inhibits the fibril formation of amyloid-β proteins, counteracting cell lyses and inflammatory cascade pathways. In this review, we provide a synopsis of the recent literature exploring the relationship between quercetin and cognitive performance in Alzheimer's disease and its potential as a lead compound in clinical applications.

Keywords: quercetin; polyphenols; Alzheimer's disease; mechanistic insights; clinical directions

1. Introduction

Alzheimer's disease (AD) contributes to 60–80% of total dementia cases, and it mostly affects elder people (65 years of age or older) [1]. The pathogenesis of AD is typically associated with the accumulation of amyloid-β (Aβ) aggregates and the hyperphosphorylation of tau proteins, leading to neurofibrillary tangles (NFTs) and synaptic dysfunction [2–4]. Around 35.6 million people worldwide are estimated to be affected with AD, with a prevalence rate of 4.6 million new cases each year. The prevalence rate of AD increases with age: the rate doubles every 5 years from 60 years of age [5,6].

Early studies led to the cholinergic deficit hypothesis of AD, which states that deficiency in acetylcholine is the main cause of the disease. In the pursuit of drugs that are able to restore acetylcholine levels, the first acetyl cholinesterase inhibitors were developed, including tacrine. Since then, other drugs in the same class have been pursued, namely donepezil, rivastigmine, and galantamine. Current AD therapy consists of cholinesterase inhibitors and *N*-methyl-D-aspartate (NMDA) antagonists, including memantine. Acetyl cholinesterase inhibitors prevent the hydrolysis of acetylcholine, and memantine modulates NMDA receptor activity, causing a reduction in excitatory glutamate signals. However, these drugs offer little palliative effects, and they also have numerous undesirable safety profiles with a number of adverse side effects [7,8]. Acetyl cholinesterase inhibitors are associated with gastrointestinal side effects such as nausea, diarrhea, and abdominal pain, as well as urinary incontinence, insomnia, and nightmares. The use of tacrine has been limited because of its poor bioavailability and reported hepatotoxicity. Memantine is clinically less effective compared

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A phytopharmacological overview of medicinal plants used for prophylactic and treatment of colitis

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ABSTRACT

Inflammatory bowel diseases are chronic diseases that develop on the genetic background. They are characterized by an idiopathic, chronic course and periods of activation and remission. However, genetic and environmental factors are thought to play a role in its pathogenesis. Significant improvements in treatment strategies have been witnessed. Depending on the severity of the disease, mesalamine, immunosuppressants, anti-TNF, anti-integrin, Janus kinase inhibitors, and thiopurines can be used for treatment. However, these treatments have side effects such as headache, dizziness, nausea, loss of appetite, hair loss, gas, vomiting, rash, fever, and decreased white blood cell count. The search for treatment that may be a safer alternative, immunomodulatory, and immunosuppressive therapy has gained importance nowadays. Herbal medicine is preferred to treat a wide range of acute and chronic gastrointestinal diseases, including ulcerative colitis. Preclinical and clinical studies show that plants are promising in terms of their use in treating pathological conditions. The effectiveness of plants in treating ulcerative colitis has been determined. However, more studies are needed to explore the long-term effects of these herbal medicines. The present review presents information on medicinal plants and phytochemicals reported for use or potential of application in ulcerative colitis, a type of inflammatory bowel diseases.

1. Introduction

Inflammatory bowel diseases (IBDs) are lifelong chronic diseases with an idiopathic, chronic course on genetic background. They are characterized by periods of activation and remission and have adverse effects on physical, psychological, social, and professional functions. The course of the disease affects any part of the gastrointestinal tract, causing oedema, ulceration, bleeding, and fluid and electrolyte losses (Akyüz and Akyüz, 2011; Arslantaş et al., 2006; Avdal et al., 2011; Avşar and Kaşıkçı, 2009; Aydıntuğ, 1992; O'Connor et al., 2013; Stansfield et al., 2007; Stretton et al., 2014). The IBDs are of two types: ulcerative colitis (UC) and Crohn's disease (CD). The UC and CD affect different parts of the digestive system and show partially different symptoms. A comparative evaluation of UC and CD is presented in Table 1 (Molodecky et al., 2012).

The UC, first described by Samuel Wilks in 1859, is more common in the world compared with CD (Wilks, 1859). It is characterized by acute non-infectious inflammation of the colonic mucosa, which usually includes the rectum and can be proximal and elongated to include other parts of the colon (Baumgart, 2008; Cedas et al., 2012; Probert et al., 1992). Relapsing-remitting UC is an idiopathic disease which develops in the second or third decade of life and affects patients with clinical symptoms such as bloody diarrhea and rectal urgency tenesmus (Danese and Fiocchi, 2011; Meyers and Janowitz, 1989). At any time, 50% of patients are symptomatic, 30% have mild symptoms, and 20% have moderate symptoms (Hendriksen et al., 1985). It shows a clinical course characterized by exacerbations and remissions that may occur spontaneously or in response to treatment changes (Kornbluth et al., 1993;

Abbreviations: CD, Crohn's disease; FMT, fecal microbiota transplantation; GBF, Germinated barley foodstuff; GI, gastrointestinal; IBDs, Inflammatory bowel diseases; ICAM-1, intercellular adhesion molecule; IEC, intestinal epithelial cells; IL, interleukin; LPS, lipopolysaccharide; NF-κB, Nuclear Factor kappa B; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis.

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Review

Coumarins and Coumarin-Related Compounds in Pharmacotherapy of Cancer

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Abstract: Cancer is one of the most common causes of disease-related deaths worldwide. Despite the discovery of many chemotherapeutic drugs that inhibit uncontrolled cell division processes for the treatment of various cancers, serious side effects of these drugs are a crucial disadvantage. In addition, multi-drug resistance is another important problem in anticancer treatment. Due to problems such as cytotoxicity and drug resistance, many investigations are being conducted to discover and develop effective anticancer drugs. In recent years, researchers have focused on the anticancer activity coumarins, due to their high biological activity and low toxicity. Coumarins are commonly used in the treatment of prostate cancer, renal cell carcinoma and leukemia, and they also have the ability to counteract the side effects caused by radiotherapy. Both natural and synthetic coumarin derivatives draw attention due to their photochemotherapy and therapeutic applications in cancer. In this review, a compilation of various research reports on coumarins with anticancer activity and investigation and a review of structure-activity relationship studies on coumarin core are presented. Determination of important structural features around the coumarin core may help researchers to design and develop new analogues with a strong anticancer effect and reduce the potential side effects of existing therapeutics.

Keywords: Benzopyrone; coumarin; cancer; drug discovery; natural product

1. Introduction

Coumarins are polyphenolic compounds belonging a group of colorless and crystalline oxygenated heterocyclic compounds first isolated from the plant named *Dipteryx odorata* Willd. (Fabaceae) known locally as "coumaroun" by Vogel in 1820 [1,2]. Oxygenated heterocyclic compounds are furan derivatives with 4C atoms or pyran derivatives with 5C atoms. Although furan derivatives are rarely present in plants, pyran derivatives forming the structure of various compounds are encountered more frequently. The pyran derivatives are ketonic compounds that in the form of α-pyron or γ-pyron. Secondary metabolites called benzo-α-pyrone (coumarin) and benzo-γ-pyrone (chromone) occur due to condensation of pyron derivatives with benzene in plants [3,4].

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REVIEW ARTICLE

Roles of Medicinal Plants and Constituents in Gynecological Cancer Therapy: Current Literature and Future Directions

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Abstract: Gynecologic cancers, including cervical, primary peritoneal, ovarian, uterine/endometrial, vaginal and vulvar cancers and gestational trophoblastic disease, are characterized by abnormal cell proliferation in female reproductive cells. Due to the variable pathology of these cancers and the lack of appropriate screening tests in developing countries, cancer diagnosis can be reported in advanced stages in most women and this situation adversely affects prognosis and clinical outcomes of illness. For this reason, many researchers in the field of gynecological oncology have carried out many studies.

The treatment of various gynecological problems, which cause physical, biological and psychosocial conditions such as fear, shame, blame and anger, has been important throughout the history. Treatment with herbs has become popular nowadays due to the serious side effects of the synthetic drugs used in treatment and the medical and economical problems caused by them. Many scientists have identified various active drug substances through *in vivo* and *in vitro* biological activity studies on medicinal plants from the past to the present. While the intrinsic complexity of natural product-based drug discoveries requires highly integrated interdisciplinary approaches, scientific and technological advances and research trends clearly show that natural products will be among the most important new drug sources in the future.

In this review, an overview of the studies conducted for the discovery of multitargeted drug molecules in the rational treatment of gynecological cancers is presented.

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1. INTRODUCTION

Cancer is one of the most important medical problems of humanity, which evokes feelings of fear, hopelessness, helplessness, guilt, unbearable pain, abandonment and death. In developed countries, cancer (11.6 %) is the second leading cause of death after heart disease (40.6 %) [1]. According to the World Health Organization (WHO), it is estimated that there will be 27 million cancer cases in the year 2030, 17 million of which will result in death [1]. 53 % of cancer cases and 60 % of cancer-related deaths occur in underdeveloped countries [2].

Gynecologic cancers, including cervical, primary peritoneal, ovarian, uterine/endometrial, vaginal and vulvar cancers and gestational trophoblastic disease, are characterized by abnormal cell proliferation in tissues or organs of the female reproductive system [3-6]. Gynecologic cancers are one of the important causes of morbidity and mortality in women after breast cancer. In addition to being a medical, physical disease, it can cause many psychological problems in women diagnosed with gynecological cancer due to its fatal consequences [7, 8].

Each year, approximately 80,000 women are diagnosed with gynecological cancer, especially related to the ovary or uterine. In addition to the early detection of cancer at an early age, advances in medicine and technology increase the survival rate of such cancers [9, 10]. While cancer remains the second leading cause of death in the world, gynecological cancers are unfortunately increasing day by day.

Primary and secondary metabolites in different chemical structures that occur because of photosynthesis in plants play a role in various tasks such as plant development and self-defense. In addition to nutrition, mankind has used plants for thousands of years for treatment because of their rich chemical composition [11-14]. Furthermore, the interest in herbal medicine has increased in recent years due to the various harmful effects of synthetic drugs on humans and the environment. Today, it is aimed not only to treat patients but also to produce multifaceted solutions to the mass health prob-

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Research review paper

Flavonoid biosynthetic pathways in plants: Versatile targets for metabolic engineering

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ABSTRACT

Plants, fungi, and microorganisms are equipped with biosynthesis machinery for producing thousands of secondary metabolites. These compounds have important functions in nature as a defence against predators or competitors as well as other ecological significances. The full utilization of these compounds for food, medicine, and other purposes requires a thorough understanding of their structures and the distinct biochemical pathways of their production in cellular systems. In this review, flavonoids as classical examples of secondary metabolites are employed to highlight recent advances in understanding how valuable compounds can be regulated at various levels. With extensive diversity in their chemistry and pharmacology, understanding the metabolic engineering of flavonoids now allows us to fine-tune the eliciting of their production, accumulation, and extraction from living systems. More specifically, recent advances in the shikimic acid and acetate biosynthetic pathways of flavonoids production from metabolic engineering point of view, from genes expression to multiple principles of regulation, are addressed. Specific examples of plants and microorganisms as the sources of flavonoids-based compounds with particular emphasis on therapeutic applications are also discussed.

1. Introduction

Living organisms, particularly plants, fungi, and microorganisms, can synthesize various compounds known as primary metabolites, which are essential for vital processes, including photosynthesis and energy production/expenditure, as well as processes implicated in carbohydrate, fat, and protein metabolism. In addition to this group of fundamental compounds of life processes, there are a wide variety of molecules called secondary metabolites that include polyketides, terpenoids, phenylpropanoids, alkaloids, etc. They are generally known to

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Review

The role of glycogen synthase kinase 3 beta in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that leads to progressive neurological disability due to axonal deterioration. Although MS presents profound heterogeneity in the clinical course, its underlying central mechanism is active demyelination and neurodegeneration associated with inflammation. Multiple autoimmune and neuroinflammatory pathways are involved in the demyelination process of MS. Analysis of MS lesions has shown that inflammatory genes are upregulated. Glycogen synthase kinase-3 (GSK-3) is part of the mitogen-activated protein kinase (MAPK) family and has important roles in many signaling cascades. GSK-3 is a highly conserved serine/threonine protein kinase expressed in both the central and the peripheral nervous systems. GSK-3 modulates several biological processes through phosphorylation of protein kinases, including cell signaling, neuronal growth, apoptosis and production of pro-inflammatory cytokines and interleukins, allowing adaptive changes in events such as cellular proliferation, migration, inflammation, and immunity. GSK-3 occurs in mammals in two isoforms GSK-3α and GSK-3β, both of which are common in the brain, although GSK-3α is found particularly in the cerebral cortex, cerebellum, striated hippocampus and Purkinje cells, while GSK-3β is found in all brain regions. In patients with chronic progressive MS, expression of GSK-3β is elevated in several brain regions such as the corpus callosum and cerebral cortex. GSK-3β inhibition may play a role in glial cell activation, reducing pathological pain induced by nerve injury by formalin injection. According to the role of GSK-3β in pathological conditions, the aim of this article is review of the role of GSK-3β in multiple sclerosis and inflammation of neurons.

Abbreviations: GSKs, glycogen synthase kinases; MAPK, mitogen-activated protein kinase; PKA, protein kinase A; Akt, protein kinase B; PKC, protein kinase C; Wnt, wingless-int; MS, multiple sclerosis; CNS, central nervous system; TNFα, tumor necrosis factor alpha; TLR, toll-like receptor; IL, interleukin; OLP, oligodendrocyte precursors; CAMK II, Ca^{2+}/calmodulin; FZD, frizzled; DSH, dishevelled; APC, adenomatous polyposis coli; CK1, casein kinase 1; NF-kB, nuclear factor kappa B; MMP, matrix metalloproteinase; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; SCDH, spinal cord dorsal horn; EAE, experimental autoimmune encephalomyelitis; HDAC1/2, histone deacetylases 1/2; APCDD1, APC down-regulated 1; LRP6, LDL receptor related protein 6; PPAR-γ, peroxisome proliferator-activated receptors; Nrf2, nuclear factor erythroid 2-related factor 2; CREB, cAMP response element-binding protein; STAT, signal transducer and activator of transcription; CCL, C-C motif chemokine ligand; 6-OHDP, 6-hydroxydopa; TDZD, thiadiazolidine derivative; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; CXCL10, C-X-C motif chemokine ligand 10; GFAP, glial fibrillary acidic protein; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; MIP, macrophage inflammatory protein.

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CHEMMEDCHEM Conference Reports

The 12th AFMC International Medicinal Chemistry Symposium (AIMECS 2019) in Istanbul, Turkey

Abdurrahman Olgac,[a] Ismail Yalcin,*[b] and Esin Aki-Yalcin*[b]

AFMC-AIMECS meetings are internationally organized biannually by the Asian Federation for Medicinal Chemistry (AFMC) and are focused on recent studies in drug discovery and development both in academia and industry. Member organizations of the AFMC are the Pharmaceutical Society of Japan, the Chinese Pharmaceutical Association, the Royal Australian Chemical Institute, the Pharmaceutical Society of Korea, the Korean Chemical Society, the Chemical Society Located in Taipei, the Indonesian Society of Medicinal Chemistry, the Medicinal Chemistry Section of the Israel Chemical Society, and the Computer-Aided Drug Design & Development Society in Turkey. Each time, the symposium is organized within these member countries. The AIMECS 2019 symposium was held in Turkey this year, as Prof. Dr. Esin Aki-Yalcin is the current president of the AFMC (2018–2020); the next AIMECS meeting will be organized in 2021 in Tokyo, Japan. In this report, we discuss key topics at the 12th AFMC International Medicinal Chemistry Symposium — New Avenues for Design and Development of Translational Medicine (AIMECS 2019) held in Istanbul, September 8–11, 2019.

The local management of AIMECS 2019 was covered by the Computer-Aided Drug Design & Development (CADD&D) Society, as Prof. Esin Aki-Yalcin is one of the founders of this society, acting as the current elected president of the Asian Federation of Medicinal Chemistry (AFMC) for the 2018–2020 term. Prof. Dr. Ismail Yalcin, the other founder of CADD&D Society and the former AFMC president during the 2006–2008 term, took part as the organizing committee chair of AIMECS 2019. The meeting was supported by the European Federation for Medicinal Chemistry (EFMC), the American Chemical Society Division of Medicinal Chemistry (ACS-MC), the Association of Research-Based Pharmaceutical Companies in Turkey (AIFD), and the Pharmaceutical Manufacturers Association of Turkey (IEIS). 76 female and 80 male participants from 28 countries attended the conference. Academia was represented by 62 female and 64 male attendees, and industry was represented by 14 female and 16 male attendees.

Key topics of the symposium were chosen from representatives of both academia and industry. The scientific program of the symposium included one opening lecture, 11 keynote lectures, 29 oral communications, and 58 poster presentations. The talks were grouped in 12 sessions which were held over the course of four days. The sessions of the symposium were: *Recent Developments in Drug Discovery (Sessions I & II), Association of Research-Based Pharmaceutical Companies (AIFD) Session, Advances in Medicinal Chemistry, Recent Developments in Central Nervous System Drugs (ACS Session), Recent Developments in the Therapy of Infectious & Antiviral Diseases (EFMC Session), Chemical Probes in Drug Discovery & Advances in Medicinal Chemistry, Protein–Protein Interactions and Protein Target Dynamics for Drug Discovery, Deep Learning & Miscellaneous Drug Targets, and Computer-Aided Drug Design Approaches (Sessions I & II).*

New networks were built by the attendees during the welcome cocktail, coffee breaks, lunches, poster session, with a city sightseeing tour by crossing modern and historical regions of Istanbul, and a gala dinner, which took place on a cruise tour of the Bosporus Strait.

The **opening session** of AIMECS 2019 was held Sunday evening, chaired by **Ismail Yalcin** (AIMECS 2019 Organizing Committee Chair, Ankara University). **Esin Aki-Yalcin** (Ankara University, AFMC President) briefly presented the organizational structure, roles and objectives of the AFMC along with past AFMC presidents and locations of previous AIMECS events as well as the organizational details of the 12th AIMECS. **Umit Dereli** (General Secretary of AIFD) and **Evren Algin Yapar** (Turkish Medicines & Medical Devices Agency, TMMDA) introduced AIFD and TMMDA, respectively, and joined in welcoming the symposium attendees. The opening lecture of the symposium was given by **Toshihiko Kobayashi** (University of Tokyo), who provided insight into intercultural relationships between countries and partnerships between the AFMC, ACS-MC, and EFMC. He also mentioned the impact of regenerative medicines and new regulatory frameworks for regenerative medicines, along with current trends in pharma and biotechnology industries and how Japan reacts in parallel to these changes.

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REVIEW ARTICLE

Natural Products and Extracts as Xantine Oxidase Inhibitors - A Hope for Gout Disease?

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Abstract: Xanthine oxidase (EC 1.17.3.2) (XO) is one of the main enzymatic sources that create reactive oxygen species (ROS) in the living system. It is a dehydrogenase enzyme that performs electron transfer to nicotinamide adenine dinucleotide (NAD+), while oxidizing hypoxanthin, which is an intermediate compound in purine catabolism, first to xanthine and then to uric acid. XO turns into an oxidant enzyme that oxidizes thiol groups under certain stress conditions in the tissue. The last metabolic step, in which hypoxanthin turns into uric acid, is catalyzed by XO. Uric acid, considered a waste product, can cause kidney stones and gouty-type arthritis as it is crystallized, when present in high concentrations. Thus, XO inhibitors are one of the drug classes used against gout, a purine metabolism disease that causes urate crystal storage in the joint and its surroundings caused by hyperuricemia. Urate-lowering therapy includes XO inhibitors that reduce uric acid production as well as uricosuric drugs that increase urea excretion. Current drugs that obstruct uric acid synthesis through XO inhibition are allopurinol, febuxostat, and uricase. However, since the side effects, safety and tolerability problems of some current gout medications still exist, intensive research is ongoing to look for new, effective, and safer XO inhibitors of natural or synthetic origins for the treatment of the disease. In the present review, we aimed to assess in detail XO inhibitory capacities of pure natural compounds along with the extracts from plants and other natural sources *via* screening Pubmed, Web of Science (WoS), Scopus, and Google Academic. The data pointed out to the fact that natural products, particularly phenolics such as flavonoids (quercetin, apigenin, and scutellarein), tannins (agrimoniin and ellagitannin), chalcones (melanoxethin), triterpenes (ginsenoside Rd and ursolic acid), stilbenes (resveratrol and piceatannol), alkaloids (berberin and palmatin) have a great potential for new XO inhibitors capable of use against gout disease. In addition, not only plants but other biological sources such as microfungi, macrofungi, lichens, insects (silk worms, ants, etc) seem to be the promising sources of novel XO inhibitors.

Keywords: Xanthine oxidase, inhibition, gout, plant, natural sources.

1. INTRODUCTION

Gout is a chronic inflammatory form of arthritis caused by excess uric acid (hyperuricemia), a substance that forms when the body breaks down purines, in the bloodstream. People who are obese, male gender, operated for gastric bypass or transplant surgery, and have hypertension, diabetes, thyroid or kidney problems, consume excessively red meat, own family members with gout and genetic factors, take medications such as diuretics and cyclosporine are known to be at higher risk of developing gout. The disease is mainly characterized by painful joint inflammation due to precipitation of monosodium urate crystals in a joint space [1]. Treatment strategy that targets lowering serum urate is usually applied effectively for gout management, which is mostly used increasing allopurinol dose regimen [2]. The aim is to lessen serum urate levels below 6 mg/dL, down to the saturation point of monosodium urate (6.8 mg/dL), to prevent the development of new crystals and to endorse dissolution of prevailing crystals [3].

Treatment of gout, also known among the people as "the disease of the kings or the rich", is based on hyperuricemia control, which is classified as treatment of acute gouty arthritis and chronic period therapy. The most effective drugs in the treatment of acute gouty arthritis are known as colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. Xanthine oxidase (XO) inhibitors that reduce uric acid production and uricosuric drugs that increase urea excretion are currently used in urate-lowering therapy [4]. Drugs that inhibit uric acid synthesis are allopurinol as well as febuxostat and uricase with non-purine structure, while uricosuric drugs are probenecid, sulfinpyrazone, and benzobromaron. On the other hand, pegloticase is a newly developed recombinant mammalian uricase analogue. The most important side effect of pegloticase is the development of allergic reactions and anaphylaxis due to the development of antipegloticase antibody [5]. Other notable side effects of this drug include neutrophilia, arthralgia, anemia, edema, upper respiratory tract, and urinary tract infections. It is also contraindicated as it causes hemolytic anemia in glucose-6-phosphate dehydrogenase deficiency. In case of persistent hyperuricemia and recurrent gout attacks, gout treatment should be sustained with XO inhibitors (allopurinol) or uricosuric agents (probenecid, sulfinpyrazone) [6]. However, the most common side effects of allopurinol and probenecid are itchy rashes, gastrointestinal complaints, and hypersensitivity. Another point to be considered is that allopurinol and uricosurics are not used in the treatment of acute attacks; in case the patient has been hyperuricemic for a long time. On the other hand, 4-month treatment with allopurinol in hyperuricemic individuals has been shown to reduce systolic blood pressure and proteinuria as well as improve endothelial function [7-8]. Besides, despite the fact that sulfinpyrazone is a very strong uricosuric drug derived from phenylbutasone, complications of nephrolithiasis may occur earlier than probenecid since

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REVIEW

Natural Products as Potential Leads Against Coronaviruses: Could They be Encouraging Structural Models Against SARS-CoV-2?

Ilkay Erdogan Orhan[1] · F. Sezer Senol Deniz[1]

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Abstract

New coronavirus referred to SARS-CoV-2 has caused a worldwide pandemic (COVID-19) declared by WHO. Coronavirus disease 2019 (COVID-19) is an infectious disease with severe acute respiratory syndrome caused by coronavirus-2 (SARS-CoV-2). SARS-CoV-2 is akin to SARS-CoV, which was the causative agent of severe acute respiratory syndrome (SARS) in 2002 as well as to that of Middle East respiratory syndrome (MERS) in 2012. SARS-CoV-2 has been revealed to belong to Coronaviridiae family as a member of β-coronaviruses. It has a positive-sense single-stranded RNA with the largest RNA genome. Since its genomic sequence has a notable similarity to that of SARS-CoV, antiviral drugs used to treat SARS and MERS are now being also applied for COVID-19 treatment. In order to combat SARS-CoV-2, many drug and vaccine development studies at experimental and clinical levels are currently conducted worldwide. In this sense, medicinal plants and the pure natural molecules isolated from plants have been reported to exhibit significant inhibitory antiviral activity against SARS-CoV and other types of coronaviruses. In the present review, plant extracts and natural molecules with the mentioned activity are discussed in order to give inspiration to researchers to take these molecules into consideration against SARS-CoV-2.

Keywords Coronavirus · SARS-CoV · Medicinal plants · Natural products · Antiviral

1 Introduction

Coronaviruses (family of Coronaviridiae, order of Nidovirales) named for the crown-like spikes on their surface are described as a family consisting of enveloped, single-stranded, and positive-strand RNA viruses possessing a helical nucleocapsid. They are known to cause acute and chronic respiratory, enteric, and central nervous system diseases in animals and humans [1]. Some types of coronaviruses are known to be hosted by humans including HCoV-229E, HCoV-HKU1, and HCoV-NL-63 (α-coronoviruses), HCoV-OC43, MERS-CoV, and SARS-CoV (β-coronoviruses). On the other hand, other types of coronaviruses using animal species as host are also available such as transmissible gastroenteritis virus (TGEV) and porcine respiratory coronavirus (PRCoV) in pigs, feline infectious peritonitis virus (FIPV) and feline enteric coronavirus (FeCoV) in cats, bovine respiratory coronavirus (BCoV) in cows, infectious bronchitis virus (IBV) in chickens and birds also known as avian coronavirus, mouse hepatitis virus (MHV), etc. They are generally classified under three groups as group I (TGEV, PEDV, FIPV, PRCV, and CCoV), group II (MHV, BCoV, and HCoV-OC43), and group III (TCoV and IBV) [2]. SARS-CoV was reported to cross-react with some members of group I coronavirus antibodies [3]. It should be also noted that, in addition to α- and β-coronoviruses, δ- (NHCoV HKU-19, WiCoV HKU-20, PorCoV HKU-15, CmCoV HKU21), and γ-coronoviruses (TCoV, BWCoV SW1, IBC-partridge) are present in the classification.

A coronavirus-based disease was firstly diagnosed in 1931, while the first coronavirus (HCoV-229E) was isolated from humans in 1965. Only HCoV-229E and HCoV-OC43 were known until SARS-CoV, being a member of the subgenus Sarbecovirus, which was realized as severe acute respiratory syndrome (SARS). It was defined a contagious and often fatal respiratory illness, firstly reported in Guandong province, China, in November 2002 with 11% of mortality. After that, Middle East Respiratory Syndrom (MERS-CoV) epidemic caused by the member of Merbecovirus

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molecules

MDPI

Review

Combretastatins: An Overview of Structure, Probable Mechanisms of Action and Potential Applications

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Abstract: Combretastatins are a class of closely related stilbenes (combretastatins A), dihydrostilbenes (combretastatins B), phenanthrenes (combretastatins C) and macrocyclic lactones (combretastatins D) found in the bark of *Combretum caffrum* (Eckl. & Zeyh.) Kuntze, commonly known as the South African bush willow. Some of the compounds in this series have been shown to be among the most potent antitubulin agents known. Due to their structural simplicity many analogs have also been synthesized. Combretastatin A4 phosphate is the most frequently tested compounds in preclinical and clinical trials. It is a water-soluble prodrug that the body can rapidly metabolize to combretastatin A4, which exhibits anti-tumor properties. In addition, in vitro and in vivo studies on combretastatins have determined that these compounds also have antioxidant, anti-inflammatory and antimicrobial effects. Nano-based formulations of natural or synthetic active agents such as combretastatin A4 phosphate exhibit several clear advantages, including improved low water solubility, prolonged circulation, drug targeting properties, enhanced efficiency, as well as fewer side effects. In this review, a synopsis of the recent literature exploring the combretastatins, their potential effects and nanoformulations as lead compounds in clinical applications is provided.

Keywords: combretaceae; combretastatins; drug discovery; natural compound; nanoformulation; structure-activity relationships; tubulin inhibitors

1. Introduction

Throughout the ages humans have utilized Nature, especially plants, to meet their basic to complex needs such the production of foodstuffs, shelter, clothing, means of transportation, fertilizers, flavors, fragrances and medicines as well. The World Health Organization has revealed that approximately 80% of the world's people count on medicinal plants in order to maintain their health or for treatment purposes. Newman et al. reviewed natural products as sources of new medicines between 1981 and 2002. This study showed that 67% of 877 mentioned small molecule new chemical entities were

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Importance of ethnopharmacological studies in drug discovery: role of medicinal plants

Ipek Süntar

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Abstract Ethnopharmacology can be basically defined as "the interdisciplinary scientific exploration of the biologically active agents that are traditionally employed". Therefore, the ethnopharmacological approach is based on a body of work that spans several disciplines such as botany, chemistry, and pharmacology. This includes field observations, descriptions of the utilization and bioactivities of folk remedies, botanical identification of the plant material as well as phytochemical and pharmacological research. Investigations of the indigenous remedies and their possible effects have attracted attention of many researchers for ages. Drug discovery from natural sources in the light of ethnopharmacological studies has an important role in the development of current therapeutic systems. Plants, animals and minerals are among the natural products that have been the basis in the treatment of many diseases for centuries. Recently, much attention has been paid to pharmacognostical, phytochemical and pharmacological studies of traditional medicinal plants. Moreover, biological activity potential of natural medicines has been investigated in many preclinical and clinical studies, revealing diverse biological effects of a wide range of plant derived compounds in various classes of chemical groups. The majority of the natural sources whose active compounds are currently employed actually has an ethnomedical use. Therefore, recently, many of the pharmaceutical companies have renewed their strategies in the field of natural product research in order to bring out potential sources and new molecules for the drug development. For the discovery and development of novel, safe and affordable medicines, the ethnopharmacological knowledge could be beneficial thanks to its approach that could be supported by experimental base. In the present study, ethnopharmacological aspects of herbal medicine and plant-based drug discovery process will be emphasized and important issues in their use as complementary medicine will be mentioned.

Keywords Ethnobotany · Ethnopharmacology · Folk remedy · Medicinal plants · Phytopharmacovigilance

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Introduction

Plants have been utilized for various purposes since early human history. The oldest written evidence for the use of plants for health purposes has been found on a Sumerian clay slab from Nagpur, which is approximately 5000 years old. Other historical written records were found in Mesopotamia, Egypt, Greek, and Islamic civilizations (Petrovska 2012). The

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REVIEW

Natural products, PGC-1α, and Duchenne muscular dystrophy

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Abbreviations: AAV, adeno-associated virus; AMP, adenosine monophosphate; AMPK, 5′ adenosine monophosphate-activated protein kinase; ASO, antisense oligonucleotides; ATF2, activating transcription factor 2; ATP, adenosine triphosphate; BMD, Becker muscular dystrophy; cGMP, cyclic guanosine monophosphate; CnA, calcineurin a; COPD, chronic obstructive pulmonary disease; CREB, cyclic AMP response element-binding protein; DAGC, dystrophin-associated glycoprotein complex; DGC, dystrophin–glycoprotein complex; DMD, Duchenne muscular dystrophy; DRP1, dynamin-related protein 1; DS, Down syndrome; ECM, extracellular matrix; EGCG, epigallocatechin-3-gallate; ERRα, estrogen-related receptor alpha; FDA, U.S. Food and Drug Administration; FGF, fibroblast growth factor; FOXO1, forkhead box class-O1; GABP, GA-binding protein; GPX, glutathione peroxidase; GSK3b, glycogen synthase kinase 3b; HCT, hydrochlorothiazide; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factors; IL, interleukin; iPSCs, induced pluripotent stem cells; LDH, lactate dehydrogenase; MCP-1, monocyte chemoattractant protein-1; MD, muscular dystrophy; MEF2, myocyte enhancer factor 2; MSCs, mesenchymal stem cells; MyoD, myogenic differentiation; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMJ, neuromuscular junctions; NO, nitric oxide; NOS, NO synthase; p38 MAPK, p38 mitogen-activated protein kinase; PDGF, platelet derived growth factor; PGC-1, peroxisome proliferator-activated receptor γ coactivator 1; PPARγ, peroxisome proliferation-activated receptor γ; ROS, reactive oxygen species; SIRT1, silent mating type information regulation 2 homolog 1; SOD, superoxide dismutase; SPP1, secreted phosphoprotein 1; TNF-α, tumor necrosis factor-α; UCP, uncoupling protein; VEGF, vascular endothelial growth factor.

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Berberine, a popular dietary supplement for human and animal health: Quantitative research literature analysis – a review*

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Review

Peptide-protein based nanofibers in pharmaceutical and biomedical applications

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ABSTRACT

In recent years, electrospun fibers have found wide use, especially in pharmaceutical area and biomedical applications, related to the various advantages such as high surface-volume ratio, high solubility and having wide usage areas they have provided. Biocompatible and biodegradable fibers can be obtained by using peptide-protein structures of plant and animal derived along with synthetic polymers. Plant-derived proteins used in nanofiber production can be listed as, zein, soy protein, and gluten and animal derived proteins can be listed as casein, silk fibroin, hemoglobine, bovine serum albumin, elastin, collagen, gelatin, and keratin. Plant and animal proteins and synthetic peptides used in electrospun fiber production were reviewed in detail. In addition, the important physical properties of these materials for the electrospinning process and their use in pharmaceutical and biomedical areas were discussed.

Contents

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DERLEME REVIEW

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Mikrobiyal Biyofilm Kontrolünde Lipozom Bazlı İlaç Taşıyıcı Sistemler

Liposome Based Drug Delivery Systems for Control of Microbial Biofilms

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ÖZET Biyofilmler, bir yüzeye yapışarak kendi ürettikleri jelsi bir tabaka içinde yaşayan mikroorganizmaların oluşturduğu topluluk olarak tanımlanmaktadır. Biyofilm varlığı geleneksel antimikrobiyallerin kullanımı için büyük zorluklar doğurmaktadır. Biyofilmle ilgili klinik enfeksiyonlara kronik otitis media, tekrarlayan tonsilit, kronik yaralar, kistik fibrozis akciğer enfeksiyonları, üriner sistem enfeksiyonları, kronik rinosinüzitler, diş çürükleri ve alet kaynaklı enfeksiyonlar örnek verilebilir. Bakteri türleri tüm mikroorganizmalar arasında diğerlerinden daha fazla biyofilm üretme kapasitesine sahiptir. Çoğu tür, hücre dışı yapılarıyla mikropları yaşam ortamlarında korumaktadır ve olumsuz koşullarda bile mükemmel kolonizasyon yeteneğine sahiptir. Geniş spektrumlu antibiyotiklerin kullanımı, nötropeni, parenteral nütrisyon, kalıcı kateterler, immünsupresyon, cerrahi, kemoterapi ve radyoterapi mantar enfeksiyonları için en önemli faktörler arasındadır. Biyofilmlerin ortadan kaldırılmasındaki ana problem, şu anda klinikte kullanılan ilaçlara karşı oluşan dirençtir. Antibiyotiğin biyofilm içine yavaş ve düşük penetrasyonu, biyofilm içinde değişen kimyasal mikroçevre ve efluks pompalarının ekspresyonu direnç nedenleri arasındadır. Bu sebeple antibiyofilm aktivitesi olan yeni bileşiklerin ve ilaçların araştırılması zorunlu hâle gelmiştir. Lipozomlar, birçok alanda kullanılan önemli ilaç taşıyıcı sistemlerden biridir. Lipozomlar enkapsüllenmiş ilacın biyoyararlılığını, biyouyumluluğunu ve güvenlik profilini artırmaktadır. Bu bağlamda, lipozomlar biyofilmlerin neden olduğu çok sayıda mikrobiyal enfeksiyonu tedavi etmede ve ilaçların hedefe ulaştırılmasında güvenli platformlar sağlamaktadır. Bu derlemede, mikrobiyal biyofilmlerin enfeksiyon hastalıklarına olan etkisi ve lipozom bazlı ilaç taşıyıcı sistemlerle biyofilmlerin kontrolü ve tedavisi özetlenmiştir.

Anahtar Kelimeler: Lipozom; biyofilmler

ABSTRACT Biofilms are defined as a group of microorganisms that live in a gelled layer that they produce by adhering to a surface. The presence of biofilm poses great challenges for the use of conventional antimicrobials. Biofilm-related clinical infections include chronic otitis media, recurrent tonsillitis, chronic wounds, cystic fibrosis lung infections, urinary tract infections, chronic rhinosinusitis, dental caries and instrument-borne infections. Bacterial species are capable of producing more biofilm among all microorganisms than others. Most species, with their extracellular structures, protect microbes in their habitats and have excellent colonization ability even in adverse conditions. Use of broad spectrum antibiotics, neutropenia, parenteral nutrition, permanent catheters, immunosuppression, surgery, chemotherapy and radiotherapy are among the most important factors for fungal infections. The main problem in eliminating biofilms is the resistance to drugs currently used in the clinic. The slow and low penetration of the antibiotic into the biofilm, the chemical microenvironment changing in the biofilm and the expression of efflux pumps are among the causes of resistance. Therefore, it has become necessary to search for novel compounds and drugs with anti-biofilm activity. Liposomes are one of the important drug delivery systems used in many areas. Liposomes increase the bioavailability, biocompatibility and safety profile of the encapsulated drug. In this regard, liposomes are safe in treating a large number of microbial infections caused by biofilms and delivering drugs to the target. In this review, the effect of microbial biofilms on infectious diseases and the control and treatment of biofilms with liposome based drug delivery systems are summarized.

Keywords: Liposom; biofilms

Biyofilmler, hastane enfeksiyonlarının yaklaşık %80'ine neden olan önemli bir sağlık sorunudur. Biyofilmler, bir yüzeye yapışarak kendi ürettikleri jelsi bir tabaka içinde yaşayan mikroorganizmaların oluşturduğu topluluk olarak tanımlanmaktadır. Biyofilmler, doğal olarak antibiyotiklere ve diğer antimikrobiyal tedavi biçimlerine daha dirençlidir ve bu da klinikte tekrarlayan enfeksiyonlara neden olur.[1]

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ERODIUM L'HER. (DÖNBABA/İĞNELİK)

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ÖZET

Geraniaceae (Turnagagasıgiller) familyası içerisinde yer alan *Erodium* L'Her. cinsine ait taksonlar, Türkiye'de halk arasında "dönbaba" ve "iğnelik" olarak bilinmektedir. Ülkemiz florasında 26 tür ile temsil edilmekte olan *Erodium* cinsinin çeşitli ülkelerde ödem, karaciğer rahatsızlıkları, kabızlık, diş ve mide ağrısı, şeker hastalığı ve iltihaplara karşı olmak üzere farklı etnobotanik kullanımlarının yanı sıra, bazı *Erodium* türleri, Türkiye, Kuzey Amerika bölgesi ve İtalya gibi bazı ülkelerde sebze olarak da tüketilmektedir. *Erodium* türleri üzerinde yapılan fitokimyasal çalışmalar, fenolik bileşikler (flavonoitler, fenolik asitler ve tanenler) ve uçucu yağ içerdiğine işaret etmektedir. Bu bitki cinsi üzerinde şu ana kadar yapılan kısıtlı sayıdaki biyolojik aktivite araştırmaları, farklı türlerinin güçlü antimikrobiyal ve antioksidan etkiye sahip olduğunu göstermektedir. Diğer yandan bazı türlerin enzim inhibitör, anti-enflamatuvar ve sitotoksik etkileri de az sayıdaki çalışmada bildirilmiştir. Bu derlemede, *Erodium* cinsinin genel botanik özellikleri, değişik türlerinin etnobotanik kullanımının yanı sıra, cins üzerinde yapılan fitokimyasal ve biyoaktivite çalışmaları hakkında bilgi verilecektir.

Anahtar kelimeler: *Erodium*, Dönbaba, İğnelik, Etnobotanik, Fitokimya, Biyoaktivite.

ERODIUM L'HER. (DÖNBABA/İĞNELİK)

ABSTRACT

The taxa belonging to the genus *Erodium* L'Her., placed in the family Geraniaceae (Turnagagasıgiller), is known as "dönbaba" and "iğnelik" in Turkey. *Erodium genus*, represented by 26 species in our flora, has been reported to have different ethnobotanical uses in various countries against edema, liver disorders, constipation, tooth and stomach pain, diabetes, and inflammation in addition to use of some species of *Erodium* are consumed as vegetable in some countries, such as Turkey, North America region, and Italy. Phytochemical studies on *Erodium* species indicate that it contains phenolic compounds (flavonoids, phenolic acids, and tannins) and essential oil. According to

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Kistik Fibroziste Yeni Terapötik Yaklaşımlar

New Therapeutic Approaches in Cystic Fibrosis

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ÖZET
Kistik Fibrozis (KF), Kistik Fibrozis Transmebran İletkenlik Düzenleyicisini (KFTR) kodlayan KFTR genindeki farklı mutasyonların neden olduğu kalıtsal, multisistemik bir hastalıktır. Kistik fibrozis, esas olarak hava yollarındaki anyon transportunun ve mukosiliyer klerensin bozulması sonucu gelişen pulmoner disfonksiyon ile karakterizedir. Mortalite, genellikle bronşektazi, bronşiyollerin tıkanması ve erken dönemde ilerleyici solunum fonksiyon bozukluğundan kaynaklanır. Son on yılda, küçük molekül yaklaşımı, iyon kanal tedavisi ve pulmoner gen tedavisi gibi semptomatik tedaviden ziyade hastalığı tedavi etmeye yönelik yeni stratejiler geliştirilmiştir. Tedavi seçeneklerindeki önemli ilerlemeler sayesinde, kistik fibrozis, artık pediatrik bir hastalıktan ziyade yetişkin hastalığı haline gelmiştir. Pulmoner gen tedavisi, mutasyon tipinden bağımsız olması ve tüm kistik fibrozis hastalarına uygulanabilirliği nedeniyle özellikle dikkat çekmiştir. Tedavideki en büyük sorun, kistik fibrozis hastalarındaki genetik heterojenite ve karmaşıklık sebebiyle ilaç cevabını öngörememektir. 3D hücre kültürü sistemlerindeki ilerlemeler, rektal hücre biyopsilerinden "organoidler" adı verilen kişiye özel mini organlar üreterek hastalığın modellenmesini ve bireysel ilaç cevabını in vitro olarak tahmin etmeyi mümkün kılmıştır. Bu derlemede, kistik fibrozis tedavisindeki yeni terapötik yaklaşımların, devam eden klinik çalışmaların ve kişiselleştirilmiş tedavi konseptindeki ilerlemelerin özetlenmesi amaçlanmıştır.
Anahtar Kelimeler: : Kistik fibrozis, gen terapisi, gen modülatörleri, rektal organoidler

ABSTRACT
Cystic Fibrosis (CF) is a hereditary, multisystemic disease caused by different mutations in the CFTR gene encoding Cystic Fibrosis Transmebrane Conductance Regulator (CFTR). Cystic fibrosis is characterized by mainly pulmonary dysfunction as a result of deterioration in the mucociliary clearance and anion transport of airways. Mortality is mostly caused by bronchiectasis, bronchioles obstruction and progressive respiratory dysfunction at the early age of life. Over the last decade, new therapeutic strategies rather than symptomatic treatment have been proposed, such as small molecule approach, ion channel therapy and pulmonary gene therapy. Due to considerable progress in the treatment options, cystic fibrosis has become an adult disease rather than a pediatric disease in recent years. Pulmonary gene therapy has gained special attention due to its mutation type independent aspect, therefore

Derleme / Review

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İlbasmış Tamer ve ark.

COVID-19 Pandemisinde Biyosidal Ürünlerin Değerlendirilmesi

Evaluation of Biocidal Products in COVID-19 Pandemic

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ÖZET

COVID-19'dan sorumlu virüs SARS-CoV-2, insandan insana doğrudan temas yoluyla veya damlacıklar yoluyla bulaşmakta ve ciddi sağlık sorunlarına yol açmaktadır. Dünya sağlık örgütü (DSÖ) hijyenik koşulların çok iyi sağlanması, enfekte olan kişilerle yakın temasın önlenmesi, sık sık el yıkama ve dezenfektanların kullanılması gibi önlemler ile COVID 19 pandemisinin kontrol edilebileceğini belirtmektedir. Dezenfeksiyon için hidrojen peroksit, alkol içeren ürünler, sodyum hipoklorit veya benzalkonyum klorür gibi çeşitli biyosidal maddeler kullanılmaktadır. Genel olarak el dezenfektanları, alkol içermeyen ve içeren olmak üzere iki kategoride incelenebilir. El dezenfektanları köpük, jel ve sprey şeklinde formüle edilebilirler. DSÖ gibi sağlık otoriteleri COVID-19 pandemisinde kullanılacak dezenfektanların özelliklerini belirten rehberler yayınlamışlardır. COVID-19 pandemisinin kontrolü için uygun ürünlerin seçimi konusunda eczacı gibi sağlık profesyonellerine danışılmalıdır. Güvenilmez ürünler satın alınmamalıdır. Bu derlemenin amacı, SARS-CoV ve MERS-CoV dahil tüm koronavirüslere karşı yaygın olarak kullanılan biyosidal ajanların, özellikle el ve yüzey dezenfektanlarının incelenmesidir.

Anahtar Sözcükler: Biyosidal ürünler, dezenfektanlar, el dezenfektanları, COVİD 19 pandemisi,

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ABSTRACT

SARS-CoV-2, the virus responsible for COVID-19, is spread by human-to-human transmission via droplets or direct contact and causes serious health problems. World Health Organization (WHO) stated that COVID 19 pandemic can be controlled by measures such as providing supreme hygienic conditions, preventing close contact with infected people, hand washing and using disinfectants. Numerous biocidal materials such as hydrogen peroxide, alcohol-containing products, sodium hypochlorite or benzalkonium chloride have been used for disinfection. Generally, hand sanitizers can be examined in two categories, with and without alcohol. Hand sanitizers can be formulated as foam, gel and spray. Health authorities such as the WHO have published guides specifying the characteristics of the disinfectants to be used in the COVID-19 pandemic. Healthcare professionals such as pharmacists should be consulted on the selection of suitable products for the control of the COVID-19 pandemic. Hence unreliable products should not be purchased. The purpose of this review is to examine biocidal agents commonly used against all coronaviruses, including SARS-CoV and MERS-CoV, especially hand and surface disinfectants.

Key Words: Biocidal products, disinfectants, hand sanitizers, COVID-19 pandemic

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DERLEME REVIEW

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Tırnak Mantarı Enfeksiyonu (Onikomikoz) ve Topikal Tedavide Yararlanımı Artırma Yöntemleri

Nail Fungal Infection (Onychomycosis) and the Methods of Increasing Usage in Topical Treatment

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ÖZET Tırnak mantarı (onikomikoz), el-ayak tırnaklarını etkileyen ve tüm tırnak hastalıklarının yaklaşık %50'sini oluşturan bir mantar enfeksiyonudur. Genellikle dermatofitler, az bir kısmı da dermatofit olmayan küfler ve mayalar tarafından oluşturulmaktadır. Obezite, diyabet, HIV, sigara içme, yaşlılık ve immün yetmezlik gibi faktörler hastalığa yakalanma riskini artırmaktadır. Onikomikoz tedavisi, enfekte bölgeye ve hastalığın şiddetine göre belirlenmektedir. Tedavi seçenekleri oral, topikal ve bir cihazın da kullanıldığı tedaviler olarak sınıflandırılmaktadır. Oral tedavi, yan etki riskinin yüksek olması nedeni ile çoğunlukla topikal tedaviden sonra düşünülmektedir. Topikal tedavi, düşük yan etki olasılığı, sistemik ilaç etkileşimine yol açmaması ve hasta uyumunun daha iyi olması açısından avantajlı görülmektedir. Fakat etken maddenin yoğun keratinize tırnağı geçmesi ve enfekte bölgeye penetrasyonu tedaviyi sınırlandırmaktadır. Topikal uygulamada karşılaşılan sıkıntıları giderebilmek, etken madde penetrasyonunu ve tedavinin etkinliğini artırmak için değişik fiziksel ve kimyasal yaklaşımlar geliştirilmiştir. Fiziksel yaklaşım; tırnak plağının aşındırılıp kalınlığının azaltılması, tırnak plağında µm boyutunda deliklerin açılması, iyontoforez ile penetrasyonun artırılması ve tırnağın hidrate edilerek geçirgenliğinin artırılması gibi yöntemleri içermektedir. Kimyasal yaklaşım ise tırnak plağının geçirgenliğinin artırılması amacıyla çeşitli penetrasyon artırıcıların kullanılmasına dayanmaktadır. Bu yaklaşımların yanı sıra bazı cihazlar da etken maddenin penetrasyonunu artırmak için tasarlanmıştır. Bu yaklaşımlar tek başına ya da birlikte kullanılarak topikal tedavinin etkinliğinin artırılıp süresinin azaltılması amaçlanmaktadır.

Anahtar Kelimeler: Onikomikoz; tırnak; tedavi; antifungal ajanlar; tırnağa penetrasyon

ABSTRACT Nail fungal (onychomycosis) is a fungal infection that affects hands and toenails and accounts for about 50% of all nail diseases. It is usually formed by dermatophytes, with a small proportion by non-dermatophytes yeasts and molds. Factors such as obesity, diabetes, HIV, smoking, old age and immunodeficiency increase risk of getting disease. Onychomycosis treatment is determined according to infected area and severity of the disease. Treatment options are classified as oral, topical and using a device. Oral treatment is usually considered after topical treatment because of the high risk of side effects. Topical treatment seems to be advantageous in terms of the possibility of low side effects, no systemic drug interaction and better patient compliance. However, penetration of the active substance through intense keratinized nail and penetration into infected area limit treatment. Various physical and chemical approaches have been developed to eliminate the problems encountered in topical application and increase the penetration of the active substance and effectiveness of the treatment. Physical approach; reduction of the thickness by etching of the nail plate, forming holes in size of µm on the nail plate, increasing penetration by iontophoresis and increasing permeability of the nail by hydrating. The chemical approach is based on the use of various penetration enhancers to increase the permeability of the nail plate. Additionally, some devices are designed to increase the penetration of the active substance. Using these approaches alone or in combination, it is aimed to increase the effectiveness and decrease the duration of topical treatment.

Keywords: Onychomycosis, nail, treatment, antifungal agents, nail penetration

Tırnak plağının mantar enfeksiyonu olan onikomikoz, dünya çapında bireylerin yaklaşık %5,5'ini etkilemektedir.[1] Görülme sıklığı yaşlı, bağışıklık sistemi baskılanmış ve kronik bir hastalığı olan bireyler arasında daha fazladır.[1] Onikomikoz genellikle tırnağın yeterince büyüyememesi, renk değişikliği ve tırnak plağının tırnak yatağından ayrılması (onikoliz) ile karakterize edilmektedir.[2] Hastalık bazı durum-

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COVID-19 SÜRECİNDE ECZACILARIN ROLÜ

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ÖZET

2019 yılı Aralık ayı sonunda Çin'in Wuhan şehrinde ortaya çıkarak, dünyaya yayılan ve 21. yüzyılın ilk pandemisine sebep olan yeni tip corona virüsün (SARS-CoV-2) neden olduğu COVID-19, Mayıs 2020 tarihi itibarıyla dünyada 4 milyondan fazla insanın enfekte olduğu küresel ölçekte bir sağlık sorunu haline gelmiştir. Bu süreçte hastalığın teşhisi ve tedavisi nedeniyle sağlık çalışanları (hekimler, hemşireler, eczacılar, hastabakıcılar, vs) COVID-19 hastalarıyla muhatap olmaları nedeniyle en büyük risk ile karşı karşıya kalan meslek grupları haline gelmiştir. Eczacılar, özellikle ülkemizde 1. basamak sağlık sunucusu statüsünde olan eczane eczacıları, halkın en kolay ulaşabildiği sağlık çalışanları olarak pandemi sürecinde hizmet vermeye devam etmiştir. Ancak damlacıklı temas yoluyla bulaşma riski çok yüksek olan yeni tip corona virüsten korunmak, günde yüzlerce hastanın ziyaret ettiği eczanelerde eczacı ve eczacı teknisyenleri için büyük bir sağlık sorunu teşkil etmesine rağmen, COVID-19 pandemi sürecinde eczaneler kişisel çapta hijyen önlemleri alarak ücretsiz maske dağıtımı görevini yüklenmiştir. Bu makalede, COVID-19 pandemi sürecinde ülkemizde eczacıların üstlendikleri görev ve sorumluluklar ile kamu hizmetleri tartışılacaktır.

Anahtar Kelimeler: Eczacı, eczane, COVID-19, pandemi, corona virüs, SARS-CoV-2

THE ROLE OF PHARMACISTS DURING COVID-19

ABSTRACT

COVID-19, caused by the new type of corona virus (SARS-CoV-2), which originated in Wuhan, China at the end of December 2019, is spreading all over the world and causing the first pandemic of the 21st century. As of May 2020, it has become a global health problem with more than 4 million people infected worldwide. In this period, healthcare professionals (physicians, nurses, pharmacists, caregivers, etc.) have become the biggest risky groups facing the COVID-19 patients during the diagnosis and treatment of the disease. Pharmacists, especially community pharmacists, who have the status of primary health care provider in our country, have continued to serve in the pandemic process as the healthcare professionals who are easily accessible by the public. However, although protection from the new type of coronavirus, which has a very high risk of transmission by droplet contact, is a major health problem for pharmacists and pharmacy technicians in community pharmacies visited by hundreds of patients *per* day, pharmacies have been assigned the duty of free mask distribution in the COVID-19 pandemic process by taking their own personal hygiene measures. In this article, the duties and responsibilities of pharmacists as well as their public services in our country during the COVID-19 pandemic process will be discussed.

Keywords: Pharmacist, pharmacy, COVID-19, pandemic, coronavirus, SARS-CoV-2

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Review / Derleme

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Orhan and Senol Deniz

Golden Pigment Curcumin: An Inspiring Antiviral Molecular Model for COVID-19 Drug Design

Altın Pigment Kurkumin: COVID-19 için İlham Veren Antiviral Bir Moleküler Model

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ABSTRACT

COVID-19 caused by a new type of coronavirus (SARS-CoV-2) originated in China has speedily become a frightening pandemic all over the world. Despite of intense efforts relevant to experimental and clinical studies since the start of the COVID-19 pandemic, no disease-specific drug or vaccine is available, yet. Several treatment strategies including already known antiviral drugs, interpherons, interleukin inhibitors, and other drugs acting through different mechanims are being implemented in COVID-19 patients. On the other hand, natural products especially pythocompounds have been proven to be lead molecules for drug design and development research. Among them, curcumin as the main constituent of *Curcuma longa* L. (turmeric), is the reputed compound displaying remarkable biological activities for human health. It has been shown to have a inhibiting effect against a wide range of viruses such as HCV, HIV, PEDV, HSV, Ebola, dengue, influenza, Zika, SARS-CoV, etc. Therefore, curcumin could be considered as a structural model for designing new molecules against COVID-19. In the present review, antiviral activity of curcumin is scrutinized thorugh the literature data relevant to its enzyme and receptor interactions, *in vitro*, *in vivo*, *in silico*, and cell-based assays.

Key Words: COVID-19, coronavirus, curcumin, antiviral activity

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ÖZET

Çin menşeli yeni bir tür koronavirüs (SARS-CoV-2) nedenli COVID-19 hızla tüm dünyada korkutucu bir salgın haline gelmiştir. COVID-19 pandemisinin başlangıcından bu yana deneysel ve klinik çalışmalarla ilgili yoğun çabalara rağmen, henüz hastalığa özgü bir ilaç veya aşı mevcut değildir. COVID-19 hastalarında halihazırda bilinen antiviral ilaçlar, interferonlar, interlökin inhibitörleri ve farklı mekanizmalarla etki eden diğer ilaçlar dahil olmak üzere çeşitli tedavi stratejileri uygulanmaktadır. Öte yandan, özellikle bitkisel bileşikler gibi doğal ürünlerin ilaç tasarımı ve geliştirme araştırmaları için öncü moleküller oldukları kanıtlanmıştır. Bunların arasında, *Curcuma longa* L.'nin (zerdeçal) ana bileşeni olan kurkumin, insan sağlığı için dikkate değer biyolojik aktiviteler sergileyen meşhur bir bileşiktir. HCV, HIV, PEDV, HSV, Ebola, dang, grip, Zika, SARS-CoV, vb. gibi çeşitli virüslere karşı inhibitör etkiye sahip olduğu gösterilmiştir. Bu nedenle, kurkumin COVID-19'a karşı yeni moleküller tasarlamak için yapısal bir model olarak düşünülebilir. Bu derlemede, kurkuminin antiviral aktivitesi, enzim ve reseptör etkileşimleri, *in vitro*, *in vivo*, *in silico* ve hücre-temelli yöntemler ile ilgili literatür verileri üzerinden irdelenmektedir.

Anahtar Sözcükler: COVID-19, coronavirus, kurkumin, antiviral aktivite

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Review / Derleme

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Şener

Antiviral Activity of Natural Products and Herbal Extracts

Doğal Ürünlerin ve Bitkisel Özlerin Antiviral Etkinliği

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ABSTRACT

Plants have been used as medicine by mankind to treat health-threatening diseases and still popular to develop new drug candidates. Plants have a combination of phytochemicals also known as secondary metabolites that are naturally occurred gives different therapeutic benefits. Natural products have been recognized as an important role in the drug discovery process moreover the other sources. Presently, over 100 natural product-derived pharmaceuticals are being used in modern medicine. Some of them play as important tools in the immune system exhibiting antiviral potentials. This review presents a survey of natural products and herbal extracts that have indicated broad antiviral activity.

Key Words: Antiviral activity, medicinal plants, extracts, phytochemicals.

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ÖZET

İnsanoğlu tarafından sağlığı tehdit eden hastalıkların tedavisinde ilaç olarak kullanılmış olan bitkiler günümüzde de yeni ilaç adaylarının geliştirilmesinde önemlidir. Doğal olarak oluşan sekonder metabolitler ismiyle bilinen fitokimyasalları içeren bitkiler farklı tedavi edici özelliklere sahiptir. Diğer kaynaklar yanında doğal maddeler ilaç keşiflerinde önemli bir yere sahiptir. Bugün 100 den fazla doğal ürünlerden elde edilen farmasötikler modern tıpta kullanılmaktadır. Bazıları antiviral etkileri nedeniyle bağışıklık sisteminde önemlidir. Geniş spektrumlu antiviral aktiviteye sahip doğal maddeler ve bitki ekstreleri bu derlemede bir araya getirilmiştir.

Anahtar Sözcükler: Antiviral aktivite, tıbbi bitkiler, ekstreler, fitokimyasallar.

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Taban Akca and Suntar

An Overview on Flavonoids as Potential Antiviral Strategies against Coronavirus Infections

Koronavirüs Enfeksiyonlarına Karşı Potansiyel Antiviral Bileşikler Olarak Flavonoitlere Genel Bakış

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ABSTRACT

Coronaviruses are zoonotic viruses and can infect people, often causing respiratory and gastrointestinal complaints. Three coronavirus types namely, severe acute respiratory syndrome coronavirus (SARS-CoV), middle-east respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 (COVID-19) cause pneumonia in human resulting in severe acute respiratory syndrome (SARS). SARS-CoV-2, first appeared in Wuhan, China, in 2019, has rapidly spread to the whole world in a short time due to the speed of transmission rate. Since there is no specific drug for disease prevention and treatment, drug and vaccine development studies are proceeding rapidly. In drug development studies, natural resources draw attention due to their antiviral activity and fewer side effects. Flavonoids, a secondary metabolite group found in higher plants, have a variety of pharmacological activities, including antiviral activity. In this review, flavonoid-type compounds and plant extracts containing these constituents were summarized in terms of their antiviral activity potential against coronavirus-induced infections. Herein, we can suggest that flavonoids shown to possess antiviral effect against SARS and MERS may be used as potential test materials for the studies of novel drug search for ongoing COVID-19 pandemic.

Key Words: Antiviral, coronavirus, COVID-19, flavonoids, medicinal plants, respiratory infection

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ÖZET

Koronavirüsler zoonotik virüsler olup insanları enfekte ederek çoğu zaman solunum ve mide-bağırsak şikayetlerine neden olabilir. Şiddetli akut solunum yetmezliği sendromu koronavirüsü (SARS-CoV), ortadoğu solunum yetmezliği sendromu koronavirüsü (MERS-CoV) ve SARS-CoV-2 (COVID-19) olmak üzere üç koronavirüs türü, insanlarda şiddetli akut solunum yetmezliği sendromuna (SARS) neden olur. İlk olarak 2019 yılında Çin'in Wuhan kentinde ortaya çıkan SARS-CoV-2, yüksek bulaşma hızı nedeniyle kısa sürede tüm dünyaya yayıldı. Hastalığın önlenmesi ve tedavisine yönelik spesifik bir ilaç olmadığından ilaç ve aşı geliştirme çalışmaları hızla devam etmektedir. İlaç geliştirme çalışmalarında doğal kaynaklar, antiviral aktiviteleri ve daha az yan etki potansiyelleri ile dikkat çekmektedir. Yüksek bitkilerde bulunan sekonder metabolit grubu olan flavonoitler, antiviral aktivite dahil olmak üzere çeşitli farmakolojik aktivitelere sahiptir. Bu derlemede, flavonoit tipi bileşikler ve bu bileşenleri içeren bitki ekstreleri, koronavirüs kaynaklı enfeksiyonlara karşı antiviral aktivite potansiyelleri açısından özetlenmiştir. SARS ve MERS'e karşı antiviral etkiye sahip olduğu gösterilen flavonoitlerin, devam eden COVID-19 pandemisi için yeni ilaç geliştirme çalışmalarında potansiyel deney materyalleri olarak kullanılabileceğini önerebiliriz.

Anahtar Sözcükler: Antiviral, koronavirüs, COVID-19, flavonoit, tıbbi bitki, solunum yolu enfeksiyonu

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DERLEME REVIEW

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Meme Kanserinde MMP-2 ve MMP-9'un Rolü

The Role of MMP-2 and MMP-9 in Breast Cancer

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ÖZET Matriks metalloproteinaz (MMP)lar kalsiyum ve çinko bağımlı proteolitik enzim ailesidir. Bu ailenin bir üyesi olan MMP-2 ve MMP-9 jelatini, tip IV, V, VII ve X kollajeni parçalayan tip IV kollajenazlardır. MMP-2 fibroblastlar, endotel hücreleri ve osteoblastlar; MMP-9 inflamatuar hücreler, tümör hücreleri, keratinositler ve epitel hücreleri tarafından sentezlenmektedir. Jelatinazlar, zimojen olarak salgılanırlar ve peptidomainlerin bölünmesi ile aktif formlarına dönüşürler. MMP-2 ve MMP-9, meme kanseri hücrelerinde proliferasyon, migrasyon, invazyon ve metastaza yol açmaktadır. Hem MMP-2'nin hem de MMP-9'un, meme kanseri tedavisine yönelik olarak polimorfizmlerini ve ekspresyonlarını/aktivitelerini araştıran çalışmalar bulunmaktadır. Meme kanseri progresyonu ve metastazındaki önemli rolleri nedeni ile bu enzimlerin ortak fonksiyonel polimorfizmlerinin, hasta sağkalımını da içeren fenotipik özellikleriyle meme kanseri gelişimine katkıda bulunduğu bildirilmektedir. Di-2-Etilheksilftalat, PAX6, hücresel prion proteini, natriüretik peptid reseptörü A, aktif lökosit hücre adezyon molekülü, EZH2, eGFR'nin ligand EGF ile etkileşimi, integrin ve integrin olmayan reseptörlerle etkileşim, TF-FVIIa/tripsin aracılı protaz ile reseptör 2'nin aktivasyonu ile MMP-2 ve/veya MMP-9'un ekspresyonunun arttığı gösterilmektedir. Meme kanserinde invazyon ve metastaz üzerindeki etkileri nedeni ile potansiyel tedavi hedefi olarak MMP-2 ve MMP-9'u inhibe etmeye yönelik olarak Alisol A, Casticin, Orientin, Luteolin ve [15]pyN5 ve [16]pyN5 üzerinde yapılan çalışmalar bulunmaktadır. Bu derlemede, meme kanserinde MMP-2 ve MMP-9'un rolü, polimorfizmleri, bu enzimlerin ekspresyonunu/aktivitesini artıran etkileşimleri, moleküller ile inhibisyonları incelenecek ve son yıllarda yapılan çalışmalar sunulacaktır.

Anahtar Kelimeler: Matriks metalloproteinaz; jelatinaz; MMP-2; MMP-9; meme kanseri

ABSTRACT Matrix metalloproteinases (MMPs) are a family of calcium and zinc-dependent proteolytic enzymes. MMP-2 and MMP-9 are members of this family; type IV collagenases which degrade gelatin, types IV, V, VII and X collagen. MMP-2 is synthesized by fibroblasts, endothelial cells and osteoblasts, MMP-9 is synthesized by inflammatory cells, tumor cells, keratinocytes and epithelial cells. Gelatinases are secreted as inactive zymogens and turn into active forms by dividing prodomains. MMP-2 and MMP-9 cause proliferation, migration, invasion and metastasis in breast cancer cells. There are studies investigating the polymorphisms and expressions/activities of both MMP-2 and MMP-9 for breast cancer treatment. Due to their important role in breast cancer progression and metastasis, common functional polymorphisms of these enzymes have been reported to contribute to breast cancer development with their phenotypic properties, including patient survival. Di-2-Ethylhexylphthalate, PAX6, cellular prion protein, Natriuretic peptide receptor A, active leukocyte cell adhesion molecule, EZH2, interaction of eGFR with ligand EGF, interaction with integrin and non-integrin receptors, with TF-FVIIa / trypsin mediated protease of receptor 2 activation is shown to increase expression of MMP-2 and / or MMP-9. There are studies on Alisol A, Casticin, Orientin, Luteolin and [15] pyN5 and [16] pyN5 to inhibit MMP-2 and MMP-9 as potential treatment targets due to their effects on invasion and metastasis in breast cancer. In this review, in breast cancer MMP-2 and MMP-9 role, polymorphisms, interactions that increase the expression / activity of these enzymes, and their inhibition with molecules will be presented and studies conducted in recent years will be presented.

Keywords: Matrix metalloproteinase; gelatinase; MMP-2; MMP-9; breast cancer

Matriks metalloproteinaz (MMP)lar kalsiyum ve çinko bağımlı proteolitik enzim ailesidir. Ekstraselüler matriks (ESM) bileşenlerini bozdukları bilinmekle beraber, büyük çoğunluğu geniş substrat spesifitesine sahip olan ve matrikste bulunmayan proteinleri içeren biyolojik aktif moleküllerdir. Organizmanın işleyişinde hücreler arası etkileşim ve hücre-ESM etkileşimi kaçınılmaz olduğundan, ESM'nin yeniden şekillenmesinde MMP'ler kilit rol oynamaktadır.[1-3] MMP'ler, ESM'nin yapısını ve bileşimini düzenleyerek, büyüme faktörünün üretiminde ve hücre yüzeyi sinyal sistemlerinin işleyişinde ana rol oynarlar.

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Review / Derleme

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Modulator Role of Oral Antidiabetic Metformin on Intestinal Microbiota

Oral Antidiyabetik Metforminin Bağırsak Mikrobiyotası Üzerine Modülatör Rolü

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ÖZET

Metformin (1,1-dimetilbiguanidhidroklorür), tip 2 diabetes mellitus (T2DM) için birinci basamak tedavi olarak yaygın olarak kullanılmakta olup ABD'de en çok reçete edilen antidiyabetik ilaçtır. Metforminin karaciğer glikoz üretimini inhibe ettiği, hem karaciğer hem de iskelet kasındaki periferik glikoz alımını düzenlediği ve insülin duyarlılığını artırdığı gösterilmiştir. Metforminin karaciğerde adenozinmonofosfat (AMP) ile aktive olan protein kinaz (AMPK) bağımlı ve AMPK bağımsız yolakların aktivasyonu yoluyla hepatik glikoz çıkışını baskılayarak anti-hiperglisemik etki gösterdiği düşünülse de yapılan çalışmalar bağırsaktaki yolaklar aracılığıyla da etki gösterebileceğini ortaya koymaktadır. Metforminin hem terapötik hem de advers etkilerinin nedeni olduğunu öne sürülen mikrobiyota aracılı etkileri ve bu etkilerin mekanizmaları konu ile ilgili mevcut makalelere dayanarak incelenmiştir.

Anahtar Sözcükler: Metformin, Tip 2 Diyabet, Bağırsak Mikrobiyotası, Mikrobiyom, Biguanidler, Bakteriler.

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ABSTRACT

Metformin (1,1-dimethylbiguanidhydrochloride) is widely used as a first-line treatment for type 2 diabetes mellitus (T2DM) and is the most prescribed antidiabetic drug in the USA. Metformin has been shown to inhibit liver glucose production, regulate peripheral glucose uptake in both liver and skeletal muscle, and increase insulin sensitivity. Even though metformin is thought tohave an anti-hyperglycemic effect bysuppressing the hepatic glucose output through activation of adenosinemonophosphate (AMP)-activated protein kinase (AMPK) dependent and AMPK independent pathways in the liver, studies reveal that it may also act through pathways in the intestine. Microbiota-mediated effects of metformin, which are claimed to be the cause of both therapeutic and adverse effects and the mechanisms of these effects have been investigated based on currentarticles on the subject.

Key Words: Metformin, Type 2 Diabetes, Intestinal Microbiota, Microbiome, Biguanides, Bacteria.

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Derleme / Review

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Yılmaz Usta ve Teksin

COVID-19 Tedavisinde Kullanılan İlaçların Biyofarmasötik, Farmakokinetik ve Patent Değerlendirmeleri: Ülkemizde Eşdeğer İlaçların Geliştirilmesindeki Güncel Durum

Biopharmaceutics, Pharmacokinetics and Patent Evaluations of Drugs Used in the Treatment of COVID-19: Current Status in the Development of Generic Drugs in Turkey

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ÖZET

COVID-19'un hızla yayılıp pandemi haline dönüşmesi sonucu hastalığa yakalanan pek çok kişinin durumunun hızla kötüleşmesi ve ölümlerin artışı acil tedavi gereksinimini doğurmuştur. Hastalıkla ilk kez karşılaşılmasından dolayı tedavi için sağlık otoriteleri tarafından onaylanmış bir ilaç ve/veya aşı bulunmamaktadır. Mevcut ilaçlar ortaya çıkan semptomların giderilmesi ve hastalığın ilerleyişini yavaşlatması amacıyla tedavide bilinen başka endikasyonlar için kullanılan ilaçlardır. Bu durum, hastalık hakkında veri yetersizliğinin yanı sıra kullanılan ve/veya kullanılması amaçlanan ilaçlar ve tedavi yaklaşımlarında da veri yetersizliğine neden olmaktadır. Bu derleme makalesinde, Türkiye'de ve dünyada COVID-19 tedavi protokollerinde kullanılan ilaçların biyofarmasötik ve farmakokinetik özellikleri, tedavi uygulamaları ve klinik araştırmaları, eşdeğer ilaç geliştirilmesi ve patent durumlarının güncel verilerle değerlendirilmesi amaçlanmıştır.

Anahtar Sözcükler: COVID-19, biyofarmasötik, farmakokinetik, eşdeğer ilaç, patent

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ABSTRACT

As a result of the rapid spread of COVID-19 and turning into a pandemic the deterioration of the condition of many people and the increase of deaths, caused the need for urgent treatment. There is no drug and/or vaccine approved by the health authorities for treatment because it is the first time the disease is encountered. The existing drugs are medicines used for other known indications in the treatment to relieve the symptoms and slow the progression of the disease. This situation causes data insufficiency in the drugs and treatment approaches used and/or intended to be used, as well as insufficient data on the disease. In this review article, it is aimed to evaluate the biopharmaceutics and pharmacokinetics properties, treatment applications and clinical researches, generic drug development and patent status of the drugs used in COVID-19 treatment protocols in Turkey and worldwide, with current data.

Key Words: COVID-19, biopharmaceutics, pharmacokinetics, generic drug, patent

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DERLEME MAKALE / REVIEW ARTICLE

HARPAGOPHYTUM PROCUMBENS VE FİTOTERAPİDE KULLANIMI

HARPAGOPHYTUM PROCUMBENS AND USE IN PHYTOTHERAPY

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ÖZ

Amaç: *Bu derlemede, Harpagophytum procumbens ile ilgili genel bilgi verilip analjezik ve antienflamatuvar aktiviteleri üzerinde yapılmış in vitro, in vivo ve klinik çalışma bulguları sunulacaktır.*

Sonuç ve Tartışma: *H. procumbens kökleri Güney Afrika'da geleneksel halk tıbbında, romatizma ve ağrı tedavisinde uzun yıllardan beridir kullanılmaktadır. Günümüzde, standardize edilmiş kök ekstrelerinin (%1 harpagozit içerir) antienflamatuvar etkilere sahip olmasından dolayı osteoartrit hastalarında akılcı fitoterapi uygulamaları kapsamında kullanılmaktadır. Harpagozitin, nükleer faktör-kappa B'yi inhibe ederek lipopolisakkarit kaynaklı indüklenebilir nitrik oksit sentaz ve siklooksijenaz-2 ekspresyonu üzerinde inhibisyon sağlayarak antienflamatuvar etki gösterdiği tespit edilmiştir. Ayrıca standardize ekstreler, kıkırdak degredasyonunda anahtar rol oynayan matriks metalloproteinaz ve elastaz enzimlerini inhibe ederek kondroprotektif etkiler göstermektedir. Osteoartrit hastalarında minimum 2-3 ay kullanılması gerektiği önerilen ekstrenin, herhangi bir ciddi ilaç etkileşmesi oluşturmadığı da belirtilmektedir. Kanıta dayalı fitoterapi uygulamaları açısından; standardize H. procumbens kök ekstrelerinin osteoartritli hastalarda kullanımı ile ilgili yapılmış klinik çalışmalar mevcuttur ve çalışmalar devam etmektedir.*

Anahtar Kelimeler: *Fitoterapi, Harpagophytum procumbens, osteoartrit, şeytan pençesi*

ABSTRACT

Objective: *In this review, general information about Harpagophytum procumbens will be given and findings of in vitro, in vivo and clinical studies on analgesic and anti-inflammatory activities will be presented.*

Result and Discussion: *For many years, H. procumbens roots have been used to treat rheumatism and pain in traditional folk medicine in South Africa. Today, it is used within the scope of rational phytotherapy applications in osteoarthritis patients, since its standardized root extracts (containing 1% harpagozite) have anti-inflammatory effects. It has been found that harpagozite has an anti-inflammatory effect by inhibiting nuclear factor-kappa B, providing inhibition on the expression of lipopolysaccharide-inducible nitric oxide*

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REVIEW

Psychoactive Bath Salts and Neurotoxicity Risk

Psikoaktif Banyo Tuzları ve Nörotoksisite Riski

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ABSTRACT

Synthetic cathinones are new designer drugs that possess hallucinogenic and psychostimulant properties, and are designed to mimic the effects of illegal substances such as cocaine, amphetamines, and 3,4-methylenedioxymethamphetamine (ecstasy) and to produce rewarding effects, circumventing existing laws and penalties. Synthetic cathinones, also referred to as 'bath salts', have become popular particularly among young people since the mid-2000s. Similar to other psychomotor stimulants, synthetic cathinones have the potential to increase monoamine concentration in the synaptic cleft by targeting the plasma membrane transporters of dopamine, norepinephrine, and serotonin. Because of their structural similarities to amphetamines, it has been suggested that synthetic cathinones may have a neurotoxicity profile similar to that of their amphetamine congeners. Therefore, it has been hypothesized that synthetic cathinones may induce neurotoxicity on monoamine nerve endings in the striatum, hippocampus, and cortex. To date, with regard to synthetic cathinone neurotoxicity, parameters such as monoamine depletion, biosynthetic enzyme inhibition, cytotoxicity, generation of reactive oxygen species, pro-oxidation status, and the ability to induce neuroinflammation were investigated in both *in vitro* and *in vivo* experimental studies. Compared with amphetamines, synthetic cathinones appear to have more moderate effects than their amphetamine congeners in terms of neurotoxic effects. However, many synthetic cathinone users take these substances simultaneously with other substances such as benzodiazepines, amphetamines, ecstasy, tetrahydrocannabinol, and ethanol and this abuse can modify their neurotoxic effects. Hence, it is important to understand the underlying mechanism of early neurotoxic effects in case of polysubstance use. In this review, we aimed to present up-to-date information on the abuse potential of synthetic cathinones, their legal status, mechanism of action, and particularly their neurotoxic effects.

Key words: Psychoactive, hallucinogen, bath salts, synthetic cathinones, neurotoxicity

ÖZ

Sentetik katinonlar, mevcut yasa ve cezaları atlatabilmek amacıyla, kokain, amfetamin ve 3,4-metilendioksimetamfetamin (ekstazi) gibi yasadışı maddelerin etkilerini taklit etmek ve benzer ödüllendirici etkiler yaratmak üzere geliştirilmiş halüsinojenik ve psikostimülan özellikte yeni tasarlanmış yasadışı maddelerdir. Banyo tuzları olarak da bilinen sentetik katinonlar, 2000'li yılların ortalarından itibaren özellikle genç bireyler arasında popüler hale gelmeye başlamıştır. Diğer psikomotor uyarıcılara benzer şekilde, sentetik katinonlarda, dopamin, norepinefrin ve serotoninin plazma membran taşıyıcılarını hedef alarak sinaptik aralıktaki monoamin konsantrasyonunu arttırmaktadır. Amfetaminlere olan yapısal benzerlikleri nedeniyle, sentetik katinonların amfetamin homologları ile benzer nörotoksisite profiline sahip olabileceği düşünülmüştür. Bu nedenle, sentetik katinonların striatum, hipokampus ve kortekste monoamin sinir uçları üzerinde nörotoksisiteyi indükleyebileceği hipotezi öne sürülmüştür. Şimdiye dek sentetik katinonların nörotoksisitesi ile ilgili olarak yapılan *in vitro-in vivo* deneysel çalışmalarda, monoamin deplesyonu, biyosentetik enzim inhibisyonu, sitotoksisite, reaktif oksijen türlerinin oluşumu, pro-oksidasyon durumu ve nöroenflamasyon indükleme yeteneği gibi parametreler incelenmiştir. Sentetik katinonların nörotoksik etkiler açısından amfetamin homologlarından daha ılımlı olduğu görülmektedir. Ancak, pek çok sentetik katinon kullanıcısının bu maddeleri benzodiazepinler, amfetaminler, ekstazi, tetrahidrokannabinol ve etanol gibi diğer yasal olmayan ilaç veya bağımlılık yapıcı maddelerbirlikte almaktadır. Çünkü bu maddelerin nörotoksik etkileri değil, bu maddeler, sentetik katinonların nörotoksik etkilerini modifiye edebilmektedir. Bu nedenle, çoklu madde maruziyeti durumundaki erken nörotoksik etkilerin altında yatan mekanizmaların anlaşılması önemlidir. Bu derlemede, sentetik katinonların suistimal potansiyeli, yasal durumları, etki mekanizmaları ve özellikle nörotoksik etkileri hakkında güncel bilgi sunulması amaçlanmıştır.

Anahtar kelimeler: Psikoaktif, halüsinojen, banyo tuzları, sentetik katinonlar, nörotoksisite

INTRODUCTION

Synthetic cathinones are a subgroup of new psychoactive substances (NPSs) that possess hallucinogenic and psychostimulant properties and are designed to mimic the effects of illegal substances such as cocaine, 3,4-methylenedioxymethamphetamine (MDMA), and other amphetamines, circumventing existing laws.[1] NPSs, or to use the other term 'designer drugs', are intentionally mislabeled and marketed as bath salts, fertilizers (although they have no such purpose), plant food, laboratory chemicals, or reagents and are marked as 'not for human consumption' or 'not tested for danger/toxicity' to avoid criminal liability.[2,3] Synthetic cathinones are one of the most commonly found psychoactive substances in these designer drug mixtures.[1]

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Review / Derleme

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Hacisevki and Baba

An Overview of Vitamins and Minerals in the Prevention of COVID-19 Infection

COVID-19 Enfeksiyonunun Önlenmesinde Vitamin ve Minerallere Genel Bakış

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ABSTRACT

The COVID-19 pandemic originated from infection of SARS-CoV-2, is an important international public health concern, threatening to human life. Infection with SARS-CoV-2 can be asymptomatic or can progress to severe disease with crucial respiratory symptoms and important pulmonary changes. The pathological mechanisms underlying of COVID-19 are still unknown, and to date, suitable vaccines or antivirals have not been found for effective treatment for COVID-19. Therefore, reduction of the incidence or severity of infection are of vital importance, and alternative approaches should be explored like nutritional strategies for supporting immune functions. Nutrients with antioxidant and anti-inflammatory properties, may be preventive or attenuant the inflammatory outcomes related to COVID-19. In this review, an overview of some vitamins and minerals is presented in the prevention and management of COVID-19 infection. In particular, we focused on the potential role of micronutrients such as vitamin D, vitamin C, zinc and selenium in all therapeutics, including prevention strategies and mitigation interventions for COVID-19.

Key Words: COVID-19, immune response, micronutrients, SARS-CoV-2, trace elements, viral infection

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ÖZET

SARS-CoV-2 enfeksiyonundan kaynaklanan COVID-19 pandemisi, insan yaşamını tehdit eden önemli bir uluslararası halk sağlığı sorunudur. SARS-CoV-2 enfeksiyonu asemptomatik olabilir veya önemli solunum semptomları ve önemli akciğer değişiklikleri ile ciddi hastalığa ilerleyebilir. COVID-19'un altında yatan patolojik mekanizmalar hala bilinmemektedir ve bugüne kadar COVID-19'un etkili tedavisi için uygun aşılar veya antiviraller bulunamamıştır. Bu nedenle, enfeksiyon insidansının veya şiddetinin azaltılması hayati öneme sahiptir ve bağışıklık fonksiyonlarını desteklemek için beslenme stratejileri gibi alternatif yaklaşımlar araştırılmalıdır. Antioksidan ve antienflamatuar özelliklere sahip besinler, COVID-19 ile ilişkili enflamatuar sonuçları önleyici veya hafifletici olabilir. Bu derlemede, COVID-19 enfeksiyonunun önlenmesi ve tedavisinde bazı vitamin ve minerallere genel bakış sunulmaktadır. Özellikle, COVID-19 için önleme stratejileri ve hafifletme müdahaleleri de dahil olmak üzere tüm terapötiklerde D vitamini, C vitamini, çinko ve selenyum gibi mikrobesinlerin potansiyel rolüne odaklanılmıştır.

Anahtar Sözcükler: COVID-19, immün cevap, mikrobesinler, SARS-CoV-2, eser elementler, viral enfeksiyon

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REVIEW

Toxicological Evaluation of Bisphenol A and Its Analogues

Bisfenol A ve Analoglarının Toksikolojik Değerlendirilmesi

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ABSTRACT

Bisphenol A (BPA) is known as one of the oldest synthetic compounds with endocrine disrupting activity. It is commonly used in the production of epoxy resins, polycarbonates, dental fillings, food storage containers, baby bottles, and water containers. BPA is associated with various health problems such as obesity, diabetes, chronic respiratory diseases, cardiovascular diseases, renal diseases, behavior disorders, breast cancer, tooth development disorders, and reproductive disorders. Increasing health concerns have led the industry to seek alternatives to BPA. As BPA is now being excluded from several consumer products, the use of alternative compounds is increasing. However, the chemicals used to replace BPA are also BP analogues and may have similar or higher toxicological effects on organisms. The aim of this review is to focus on the toxicological profiles of different BP analogues (i.e. BPS and BPF) which are increasingly used today as alternative to BPA.

Key words: Bisphenols, bisphenol A, endocrine disruptor, bisphenol S, bisphenol F

ÖZ

Bisfenol A (BPA) endokrin aktiviteye sahip bilinen en eski bileşiklerden biridir. BPA epoksi reçineler, polikarbonatlar, diş dolguları, yemek saklama kapları, bebek biberonları ve su bidonlarının üretiminde yaygın olarak kullanılmaktadır. BPA obezite, diyabet, kronik solunum hastalıkları, kardiyovasküler hastalıklar, renal hastalıklar, davranış bozuklukları, meme kanseri, diş gelişimi bozuklukları ve üreme bozuklukları gibi çeşitli sağlık sorunlarıyla ilişkilendirilmiştir. Artan sağlık endişeleri endüstriyi BPA alternatifleri aramaya yönlendirmiştir. Günümüzde BPA tüketici ürünlerinden çıkarılmaya başlandığı için, alternatif bileşiklerin kullanımı artmaktadır. Ancak, BPA yerine kullanılan kimyasallar da BP analoglarıdır ve organizmalar üzerinde benzer toksikolojik etkileri olabilir. Bu derlemenin amacı günümüzde BPA'ya artan miktarlarda alternatif olarak kullanılan BP analoglarının (BPS ve BPF) toksikolojik profillerine odaklanmaktadır.

Anahtar kelimeler: Bisfenoller, bisfenol A, endokrin bozucu, bisfenol S, bisfenol F

INTRODUCTION

Endocrine disruptors, such as pesticides and bisphenol A (BPA), can be defined as exogenous substances that cause different levels of changes in the evolution and function of the endocrine system.[1]

BPs are a class of chemicals known as diphenylmethanes. BPs contain two benzene rings separated by a central carbon atom. They mostly have 4-OH substitutes on both benzene rings. Some BPs may have a sulfone group or a sulfide instead of a central carbon atom.[2]

Regulations and increasing concerns among the public have led the industry to seek alternatives for BPA, and as BPA has begun to be excluded from products due to consumer concern the use of alternative BPs has increased and BPA has begun to be replaced by its chemical analogues.[3-6]

The chemicals used to replace BPA also have BP structures and may have similar effects on organisms.[6] According to research, BPA analogues may result in toxic effects similar to or greater than those of BPA.[4]

Bisphenol

The chemical nomenclature of BPA is 2,2-bis (4-hydroxyphenyl) propane and it has a molecular weight of 228.29 g/mol.[4,7,8] If its physical properties are examined it is seen that it has water solubility of approximately 120-130 ppm, low volatility, low air emission, and a short photooxidation half-life (<7 h).[1,8]

BPA is known as one of the oldest synthetic compounds with endocrine activity and was first discovered by Dianin in 1891.[1,9] It is one of the chemicals produced in the largest quantities in the world, with an estimated 5-6.8 million tons produced per year, and it is used in a wide range of areas.[1,4,10] While 70% of the BPA

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Review / Derleme

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Karahalil and Elkama

The Impact of ACE2 Gene Polymorphism in the Development of COVID-19 Disease

COVID-19 Hastalığının Gelişiminde ACE2 Gen Polimorfizminin Etkisi

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ABSTRACT

Coronavirus disease 2019 (COVI-19) was first reported in December, 2019 and virus caused COVID-19 have rapidly spread all over world. Transmission occurs very easily via droplet, aerosol and contact, so mask, hygiene and social distance are important protective factors. Some subjects showed severe findings when some subjects develop disease without any symptoms, so responses to disease differ individually. Genetic structure of subjects may be responsible for different responses. Angiotensin converting enzyme 2 is a polymorphic enzyme and has a crucial role for viral entry. Virus called Severe Acute Respiratory Disease (SARS) Cov-2 uses ACE2 receptor as a substrate to enter into host cells so it is considered that *ACE2* gene polymorphism may be responsible for different response to disease. In this study, the distribution of *ACE2* gene polymorphism and infected cases were presented in 6 populations all over the world and the related evaluations were made. It has been observed that *ACE2* gene polymorphism is protective against the development of COVID-19 disease in Africa and Eastern Mediterranean populations. However, there was no any association between *ACE2* gene polymorphism and the number of infected cases in American and European populations. Cytokines are important immune system parameters since they cause cytokine storm. Not only *ACE2* gene polymorphisms but also cytokine gene polymorphisms should be investigated for subjects' different responses to COVID-19 disease. Studies should be made to find out responsible factor for these different responses to disease, the associations between gene polymorphisms of other proteins on immune system and development of COVID-19 disease.

Key Words: COVID-19, *ACE2* gene polymorphism, infected cases, disease development

Received: 06.24.2020 **Accepted:** 08.27.2020

ÖZET

Corona virus hastalığı ilk kez Aralık 2019'da rapor edilmiştir ve virüsün neden olduğu COVID-19 tüm Dünyada hızlıca yayılmıştır. Bulaşma damlacık, aerosol ve temasla kolayca meydana geldiği için maske, hijyen ve sosyal mesafe önemli koruyucu faktörlerdir. Bazı bireyler hastalık çok ciddi bulgularla seyrederken bazı bireylerde herhangi semptom vermeden gerçekleşmektedir yani hastalığa cevap bireysel olarak farklılık göstermektedir. Bireylerin genetic yapısı bu farklılıktan sorumlu olabilir. Anjiotensin dönüştürücü enzim 2 polimorfik bir enzimdir ve viral girişte kritik role sahiptir. Şiddetli Akut Solunum Yolu Hastalığı (SARS) Cov-2 adı verilen virüs, konakçı hücrelere girmek için substrat olarak ACE2 reseptörünü kullanır, bu nedenle ACE2 gen polimorfizminin hastalığa karşı farklı yanıtlardan alınmasından sorumlu olabileceği düşünülmektedir. Bu çalışmada ACE2 gen polimorfizmi ve enfekte vakaların dağılımı tüm dünyadaki 6 popülasyonda sunulmuş ve ilgili değerlendirmeler yapılmıştır. ACE2 gen polimorfizminin Afrika ve Doğu Akdeniz popülasyonlarında COVID-19 hastalığının gelişmesine karşı koruyucu olduğu görülmüştür. Bununla birlikte, ACE2 gen polimorfizmi ile Amerikan ve Avrupa popülasyonlarındaki enfekte vaka sayısı arasında herhangi bir ilişki yoktu. Sitokinler, sitokin fırtınasına neden oldukları için önemli bağışıklık sistemi parametreleridir. Sadece ACE2 gen polimorfizmleri değil, aynı zamanda sitokin gen polimorfizmleri de bireylerin COVID-19 hastalığına farklı yanıtları için araştırılmalıdır. Hastalığa verilen bu farklı yanıtlardan sorumlu faktörü, bağışıklık sistemi üzerindeki diğer proteinlerin gen polimorfizmleri arasındaki ilişkileri ve COVID-19 hastalığının gelişimini ortaya çıkarmak için daha fazla çalışma yapılmalıdır.

Anahtar Sözcükler: COVID-19, ACE2 gen polimorfizmi, enfekte vakalar, hastalık gelişimi

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Review / Derleme

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Karahalil et al.

Effects of COVID-19 on Respiratory System

Solunum Sistemi Üzerinde COVID-19'un Etkileri

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ABSTRACT

Coronavirus disease 2019 (COVID-19) was caused by a novel type of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was originated in Wuhan, China in December 2019. It spreads rapidly all over the world since respiratory virus infection can occur through many easy ways (*e.g.* contact, droplet spray, aerosol) and besides, asymptomatic people also have contagiousness. So far, there have been 23,491,520 confirmed cases of COVID-19, including 809,970 deaths, reported to World Health Organization (WHO), which declared it as a significant threat to global health. Fever, fatigue, and dry cough are the commonly observed symptoms in the patients. In COVID-19, the main affected system is respiratory system and some cases demonstrate a rapid progression to acute respiratory distress syndrome (ARDS), while other organs are less involved. Angiotensin-converting enzyme 2 receptor-virus association is essential and responsible for the development of the disease. SARS-CoV-2 causes deaths through its severe effects on the respiratory system.

Key Words; COVID-19, viral entry, ACE2 receptor, respiratory system, SARS-CoV, ARDS

Received: 06.25.2020 **Accepted:** 08.25.2020

ÖZET

Coronavirus hastalığı 2019 (COVID-19) ağır akut solunum sendromu coronavirus 2 (SARS-CoV-2) nedeniyle oluşmaktadır. Wuhan'da (Çin) Aralık 2019'da ortaya çıkmıştır. Solunum yolunun viral enfeksiyonu kolay yolla bulaşması (temas, damlacık, aerosol) ve asemptomatik kişilerin bulaştırıcı olması nedeniyle dünya çapında hızla yayılmaktadır. Şimdiye kadar Dünya Sağlık Örgütü'ne (DSÖ) bildirilmiş 23,491,520 onaylanmış COVID-19 vakası, 809,970 ölüm (dahil) bulunmaktadırr ve DSÖ bunu küresel sağlığa yönelik önemli bir tehdit olarak bildirmiştir. Hastalarda ateş, yorgunluk, kuru öksürük yaygın olarak gözlenen semptomlardır. COVID-19'da esas etkilenen sistem solunum sistemidir ve bazı vakalar akut solunum sıkıntısı sendromuna (ARDS) hızla yönelmektedir, diğer organların etkilenmesi daha az gerçekleşmektedir. Anjiyotensin dönüştürücü enzim 2 reseptör ile virüs ilişkisi hastalığın ilerlemesinden sorumludur ve SARS-CoV-2 solunum sisteminde ciddi etkileri olmasından dolayı ölümlere neden olmaktadır.

Anahtar Sözcükler; COVID-19, viral giriş, ACE2 reseptör, solunum sistemi, SARS-CoV-2, ARDS

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Review / Derleme

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Köylü et al.

Histopathologic Examinations and a Research Field of Endometriosis

Histopatolojik Değerlendirmeler ve Bir Araştırma Alanı Olarak Endometriozis

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ABSTRACT

Endometriosis is an estrogen-dependent diseases associated with pain and infertility with features of most frequently symptoms according chronic inflammation, dysmenorrhoea, deep dyspareunia, dyschezia and dysuria. Functional endometrial and stromal tissue implants exist outside the uterine cavity and causes inflammatory processes. Therefore, several undesirable reactions can occur. There are several diagnostic methods however histopathology is one of the gold standards. This review summarizes the histopathological indications of endometriosis disease with different researches.

Key Words: Endometriosis, endometrium, gland, histopathology, inflammation

Received: 08.19.2020 **Accepted:** 09.01.2020

ÖZET

Endometriozis ağrı ve infertilite ile ilişkili östrojen-bağımlı bir hastalık olup en sık görülen semptomlar içerisinde kronik inflamasyon, dismenore, derin disparoni, diskezi ve dizüri yer almaktadır. Fonksiyonel endometrial ve stromal doku implantları rahim boşluğunun dışında bulunur ve inflamatuvar süreçlere neden olur. Bu nedenle, istenmeyen birkaç reaksiyon meydana gelebilir. Birkaç tanı yöntemi vardır ancak histopatoloji altın standartlardan birisidir. Bu derleme, endometriozis hastalığının histopatolojik endikasyonlarını farklı araştırmalarla özetlemektedir.

Anahtar Sözcükler: Bez, endometriozis, endometrium, histopatoloji, inflamasyon

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ÜLKEMİZDE TIBBİ VE AROMATİK BİTKİLER

Kanıta Dayalı Fitoterapi ve Aromaterapi

Prof.Dr. İlkay ERDOĞAN ORHAN*

Tıbbi ve aromatik bitkiler insanlık tarihi boyunca gerek gıda, gerekse şifa amacıyla kullanılagelmekte olup, son yıllarda dünyanın gelişmiş veya az gelişmiş ülkelerinden artan bir trend ile rağbet görmektedir. Ülkemiz 10 binden fazla bitki türünden oluşan zengin florası ile geniş bir biyolojik çeşitliliğe sahiptir ve Anadolu birçok bitkinin de gen merkezi durumundadır. Daha net rakamlarla ifade edilirse; ülkemizde bulunan toplam tür ve tür altı takson sayısı, yabancı kaynaklı ve kültür bitkileri dahil 11.707, endemik takson sayısı 3.649 ve endemizm oranını % 31.82 olarak bilinmektedir. Bu türlerin yaklaşık %32'sinin endemik olması, bu türlerin dünya üzerinde sadece Türkiye'de yetişen türler olduğuna işaret etmektedir. Floramızdaki bitki sayısı ve endemizm oranı göz önüne alınarak; bu rakam-

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DERLEME / REVIEW

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Krill Yağı ve Sağlık Faydaları

Burçin ÖZÜPEK [1], Didem DELİORMAN ORHAN [1]

ÖZ

Krill yağı, okyanuslarda yaşayan *"Euphausia superba"* isimli deniz canlısından elde edilen bir maddedir. Krill yağında yüksek oranda Omega 3 yağ asitleri bulunur ve bu yağ asitleri fosfolipitler şeklindedir. Ayrıca, astaksantin, A vitamini ve E vitamini içeren bir besin takviyesidir. Astaksantin kuvvetli antioksidan özelliğe sahip bir maddedir. Omega 3 yağ asit takviyelerinin; zihinsel gelişimde, hiperlipidemide, premenstrual sendromlarda, enflamatuvar ve kardiyolojik hastalıklarda önemli olduğu bilinmektedir. Son yıllarda Krill yağı balık yağından daha fazla önem kazanmıştır. Ayrıca, okyanuslarda yüzeyde yaşadıkları için toksin ve çevresel kirlilik içerme riski de daha azdır. Çalışmalarda genellikle terapötik etki için günlük doz 1-3 g olarak belirlenmiştir. Takviye edici olarak kullanıldığında ise 500 mg dozda alınması önerilmektedir. Hamilelerde de kullanımı güvenlidir. Dokosaheksanoik asit ve Eikosapentaenoik asit içeriğinin yüksek olması Krill yağının önem kazanmasına sebep olmuştur. Ayrıca bu yağın emiliminin fazla olmasından dolayı araştırmacıların yeni odak noktası Krill yağı olmuştur. Bu makalede, Krill yağının içeriği, biyoyararlanımı, *in vivo* ve klinik aktivite çalışmaları, yan etkileri ile ilgili yayınlanmış olan bilimsel çalışmalar derlenmiştir.

Anahtar Kelimeler: Omega 3 yağ asitleri; karidesgiller.

Krill Oil and Its Health Benefits

ABSTRACT

Krill oil is obtained from *Euphausia superba*, which lives in the oceans. Omega 3 fatty acids in Krill oil are found in the form of phospholipids. Astaxanthin is a strong antioxidant compound. Also, it is a food supplement containing astaxanthin, Vitamin A, and Vitamin E. Omega 3 fatty acid supplements; It is known to be important in mental development, hyperlipidemia, premenstrual syndromes, inflammatory and cardiological diseases. In recent years, Krill oil has gained more importance than fish oil. Also, because Krill lives on the surface in the oceans, there is less risk of containing toxins and environmental pollution. In studies, it is generally recommended to take 1-3 g daily for therapeutic effect and 500 mg as a supplement. It is safe to use in pregnant women. Due to the high content of docosahexaenoic acid and eicosapentaenoic acid and the high absorption rate, the new focus of researchers has been on Krill oil. In this article, published scientific studies on the content, bioavailability, *in vivo* and clinical activity studies and side effects of krill oil have been reviewed.

Keywords: Omega 3 fatty acids; euphausiacea.

GİRİŞ

Euphausiacea familyasından olan karides benzeri kabuklulara genel olarak 'Krill' denir ve 86 türden oluşur. "Antarktika Krill"i olarak da bilinen *Euphausia superba*, Antarktika'yı çevreleyen bozulmamış okyanuslardaki en yaygın Krill türüdür. Birçok deniz canlısını besledikleri için besin zincirinin en alt kısmında bulunurlar (1). 1970'den beri Japonya, Rusya, Ukrayna ve Fransa'da Antartika Krill'i yiyecek olarak tüketilmektedir. 1980'li yıllarda 30.000 ton Krill toplanmış ve Japonya'da yaklaşık her yıl 6.000 tonu gıda olarak tüketilmiştir. Avrupa Komisyonu *E. superba*'dan elde edilen lipit fraksiyonunu güvenli bir gıda olarak tanımıştır. Gıda ve İlaç İdaresi (FDA), Krill yağını gıda olarak tüketimini Generally Recognized As Safe (GRAS) kategorisine almıştır (2). Vücutlarında ve yumurtalarında omega-3 (Eikosapentaenoik asit (EPA), Dokosaheksanoik asit (DHA)) sentezleyebilmek için alg ile beslenirler.

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DERLEME MAKALE / REVIEW ARTICLE

KENEVİR VE SAĞLIK ALANINDA KULLANIMI

HEMP AND ITS USE IN HEALTH

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ÖZ

Amaç: *Kenevir, binlerce yıldır özellikle liflerinden ve tohumları olmak üzere tüm kısımlarından çeşitli amaçlarla (yapı-tekstil malzemesi, kağıt, besin, insan ve hayvan sağlığında ilaç vb.) yararlanılan, ilk kültürü yapılan bitkilerdendir. 1930'lu yıllarda öforik amaçla kullanımının suistimal edilmesi ve ticari kaygılardan dolayı uzun yıllar yasaklı/kısıtlı bitki olarak kalan kenevir, yeni nesil kullanım alanları ve özellikle insan sağlığıyla ilgili etkilerinin bilimsel araştırmalarla kanıtlanmasıyla son yıllarda tekrar ön plana çıkmıştır. Günümüzde pek çok ülke kenevirle ilgili yasaların güncellenmesiyle kenevirin hem endüstriyel hem de medikal etkilerinden faydalanmaya başlamıştır. Ülkemizde ise son yıllarda endüstriyel kenevir üretimi ve kullanımı ile ilgili birtakım gelişmeler yaşanmaktadır.*

Gereç ve Yöntem: *Bu çalışmada, kenevirin botanik özellikleri, tarihçesi, fitokimyasal içeriği, terapötik kullanımları ve sağlık alanında yapılan bilimsel çalışmalar derlenmiştir.*

Sonuç ve Tartışma: *Kenevir bitkisinin botanik özellikleri, genel kullanım alanları ile birlikte geçmişten günümüze sağlık alanında kenevirden elde edilen kullanımda olan ilaçlardan örnekler verilerek fitokimyasal içeriği ve etkileri detaylı olarak verilmiştir. Kenevir tohumu yağı ve kökündeki aktif bileşenlere de değinilmiş, kenevirin terapötik kullanımı tartışılmıştır. Hem endüstriyel hem sağlık alanında kullanılan fakat üretimi ve kullanımı ülkemizde kısıtlı olan kenevir ile ilgili yasaların bilimsel destekli olarak yeniden gözden geçirilmesi ülke ekonomisi ve sağlık sektörü için oldukça önemli sonuçlar sağlayacaktır.*

Anahtar kelimeler: *Cannabis; kenevir, kannabinoitler, kenevir tohumu yağı*

ABSTRACT

Objective: *Hemp is one of the first cultivated plants that have been used for thousands of years, specifically on behalf of its fibers and seeds, for various purposes (building-textile material, paper, nutrients, human and animal health). In the 1930s, since the abuse of the euphoric use for abstinence, hemp was banned/restricted and remained restricted for many years, hemp has emerged once again in recent years with the usage of the plant in new generation areas and in particular the impacts of human health. Nowadays, many countries have begun to benefit from the both industrial and medical effects of hemp by updating the laws related to hemp. In our country, there have been some developments regarding the production and use of industrial cannabis in recent years.*

Material and Method: *In this study, the botanical characteristics, history, phytochemical content, therapeutic uses of hemp and scientific studies in the field of health were reviewed.*

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REVIEW ARTICLES

Tümöral Ekstraselüler Matriks Bileşenlerine Kemoterapötik İlaç Hedefleme

Aysel YILMAZ*, Sevgi TAKKA**

Chemotherapeutic Drug Targeting to Tumoral Extracellular Matrix Components

SUMMARY

Cancer is one of the most important diseases of our century and it is a serious health problem caused by uncontrolled proliferation and spread of body cells. Conventional chemotherapy is one of the most important treatment methods in cancer, but it has results of significant side effects and unfavorable biodistribution. Targeted drug delivery systems are systems in which studies are underway to overcome these problems. However, most targeting strategies today focus on targeting tumor cells themselves. Therefore, untargeted tumor cells, tumor supportive cells and tumor supportive media are ignored. As an alternative approach to prevent this situation, targeting to the extracellular matrix (ECM) of the tumor is discussed. ECM is a general term for a variety of proteins and polysaccharides that act as binders in a multicellular organism that fill the cells secreted by some cells and retain cells in a defined area. Although ECM is tightly controlled during embryonic development and organ homeostasis, it becomes irregular in diseases such as cancer. It is known that the tumor-derived ECM is biochemically different compared to the normal ECM. Studies have shown that ECM components such as endothelial cells, fibroblasts, macrophages, fibronectin, laminin, tenascin contribute to tumor development and these components increase in tumoral ECM. Targeting ECM proteins by recognizing changes in ECM homeostasis that support cancer progression has become an increasingly therapeutic approach to prevent cancer progression. Today, this aproach,which simultaneously affects tumor cells, tumor supportive cells and tumor supportive media, can be useful in improving treatment effectiveness.

Key Words: *Cancer, Tumor, Extracellular matrix, Targeting to extracellular matrix, Drug delivery systems, Drug targeting*

Tümöral Ekstraselüler Matriks Bileşenlerine Kemoterapötik İlaç Hedefleme

ÖZ

Kanser çağımızın en önemli hastalıklarından biridir ve vücut hücrelerinin kontrolsüz çoğalması ve yayılmasıyla oluşan ciddi bir sağlık sorunudur. Konvansiyonel kemoterapi kanserde en önemli tedavi yöntemlerinden biri olmakla birlikte önemli yan etkilerle ve istenmeyen biyodağılımla sonuçlanabilmektedir. Hedeflendirilmiş ilaç taşıyıcı sistemler bu sorunların üstesinden gelebilmek için üzerinde çalışmaların devam ettiği sistemlerdir. Fakat günümüzde hedefleme stratejilerinin çoğunluğu tümör hücrelerinin kendisini hedeflemeye odaklanır. Bu nedenle hedeflenmeyen tümör hücreleri, tümör destekleyici hücreler ve tümör destekleyici ortam göz ardı edilmektedir. Bu durumun önüne geçebilmek için alternatif bir yaklaşım olarak tümörün ekstraselüler matriksine (extracellular matrix-ECM) hedefleme tartışılmaktadır. ECM, çok hücreli bir organizmada bazı hücreler tarafından salgılanan hücreler arasını dolduran ve tanımlanmış bir alanda hücreleri tutan bağlayıcı madde olarak işlev gören çeşitli proteinler ve polisakkaritler için kullanılan genel bir terimdir. ECM, embriyonik gelişim ve organ homeostazı sırasında sıkı bir şekilde kontrol edilmesine rağmen kanser gibi hastalıklarda düzensiz hale gelmektedir. Tümörden türetilen ECM'nin, normal ECM ile karşılaştırıldığında biyokimyasal olarak farklı olduğu bilinmektedir. Yapılan çalışmalar endotel hücreleri, fibroblastlar, makrofajlar, fibronektin, laminin, tenaskin gibi ECM bileşenlerinin tümör gelişimine katkıda bulunduğunu ve tümöral ECM'de bu bileşenlerin arttığını göstermiştir. Kanserin ilerlemesini destekleyen ECM homeostazındaki değişikliklerden faydalanarak ECM bileşenlerinin hedeflenmesi kanser ilerlemesini önlemek için giderek daha ilgi gören bir tenapötik yaklaşım haline gelmiştir. Bugün tümör hücrelerini, tümör destekleyici hücreleri ve tümör destekleyici ortamı eş zamanlı olarak etkileyen bu yaklaşım, tedavi etkinliğinin iyileştirilmesinde faydalı olabilir.

Anahtar Kelimeler: *Kanser, Tümör, Ekstraselüler matriks, Ekstraselüler matrikse hedefleme, İlaç taşıyıcı sistemler, İlaç hedefleme*

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EDİTÖRE MEKTUP

- **SCI/SCIE'da Taranan Hakemli Dergilerde**

Balli, F.N., Kara, E., Demirkan, K., The another side of COVID-19 in Alzheimer's disease patients: drug-drug interactions. International Journal of Clinical Practice 2020;74:e13596.

- **Diğer İndeks'lerde Taranan Hakemli Dergilerde**

Goncuoglu, C., Balli, F.N., Ekincioglu, A., The Effect of Therapeutic Plasma Exchange on COVID-19 Therapy. Turk J Pharm Sci 2020;17(5):463-464.

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LETTER
GERIATRICS

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

The another side of COVID-19 in Alzheimer's disease patients: Drug-drug interactions

Coronavirus Disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a major public health problem. The elderly people are the most affected population by the COVID-19 outbreak in terms of mortality and morbidity. Delirium caused by hypoxia, a prominent clinical feature of COVID-19, may increase the need for treatment of Alzheimer's disease (AD) patients.[1] Therefore, drug-drug interactions should be considered in AD patients while receiving COVID-19 treatment.

Alzheimer's disease treatment consists of cholinesterase inhibitors (ChEIs) (donepezil, rivastigmine and galantamine) and memantine. In addition, antidepressants and antipsychotics are used to control for behavioural and psychiatric symptoms of patients.[2] Despite ChEIs have few pharmacokinetic drug-drug interactions, donepezil and galantamine can be affected by specific substrates, inhibitors or inducers of the cytochrome P450 (CYP450) enzymes (such as CYP2D6, CYP3A4). Chloroquine (CQ) and hydroxychloroquine (HCQ) are metabolised by CYP2C8, CYP2D6, CYP3A4 and inhibits CYP2D6. Pharmacological effects of galantamine and donepezil may increase during CQ/HCQ treatment. Azithromycin has a low risk for CYP450 mediated drug interactions. Cardiac adverse effects (such as bradycardia, heart block and QT interval prolongation) may appear related to both ChEIs and CQ/HCQ or azithromycin. Thus, more frequently electrocardiography monitoring should be considered when concomitant use. Lopinavir is primarily metabolised by CYP3A enzymes and ritonavir is a potent inhibitor for CYP3A and CYP2D6. Additionally, lopinavir-ritonavir are inhibitors of drug transporters such as p-glycoprotein, breast cancer resistance protein and inducers of CYP1A2, CYP2B6, CYP2C19, CYP2C9 and glucuronyl transferase enzymes. Lopinavir-ritonavir may increase plasma concentrations of galantamine and donepezil. Consequently, adverse reactions or toxicity risk of ChEIs may increase. In addition, caution should be advised in terms of bradycardia when using lopinavir-ritonavir and ChEIs together.[2,3]

Memantine undergoes limited hepatic metabolism and has a low risk for pharmacokinetic/pharmacodynamic drug-drug interaction. Therefore, memantine may be a safer alternative in COVID-19 treatment.[2]

QT interval prolongation and ventricular arrhythmias (including Torsades de Pointes) should be monitor in the use of azithromycin, CQ, HCQ and lopinavir/ritonavir with antipsychotics, antidepressants. Caution may be required when using strong CYP2D6 inhibitors (such as paroxetine and fluoxetine) and CYP2D6 substrate CQ.[2,3] In addition, glycemic control should be monitored as selective serotonin reuptake inhibitors may increase the hypoglycemic effect of CQ and HCQ.[4] Due to the effect of ritonavir on a large number of drug- metabolising enzymes, the dose may need to be increased/decreased when used with antipsychotic and antidepressant drugs that may potentially affect their metabolism.[3,5]

No potential interaction is expected between tocilizumab, ribavirin, favipiravir and AD' treatments.[6] Drug interactions should be evaluated in AD patient while receiving COVID-19 treatment. Principally, safer COVID-19 and AD treatments should be preferred, otherwise the patient should be closely monitored essential aspects.

DISCLOSURE

The authors declare they have no conflict of interest.

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LETTER TO EDITOR

The Effect of Therapeutic Plasma Exchange on COVID-19 Therapy

Terapötik Plazma Değişiminin COVID-19 Tedavisine Etkisi

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Key words: COVID-19 treatment, therapeutic plasma exchange, drug removal, pharmacokinetic

Anahtar Kelimeler: COVID-19 tedavisi, terapötik plazma değişimi, ilaç itrahı, farmakokinetik

Dear Editor,

The global pandemic caused by the Severe Acute Respiratory Syndrome-Coronavirus-2 started in Wuhan, China, in December 2019 and spread throughout the world. It is known that cytokine storms play an important role in acute respiratory distress syndrome and multiorgan dysfunction, which are among the main causes of mortality in Coronavirus Disease-2019 (COVID-19) patients. A cytokine storm is triggered by the secretion of proinflammatory cytokines such as tumor necrosis factor-α; interleukin (IL)-1b, IL-2, IL-6, IL-8, and IL-10; and interferon-γ. An excessive inflammatory response occurs as a result of this triggering, which leads to life-threatening clinical symptoms.[1] It has been shown that therapeutic plasma exchange (TPE) may be effective in suppressing cytokine storms.[2]

The main parameters in evaluating the effect of TPE on drug therapy are the volume of distribution and the affinity of drugs binding to plasma proteins. Drugs with low volumes of distribution (<0.2 L/kg) and high plasma protein binding (>80%) often remain in the intravascular compartment and are likely to be affected by TPE. However, not only those two parameters affect the processes of drug removal by TPE; the half-life (>2 h), endogenous drug clearance (<4 mL/min), hydrophilic/lipophilic properties of the drug, and the time between the onset of TPE and drug intake may also affect the rate of excretion. Drugs with a half-life longer than 2 h and that are slowly metabolized or have a low clearance rate are more likely to be excreted by TPE.[3]

TPE has been shown to increase interferon clearance in patients with hepatitis C-related vasculitis.[4] No studies on the effects of TPE on other drugs used in the treatment of COVID-19 have been found. The pharmacokinetic properties of the drugs used to treat COVID-19 are shown in Table 1. Accordingly, interferon, intravenous immunoglobulin, and lopinavir/ritonavir are likely to be affected by TPE. There are not enough data on favipiravir, oseltamivir, tocilizumab, and remdesivir to allow them to be evaluated; however, considering their low distribution volumes and long half-lives, it can be assumed that they are also removed by TPE. In cases when the drug is likely to be excreted with TPE, it is recommended to change the drug administration time to a time after TPE in order not to disrupt the regular blood concentration of the drug. Thus, with rational drug use, the blood level of the drug may be prevented from being affected by TPE and the patient obtains the maximum effect expected from the drug. Blood levels of drugs should be monitored if possible. Clinicians should always consider and evaluate the pharmacokinetic profiles of drugs when opting for co-administration with other therapeutic options.

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2020 YILINDA TAMAMLANAN YÜKSEK LİSANS TEZLERI

Elektro-Çekim Yöntemiyle Hazırlanan Nanoliflerin Vajinal Uygulanan İlaç Taşıyıcı Sistem Olarak Değerlendirilmesi
Yazar: ZEHRA DİK
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Yazar:DİDEM GÜNER KILIÇ
Danışman: PROF. DR. SEVGİ TAKKA
Yer Bilgisi: Gazi Üniversitesi / Sağlık Bilimleri Enstitüsü / Farmasötik Teknoloji Anabilim Dalı / Endüstriyel Eczacılık Bilim Dalı

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Yazar: AYÇA AKTAŞ ŞÜKÜROĞLU
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Siklosporinin Yeni Oral Nanoformülasyonunun Geliştirilmesi ve İn vitro/İn vivo Değerlendirilmesi
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Yeni Bir Yöntem ile Aerosol Haline Getirilen Pirfenidonun Inhalasyon Yoluyla Etkinliğinin Değerlendirilmesi
Yazar:SERKAN ÜNLÜ
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Tip 2 Diyabet Tedavisinde Kullanılmak Üzere Oral Yolla Uygulanacak Protein/Peptit Içeren Kendiliğinden Emülsifiye Olan Nanoformülasyonunun Geliştirilmesi İn vitro/İn vivo Değerlendirilmesi
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3D Baskılama Tekniği ile İlaç Formülasyonlarının Hazırlanmasına Yönelik Çalışmalar
Yazar: HAZAL EZGİ GÜLTEKİN
Danışman: PROF. DR. FÜSUN ACARTÜRK
Gazi Üniversitesi / Sağlık Bilimleri Enstitüsü / Farmasötik Teknoloji Anabilim Dalı

Yeni Izoksazol Türevlerinin Sentezi, Karaciğer Ve Meme Kanseri Hücre Hatlarına Karşı Sitotoksik Etkilerinin Incelenmesi
Yazar: KÜBRA İBİŞ
Danışman: PROF. DR. ERDEN BANOĞLU
Gazi Üniversitesi / Sağlık Bilimleri Enstitüsü / Farmasötik Kimya Anabilim Dalı

Antibiyotik Tayini Için Moleküler Baskılanmış Polimer Temelli Fosforesans Sensörü Geliştirilmesi
Yazar: HÜMA YILMAZ
Danışman: PROF. DR. HASAN BASAN
Gazi Üniversitesi / Sağlık Bilimleri Enstitüsü / Analitik Kimya Anabilim Dalı

Yüksek Fruktoz Diyetinin Oluşturduğu Metabolik Sendromda Insülin Sinyal Yolağı, Inflamasyon ve Intestinal Mikrobiyotanın Incelenmesi: Kefirin Tedavi Potansiyelinin Belirlenmesi
Yazar: ESRA ŞUMLU
Danışman: PROF. DR. FATMA AKAR
Gazi Üniversitesi / Sağlık Bilimleri Enstitüsü / Farmakoloji Anabilim Dalı / Farmakoloji Bilim Dalı

2020 YILINDA TAMAMLANAN DOKTORA TEZLERI

Endokannabinoid Sistemde Görev Alan Bazı Reseptör Ve Enzimlere Ait Çeşitli Polimorfizmlerin Sentetik Kannabinoid Bağımlılığındaki Rollerinin Araştırılması
Yazar: BERİL ALTUN
Danışman: PROF. DR. İSMET ÇOK
Gazi Üniversitesi / Sağlık Bilimleri Enstitüsü / Farmasötik Toksikoloji Anabilim Dalı

Rinoplasti Ameliyatında Kullanılan Remifentanil, Nitrogliserin, Esmolol ve Nitrogliserin+esmolol'ün Kan Basıncı ve Kalp Hızı Üzerindeki Etkinliklerinin Değerlendirilmesi ve Karşılaştırılması
Yazar: MOHAMMAD ABBAS
Danışman: PROF. DR. MECİT ORHAN ULUDAĞ
Gazi Üniversitesi / Sağlık Bilimleri Enstitüsü / Farmakoloji Anabilim Dalı / Farmakoloji Bilim Dalı

3,6-Disübstitüe Benzoksazo|-2(3HFon/Benzotiyazo1-2(3H)on Türevlerinin sentezi ve Alzheimer Hastalığı Üzerindeki Etkilerinin In Vitro Olarak İncelenmesi
Yazar: MERVE ERDOĞAN
Danışman: PROF. DR. DENİZ S. DOĞRUER
Gazi Üniversitesi / Sağlık Bilimleri Enstitüsü / Farmasötik Kimya Anabilim Dalı

Ülkemizde Yetişen Bazı Bitkilerin HMG (3-Hidroksi-3-Metil-Glutaril) KoA Redüktaz Enzim İnhibitör Etkisi Yönünden Değerlendirilmesi
Yazar: Serkan Yiğitkan
Danışman: PROF. DR. İLKAY ERDOĞAN ORHAN
Gazi Üniversitesi / Sağlık Bilimleri Enstitüsü / Farmakognozi Anabilim Dalı

E-GAZİ FARMA

Cilt 5 Sayı 1 10 Aralık 2020 Eczacılık Fakültesi Bülteni