



None Small Cell Lung Tumor Targeting with Radiolabeled D4 Peptide Conjugate as A SPECT Radiotracer

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Abstract

Introduction: None small cell lung cancer is one of the most leading causes of cancer death in the world. Early detection of cancerous mass plays an important role in cancer treatment. Molecular imaging is one of the diagnostic tools for tumor detection. Since, EGFR overexpression has been observed in many of human cancers, it has been selected as a suitable candidate for specific tumor targeting. D4 peptide (Leu-Ala-Arg-Leu-Leu-Thr) was selected as a good candidate for specific targeting of EGFR. In this study, new D4 peptide conjugate has been evaluated as a SPECT radiotracer for tumor targeting in NSCLC.

Methods : HYNIC conjugated peptide was labeled with ^{99m}Tc using tricine and mixture of EDDA/Tricine as co-ligand. Cellular EGFR-specific binding, affinity and cellular internalization as well as in-vivo tumor targeting were assessed.

Results: In each of the synthetic radiopeptides, radiochemical purity of them determined 98% without any purification. Specific binding experiment of ^{99m}Tc-HYNIC-Ser-Ser-Ser-D4 peptide showed dissociation constant of 119 ± 34 nM. Biodistribution studies in normal mice and A-549 xenografted nude mice showed rapid clearance from blood and other non-target organs. In mice bearing A-549 xenografts, ^{99m}Tc-HYNIC-Ser-Ser-Ser-D4 peptide showed rapid tumor targeting at 1 h after injection. Tumor uptake values (percentage of injection dose per gram of tissue) were $7.55 \pm 0.43\%$ and $6.82 \pm 0.32\%$ at 1 and 4 h after injection, respectively. *In vivo* blocking by presaturation of EGFR using an excess of non-labeled peptide reduced 36% tumor uptake of radioactivity at 1 h after injection and confirmed the specificity of radiopeptides tumor uptake. Finally, Gamma camera imaging was

performed at 1h after injection of radiopeptide by a dual-head e.cam gamma camera, equipped with a low-energy, high-resolution collimator.

Conclusion: Findings showed that modified radiolabeled peptide is a promising candidate for tumor targeting and molecular imaging in non-small cell lung cancer.

Keywords: Tumor Targeting, ^{99m}Tc , small peptide, EGFR, lung cancer.



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Preparation and Physicochemical Characterization of Topical Chitosan-Based Film Containing Griseofulvin-Loaded Liposomes

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Abstract

Introduction: Griseofulvin is an antifungal drug and is available as oral dosage forms. Development of topical treatment could be advantageous for superficial fungal infections of the skin.

Methods: In this study, films prepared from the incorporation of griseofulvin-loaded liposomes in chitosan film for topical drug delivery in superficial fungal infections. The properties of the films were characterized regarding mechanical properties, swelling, ability to transmit vapor, drug release, thermal behavior, and antifungal efficacy against *Microsporum gypseum* and *Epidermophyton floccosum*.

Results: The presence of liposomes led to decreased mechanical properties but lower swelling ratio. Higher amount of drug permeation and rate of flux were obtained by liposomes incorporated in films compared to liposomal formulations. Antifungal efficacy of formulations was confirmed against two species of dermatophytes *in vitro*.

Conclusion: Therefore, two concepts of using vesicular carrier systems and biopolymeric films have been combined and this topical novel composite film has the potential for griseofulvin delivery to superficial fungal infections.

Keywords: Antifungal effect, chitosan film, dermatophytes, griseofulvin, liposomes, skin permeation



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Codon Optimization, Subcloning and Expression of Recombinant Human Microplasminogen

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Abstract

Introduction: Plasmin is a serine protease that can degrade extracellular matrix (ECM) components including fibrin, laminin, and fibronectin. Microplasminogen (μ Plg) is a truncated form of plasmin which can be used as a therapeutic agent such as inducing posterior vitreous detachment (PVD) in many vitreoretinal diseases and also in the dissolution of blood clots in thrombotic diseases.

Methods: The purpose of this study was to produce recombinant human microplasminogen in the methylotrophic *Pichia pastoris*. After codon optimization and synthesis of the gene, recombinant plasmid (pPICZ α - μ Plg) constructed and transformed into X-33 cells. The cells then were grown on a YPDS plate containing Zeocin antibiotic. For protein expression, the positive recombinant clones were transferred into YPM medium and were induced by methanol. μ Plg was purified by Ni sepharose column, and the presence of the recombinant protein confirmed by SDS-PAGE.

Results: Our findings showed that the recombinant protein (28 kDa) has been successfully secreted into the supernatant of the induction medium without α -factor secretory signal. But further studies are needed to optimize the yeast cells culture conditions for increasing the concentration of secreted protein. Production of high purity μ Plg in *Pichia pastoris* implies that this system can be used to product variety of recombinant drugs.

Conclusion: In summary, μ Plg can be considered as a potentially valuable pharmaceutical agent for effective and less invasive treatment of traumatic and even prophylactic application in some disorders such as vitreoretinal and thrombotic diseases.



Synergistic Antifungal Activity of Atorvastatin and Fluconazole against the Growth and Ergosterol Biosynthesis in *Candida Albicans*

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Abstract

Introduction: Candidiasis due to *Candida* species is the most prevalent opportunistic fungal infection and a major public health problem. In the present study, the *in vitro* antifungal activity of atorvastatin alone and in combination with fluconazole was tested against *Candida albicans*.

Methods: *Candida albicans* was cultured in presence of different concentrations of atorvastatin in 6 well flat-bottom microplates for 4 days at 28 °C. Synergistic antifungal effects of atorvastatin with fluconazole were determined using checkerboard titration assay in 96 microplates. The membrane ergosterol content in control cultures and those treated with atorvastatin was determined by spectrophotometry.

Results: Significant growth inhibition was reported in *C. albicans* cultures exposed to atorvastatin with MIC and MFC values of 160 and 320 μM, respectively. Growth inhibition was significantly increased when fluconazole were combined with atorvastatin indicative of synergism between two compounds. Synergism was also confirmed by the increased reduction in cellular ergosterol levels of 32.48 to 97.64%. The IC₅₀ value of atorvastatin was measured as 81.28 μM.

Conclusion: Our results showed strong antifungal activity of atorvastatin alone and in combination with fluconazole against *C. albicans* as the major etiologic agent of candidiasis. Selected statin–azole combinations might be viable alternatives for the therapeutic management of mycosis at lower administration doses or with a higher efficiency.



Economic Burden of Irrational Acetaminophen Use in an Emergency

Department

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Abstract

Introduction: Acetaminophen is a drug that is widely used as the first line for the treatment of pain and fever. The goal of this study is utilization evaluation of intravenous acetaminophen in an emergency ward of a teaching hospital to determine the consumption pattern and calculate unnecessary costs.

Methods: Patients in whom intravenous acetaminophen was prescribed by emergency medicine specialists of the emergency ward in a teaching hospital in Tehran during a 30-day period were surveyed and compared to the TUMS therapeutic guideline.

Alternative routes for acetaminophen administration was evaluated and if available, unnecessary cost of injection (including medication, IV catheter, IV set, etc.) was calculated.

Results: Fifty-one cases (%91) of total 56 did not agree with the prescribing guidelines; and in these cases there has been the ability of using alternative route that charged 4.469.980 RLs more than it could cost if the guideline was followed.

Conclusion: Acetaminophen is one of the most prescribed drugs. Our study showed a high rate of irrational IV acetaminophen prescription. A study in Australia showed that %25 of patients who received intravenous acetaminophen was not in accordance with the guidelines, ninety percent of this group could be treated with alternative routes of administration.

Irrational drug use in the short period of our study costs 4.469.980 RLs more than if it was used in accordance with the guideline, extrapolating these data to the whole population alarms us with the huge unnecessary cost of

treatments in the country. Implementation of guidelines and pharmacist deployment in clinical wards may optimize these problems.

Keywords: Intravenous Acetaminophen, Utilization Evaluation, Prescribing guidelines.



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Antimalarial Drugs-Induced Hepatic Injury in Rats and the Protective Role of Carnosine

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Abstract

Introduction: Chloroquine and amodiaquine are used in the prophylaxis and treatment of malaria. However, hepatic injury is associated with malaria drug therapy. On the other hand, there is no promising hepatoprotective agent for prophylaxis or treatment of antimalarial drugs-induced liver injury. Carnosine is a naturally occurring peptide with pleiotropic protective properties in different tissues. This investigation aimed to evaluate the effect of carnosine administration in antimalarial drugs-induced hepatic injury in rats.

Methods: Animals were treated with amodiaquine (180 mg/kg, oral) or chloroquine (970 mg/kg, oral). Carnosine (250, 500 and 1000 mg/kg, i.p) was administered as the hepatoprotective agent against antimalarial drugs liver injury.

Results: Liver injury was manifested biochemically by a significant increase in serum level of ALT, LDH, and AST. In addition, hepatic tissue from antimalarial drugs-treated rats showed a significant increase in reactive oxygen species (ROS), lipid peroxidation and protein carbonylation along with a decrease in hepatic glutathione reservoirs and total antioxidant capacity. Moreover, the liver histopathologic evaluation revealed significant congestion, inflammation, and necrosis in amodiaquine and/or chloroquine-treated animals. Carnosine

administration significantly alleviated antimalarial drugs-induced pathologic changes in serum biochemistry and liver tissue.

Conclusion: Our data suggest that carnosine possesses protective properties against amodiaquine and/or chloroquine-induced liver injury possibly through mitigation of drug-induced oxidative stress and its consequent events.

Keywords: Antimalarial agents, Drug-induced liver injury, Hepatoprotection, Malaria, Peptide



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Hepatoprotective Effects of *Glycyrrhiza glabra* Aqueous Extract against Carbon Tetrachloride-Induced Liver Injury in Mice

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Abstract

Introduction

The hepatoprotective effects of *Glycyrrhiza glabra* (GG) aqueous extract, on the carbon tetrachloride (CCl₄)-induced liver damage in mice was investigated.

Methods: Mice received a single dose of CCl₄ (20 mg/kg, in olive oil, i.p) and different doses of GG (150, 300 and 600 mg/kg, gavage).

Results: It was found that administration of GG extract to CCl₄-treated animals significantly reduced plasma level of hepatic injury biomarkers (alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase), in a dose-dependent manner. The histopathological evaluation of the livers also revealed that GG extract effectively reduced the incidence of liver lesions induced by CCl₄. Moreover, GG extract significantly alleviated CCl₄-induced lipid peroxidation and glutathione depletion in liver.

Conclusion: These results suggest the potential hepatoprotective effects of GG extract. Mechanisms including antioxidant and radical scavenging properties of GG extract might be involved in its hepatoprotective properties.

Keywords: Hepatoprotective- Liver Injury- Carbon Tetrachloride- *Glycyrrhiza glabra*



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Comparative Study on Common Medicinal Plants in Traditional Persian Medicine and Traditional Italian medicine

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Abstract

Introduction: Traditional medicine, as a school of medicine developed in various civilizations before the era of modern medicine, is being considered more recently. Traditional Persian medicine is one of the greatest sources of the field including various Pharmacopeias compiled from 9th- 18th centuries A.D. In order to gain the most medicinal benefit of TPM (Traditional Persian Medicine), the information should be particularly coded and categorized. On the other hand, comparing valuable data mentioned in traditional medicines of different nations helps us to extract similar information and reach considerable advances in modern medicine, especially drug synthesis field. The goal of the present study is to compare the medicinal information of common medicinal plants, between TPM pharmacopeias and Traditional Italian medicine (TIM) pharmacopeias.

Methods: First by comparing the scientific names of plants from Dioscorides *Materia Medica* and *Makhzan-ol-Advieh*, common plants were gathered. Two major pharmacopeias including *Kitāb al-ḥāwī fī al-ṭibb* (The Comprehensive Book on Medicine, 9th -10th centuries A.D.), Canon of Medicine (10th -11th), were chosen to study the medicinal applications, useful parts, modes of application, and side effects of the selected plants. Moreover some specific abbreviated terms were applied to classify the plants properties. The same study was simultaneously performed on Dioscorides book in Italy.

Results: Among 428 studied medicinal plants, 223 of them were exactly the same in Canon of Medicine, *al-ḥāwī fī al-ṭibb* and Dioscorides. The result of the study is available as a searchable excel data file, bearing a complete set of information gathered out of important TPM and TIM pharmacopeias.

Conclusion: The existence of an available databank is obviously the most initial necessity in either progressing any research or manufacturing a new drug. In addition a thesaurus would be much more scientifically valuable if it contains information extracted from various international pharmacopeias.

Keywords: Traditional Persian Medicine, *Kitāb al-ḥāwī fī al-ṭibb*, *Canon of Medicine*, Data Bank, Dioscorides.



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The Drug Molecule Releases Kinetic Evaluation and Modeling from Lipid-Based Nanoparticles: A Retrospective Approach

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Abstract

Introduction: Evaluation and modeling of therapeutic molecule release from drug delivery devices is often tried to determine the main factors of the drug molecule release rate from the nanoparticles with the final goal of the recognition of the optimal conditions cause to the desired release profile *in vivo*. This study focuses to present a

comparative mathematical analysis of drug release from lipid-based nanoparticles to find a general model more applicable to multi-mechanistic release.

Methods: Drug release data from various types of lipid nanoparticles such as liposomes, nanostructured lipid carriers (NLCs) and nano/micro emulsions (NEMs/MEMs) extracted from the literatures were applied to the eight conventional models. Coefficient of determination (R^2) and final percent error (E %) were calculated for each set as well as the overall error (OE), and the number of error (NE) for all sets.

Results: The model has the highest R^2 and the number of the error (5%), as well as both the lowest overall error (OE), was considered as the best one. Among the models, Higuchi model produced R^2 and NE values of 0.91 and 30% for NLC, 0.85 and 38% for liposomal drug delivery systems, and 0.77 and 19% for NEMs/MEMs, respectively.

Conclusion: It is obvious that the Higuchi model is the best one to predict the drug release features from lipid-based nanoparticles. Kinetic models are capable of characterizing the *in vivo* release profile. Therefore, the use of *in vitro* drug release data to predict *in vivo* performance of drug substances can be considered as the rational development of controlled release formulations.

Keywords: Liposomes, Solid lipid nanoparticles, Nanostructured lipid carriers, Nano/Micro emulsions, Release kinetic.



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Application of Molecular Biology Methods in Herbal Medicine Authentication

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Abstract

Introduction: Herbal medicine as a traditional system utilizes medicinal plants, to cure various disorders. Nowadays, in medicinal plant industry, different types of substitution and adulteration with closely related species have been introduced that could decrease the efficacy of herbal products or sometimes result in adverse reactions. There are several conventional methods for the identification of medicinal plant including organoleptic methods, macroscopic and microscopic methods and chemical profiling by instrumental techniques such as chromatography.

First two methods require trained persons and chemical method highly depend on instrumental and conditional features. However, DNA based techniques for plant identification are more precise and accurate methods need simple instrumental requirements. DNA is a stable macromolecule and identification of biological specimens using short DNA sequences from either nuclear or organelle genomes can consider as taxon identifiers (1, 2).

Methods: Searching keywords such as medicinal plant, herbal medicine with authentication or adulteration resulted in about 1500 published articles considering DNA based molecular biology methods.

Results: Genome-based methods have been developed for the identification of medicinal plants since the early 1990's, greatly depend on polymerase chain reaction (PCR) and its various subclasses as DNA barcoding methods (3-5). Ribosomal DNAs (5s, 26s and 16s rDNA) and chloroplast genome are the most studied fragments. Hybridization-based microarray especially through the microfluidic systems are the rapid and high throughput tools for genotyping and medicinal plant identification (6, 7).

Conclusion: Herbal medicine authentication using DNA barcoding depends on the DNA loci that should have sufficient information to differentiate between closely related plant species and discover new cryptic species. Advances in DNA barcoding coupled with next-generation sequencing and high-resolution melting curve analysis can lead to successful species identification, even from finished herbal products (8, 9).

Keywords: Medicinal Plant, Authentication, Adulteration, DNA-based identifiers, PCR.



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Comparing Blood Lead Level among Oral/inhaled Opium Addicts with a Non-addict Control Group in the Southeast of Iran

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Abstract

Introduction: Opium is widely used among addicts in the Middle East countries such as Iran. Recent reports suggest that opium sellers cheat their customers by adding lead to the opium. Contaminated opium can threaten the health of consumers. This study was designed to evaluate the lead concentration in blood sample of oral and inhaled opium user's referring to Amir Al-Momenin Hospital in Zabol, Iran, during spring 2015 in comparison with those of control group.

Methods: Blood lead level (BLL) of 188 subjects with a mean age of 52.06 years in three categories - including oral opium addicted (55 patients), inhaled opium addicted (55 patients), and healthy control group (n = 78) - was assessed. The BLL of all the subjects was assessed using an atomic absorption spectrophotometer.

Results: Almost all participants consumed "Tariak" (99.09%). Mean \pm standard deviation (SD) duration of opium addiction was 13.21 ± 10.26 years. The average blood lead concentration among oral users, inhaled users, and control group were 34.31 ± 21.54 , 41.13 ± 26.40 , and 9.86 ± 4.40 $\mu\text{g}/\text{dl}$, respectively (P = 0.001).

Conclusion: Our study showed significant differences of BLLs between opium users and control group. We also did not find any association between blood lead concentration and method of opium consumption.

Keywords: Blood lead level, Opium, Addict, Poisoning.



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Investigation of Chemical Constituents and Essential Oil of *Stachys Setifera* and Biological Effects

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Abstract

Introduction: *Stachys* is one of the largest genres in Lamiaceae[1].It is used for treatment of skin wound, blood pressure lowering and anti-inflammation in folk medicine[2].

Methods: Aerial parts of the plant were collected from Esfahan Province in Jun 2016.It was extracted with methanol and fractionated. Main compounds were separated and isolated by means of chromatographic methods mainly column chromatography checked by TLC. Essential oil of *S.setifera* extracted by clevenger and then identified by GC-MS. The activity of Methanol, EtOAc, Chloroform and Hexane extracts were investigated by DPPH [3], FRAP and Follin-ciocalteu methods and cytotoxic effect was investigated.

Results: As a result Methanol extract had the most cytotoxic effect with $LC_{50}=39.31\mu\text{g/ml}$. And EtoAc faraction had the most antioxidant activity with $IC_{50}=16.97\ \mu\text{g/ml}$ and phenolic compounds. The main compounds of methanol extract were identified by spectroscopic methods, including $^1\text{HNMR}$ and $^{13}\text{CNMR}$. Based on the NMR data comparison of the data given in the literature, the structures of the isolated compounds were established as Stachys pinoside, Verbascoside and chlorogenic acid. The main compounds of essential oil of *S.setifera* were established as oxygenated monoterpenes with 31.35 % and nonterpenes with 33.58% and monoterpene hydrocarbons with 16.03%. Linalool with 12.5% and Pulegone with 11.8% were the most constituents in essential oil respectively.

Conclusion: Stachyspinoside, Verbascoside, and Chlorogenic acid have some therapeutic effects like inhibitory of lipid peroxidation and effect on learning, memory impairment and anti-inflammatory activity therefore these effects persuaded us to characterize this plant.

Keywords: Flavonoid, anti-oxidant activity, *Stachys setifera*, NMR, lamiaceae.



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Sedative Effect Evaluation of Sublingual Lorazepam versus Placebo in Endoscopy Candidate Patients: A Double Blind Randomized Clinical Trial

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Abstract

Introduction: Lorazepam is a benzodiazepine drug that is used as an anti-anxiety, sedative, hypnotic, and anticonvulsant (1). Sublingual delivery of this drug may accelerate the onset of its action by bypassing the enterohepatic recirculation and first-pass metabolism of it. Main aim of this study was to evaluate this effect on the drug efficiency in patients who use the drug as a premedication for endoscopic procedures(2).

Methods: The formulation that used in this study was contained: 90 mg mannitol (carrier powder), 2mg lorazepam, 6 mg cross linked poly vinyl pyrrolidone (disintegrating agent), 20.8 mg avicel (filler), and magnesium stearate (lubricant). 57 out of 114 patients were taken these immediate-release tablets before procedure of endoscopy sublingually (1). Remainders were received placebo in the same way.

Results: Overall patient response was better in the lorazepam group ($P = 0.05$). Patient-reported incidence of amnesia was significantly higher in the lorazepam than in the placebo group ($P < 0.05$).

Conclusion: Sublingual lorazepam improved patient compliance by inducing amnesia, and the premedication had not heavy sedation and did not adversely affect the procedure.

Keywords: Lorazepam, sublingual, endoscopy and premedication.



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Preparation and Characterization of Fast Dissolving Omeprazole Nanofibers Using Electrospinning Technique

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Abstract

Introduction: Fast dissolving oral drug delivery systems are the dosage forms that whenever be placed on the tongue, will be dissolved or disintegrated in less than a minute in the oral cavity without the need to fluids drinking or chewing .resulting in the enhancement of drug solubility, release, onset of action and bioavailability.(1) The aim of this study is development of omeprazole fast dissolving oral nanofibers using electrospinning technique.

Methods: Omeprazole-loaded electrospun nanofibers were prepared by different ratios of two biodegradable polymers means poly vinyl alcohol (PVA) and poly vinyl pyrrolidone (PVP) and were evaluated in the terms of morphology, folding endurance, mechanical properties, pH, drug release and disintegration time.

Results: The formulations were successfully electrospun to create the white sheets of nanofiber mats with high mechanically strength. Nanofibers solutions produced a pH within mouth pH range. All of the formulations except the one were disappeared completely in the stimulated saliva fluid during less than 3 minutes.

Conclusion: Omeprazole can be formulated as oral fast dissolving nanofibrous films by electrospinning technique.

Keywords: Omeprazole, Electrospinning, Nanofiber, Poly vinyl alcohol, Poly vinyl pyrrolidone.



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2-Benzoxazolinone Derivatives as Anti-HIV-1 Agents: Design, Synthesis, Molecular Modeling and Anti-HIV-1 Assay

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Abstract

Introduction: AIDS therapeutic targets principally consist of 3 enzymes: reverse transcriptase (RT), protease (PR) and integrase (IN) (1, 2). Integrase strand transfer inhibitors among the HIV inhibitors has the advantage of suitable safety profile and high potency (3). The chelating motif and coplanar hydrophobic aryl group are the common pharmacophores of an integrase strand transfer inhibitor (INSTI) (4).

Methods: In this research, we selected the 2-benzoxazolinone as a new chemical scaffold for INSTI inhibitory potential and joined it with a hydrazide linker that is a part of some potent INSTIs. We incorporated the aryl group in these structures to occupy the hydrophobic module of the IN active site. Benzo[*d*]oxazol-2(3*H*)-one (1) was

prepared by classical procedure starting from 2-aminophenol and urea. Then, this intermediate was treated with ethyl chloroacetate in the presence of potassium carbonate and acetone as the solvent gave the N-alkylated product. This ester intermediate reacted with hydrazine hydrate to afford the acid hydrazide. This intermediate was reacted with substituted benzoyl chlorides in dry DMF and catalytic amount of anhydrous sodium carbonate. Also, this intermediate with some phenyl isothiocyanate derivatives were heated under reflux in absolute ethanol. Dehydrocyclization of compounds with thioamide linker was performed in conc. sulfuric acid to afford the thiadiazole containing derivatives.

Results: According to the docking results, 2-benzoxazolinone ring could displaces the 3'-end reactive adenosine in the IN active site and the ligand heteroatoms complexes the magnesium cofactors in the IN. Anti-HIV activity and toxicity assay were performed in Hela cells cultures. Anti-HIV activity at 100 μ M was in the range of 5-84% and 37-94% for cell viability.

Conclusion: The novel designed scaffold for anti-HIV activity was introduced. Molecular modeling studies confirmed the integrase inhibitory potency of 2-benzoxazolinones. Considering the biological test results, incorporation of the ring in the linker potentiates the anti-HIV activity. Drawing the Comparison between linear linkers, thioamide have worked better than benzohydrazide for anti-HIV activity.

Keywords: 2-Benzoxazolinone, Anti-HIV-1 activity, Design, Synthesis, Molecular modeling.



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Evaluation of the Effect of Education by Pharmacists in Hyperlipidemic Patients Treated with Statins on Patient's Adherence to Medications and Level of Blood Lipids

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Abstract

Introduction: Hyperlipidemia is one of the most common chronic diseases that millions people suffer it approximately. Studies show that many patients have suboptimal adherence to statin medication which leads to serious negative health consequences.

This paper evaluated the effectiveness of educational intervention in hyperlipidemic patients treated with statins on adherence to statin medication and level of blood lipids.

Methods: In this interventional clinical trial study the studied population was all patients with heart disease treated with statins that had been referred to the Hamadan Farshchian hospital from January 2016 to June 2016. The sample size in this study was 50. The study data collection tools included a demographic and Morisky questionnaire and data of patient's lipid profile before and after 6 month after intervention. Data were analyzed in SPSS/19 using T-test, Mann-Whitney and X2 tests. Significant level was considered less than 0.05.

Results: Data analysis reflects the homogeneity of medication adherence and levels of lipid profile in both groups before the intervention. Before intervention the medication adherence was not significantly different in both groups ($p=0.49$) but after intervention the medication adherence increased in the intervention group ($p<0.001$) and level of LDL significantly decreased ($p=0.02$) but after intervention there were no statistical difference in level of HDL, triglyceride and total cholesterol in both groups.

Conclusion: These findings suggest that educational counseling by pharmacists could have a positive role on patient's adherence to drugs and level of LDL.

Keywords : Hyperlipidemia, medication adherence, lipid profile.



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Management of Patients Hospitalized for Diabetic Foot Infection: A Local Evaluation

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Abstract

Introduction: Diabetic foot ulcer (DFU) is the most increasing-trend complication of DM over previous decades. The present study was implemented to determine precisely how DFU is managed in the most referral hospital in Isfahan.

Methods: This prospective observational cross-sectional study was conducted from 1 July 2016 till 15 December 2017 in the biggest university affiliated hospital, Al-Zahra, in Isfahan, Iran. The information was collected by an educated pharmacy's student by filling the designed questionnaire included: Baseline characteristics, methods used to investigate the infected lesion, management of the infected wound, assessment of risk factors relate to patient's outcome.

Results: The mean age of patients was around 59 years. The majority of our patients had affected with Type 2 DM (96.3 %). Most of the patient had wound with grade 3 in Wagner classification. Lesions mainly involved toes (46.3%). The most lesions had mean size of the 5-10 centimeters (42%). The most frequently prescribed combination antibiotics were meropenem and targocid (teicoplanin) (34.1%), Tazocin[®] (Piperacillin + tazobactam) and targocid (24.3%). Mean duration of parenteral therapy (alone or in associated with oral treatment) was 14.95 ± 7.62 days. Amputation of organs had significant correlation with ulcer's size ($P= 0.001$) and Wagner classification had a significant differences with unhealed group ($P< 0.001$).

Conclusion: Although our diabetic center is university-affiliated, there are still several points and pit wall must be considered and revised in DFU patients. Obtaining microbiological sampling, antibiotic management and baseline assessment of wound in patients are the most problematic discovered parts in our investigation.

Keywords: Diabetes mellitus, Diabetic foot ulcer, Foot ulcer, Foot infection, Microbiology, Diabetic foot management.



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Study of Chlorpheniramine Interaction with Antinociceptive Effect of Tramadol and Its Possible Mechanisms in Male Mice

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Abstract

Introduction: Tramadol, an opioid pain medicine used to treat pain, has gastrointestinal complications and can result in high risk for addiction and dependence [1]. Chlorpheniramine is an antihistamine which was used, in this study, as a pain relief medicine. The simultaneous taking of this pain medicine with other pain medicines can reduce its dosage and side effects [2]. The aim of present study was to investigate the efficacy of using tramadol and chlorpheniramine simultaneously to reduce the side effects of Tramadol. Additionally, the potential mechanisms for consuming the pain medicine tramadol alone and together with chlorpheniramine were examined.

Methods: In this study, 4 groups of male mice received 5, 10, 20, and 40 mg/kg dosage of tramadol, respectively, to assess the pain relief efficacy and to determine the ED50 of Tramadol. The assessment test used in the study was the writhing test. The other three groups of mice received 10, 20, and 40 mg/kg dosage of chlorpheniramine. Moreover, the other three groups received tramadol ED50 along with 10, 20, and 40 mg/kg dosage of chlorpheniramine and the pain relief was measured. Then, the antagonist of cholinergic (atropine), serotonergic (granisetron), dopaminergic (metoclopramide) and opioidergic (naloxon) were used to examine the possible mechanisms for tramadol pain relief.

Results: The findings of this study indicated that tramadol and chlorpheniramine had a significant effect on the pain relief compared with the control group. The ED50 of tramadol was estimated to be 7.8 mg/kg. Also, the results illustrated that using chlorpheniramine in combination with tramadol significantly increases the pain relief of tramadol. The naloxon and granisetron decreased analgesic effects of tramadol.

Conclusion: According to the results chlorpheniramine can significantly increase the tramadol pain relief efficacy. Therefore, the simultaneous consumption of this combination can drastically result in a reduction in the tramadol dosage and its side-effects.

Keywords: Tramadol, chlorpheniramine, naloxone, metoclopramide, atropine, granisetron



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Microbiological Identification and Quantification of a Probiotic Product

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Abstract

Introduction: Baby colic is generally refers to a behavioral condition characterized by excessive and paroxysmal crying in 2 to 4 weeks neonates that may prolonged until 4 months. The causes of colic and its crying that mostly occurs during the evening are not generally known but less than 5% of them have a physical disorder such as constipation, acid reflux to the esophagus, lactose intolerance, neonate's migraine and etc. Probiotics protect the gastrointestinal system against disturbances by following mechanisms: 1. Production of inhibitor compounds like organic acids such as acetate and propionate 2. Competition for binding sites 3. Competition for the absorption of nutrients 4. Elimination of toxin's receptor 5. Fortification and increase in immune system. In this study, the identification and determination of the amount of lactobacillus in a probiotic product is investigated by microbiological method.

Methods: Identification and determination of the amount of lactobacillus in the product through culture of the product was performed through pure plate method on MRS agar in 3 different days. In order to confirm identity of colonies, gram staining, oxidase and sugar fermentation test were performed.

Results: The study of developed colonies and their comparison with standard sample indicated the presence of lactobacillus bacteria in the product. In addition, these bacteria were oxidase negative and could ferment sorbitol and glucose that they are features of lactobacillus species. Also result of this study show the presence of 6×10^6 cfu/g lactobacillus in the product.

Conclusion: This study was carried out to determine the quality control of a probiotic product through the identification and determination of the amount of lactobacilli contained in it by microbiological method. The resultant conclusion confirms presence of acidophilus lactobacillus and rotary and casei in the product whereas the number of alive bacteria was 95 % of avowed quantity. These results are expression of acceptable quality of product.

Keywords: Probiotic, Identification, Quantification, Microbiological, lactobacillus.



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Preparation and *In Vitro* Characterization of Ph-Sensitive Methotrexate Conjugated Chitosan Nanoparticles

Abstract

Introduction: Chitosan (CS) is a cationic hydrophilic polymer with individual properties including low cytotoxicity, low immunogenicity, biodegradability, and biocompatibility. This polymer can form complexes with negatively charged substances thanks to having highly positive surface charge (1). CS has been investigated in the pharmaceutical science in order to develop drug delivery systems (2). Methotrexate (MTX) has been employed to cure lymphoblastic leukemia, osteosarcoma, head and neck choriocarcinoma, skin, lung and breast cancers (3). Conjugation of anticancer drugs and carriers caused the high entrapment efficiency and controlled drug release.

Methods: Methotrexate (MTX) has been coupled to CS polymer by carbodiimides activation. Finally, the CS-MTX NPs were prepared by introducing TPP to the solution. The mean particle size and PDI of the NPs were measured by PCS and SEM. Prepared NPs were characterized using FT-IR techniques and *in vitro* release of MTX from NPs evaluated.

Results: The FT-IR spectra of freeze-dried CS-MTX proved the complete conjugation. The average size and encapsulation efficiency of the prepared CS-MTX NPs were found to be around 175 nm and 74%, respectively. The SEM investigation for the CS-MTX NPs showed uniform particle morphology with the average diameter of 100 ± 25 nm. The *in vitro* release profile of MTX in PBS buffer pH 7.4 and 5, under sink conditions, is investigated based on cumulative percentage release. *In vitro* release profile in a different pH showed the *in vitro* MTX release up to 90% 24 h at pH 5.

Conclusion: In this study, CS conjugated MTX as anticancer drug nanoparticles were prepared using an ionic gelation method. By this strategy, the pH sensitive delivery system was prepared by the biodegradable and biocompatible polymer.

Keywords: Chitosan, Methotrexate, TPP, Ionic gelation method.



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Variables Related To Misuse of Intravenous Immunoglobulin in Clinical Practice: A Prospective Study

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Abstract

Introduction: The dramatic increase in prescribing of intravenous immunoglobulin (IVIG) products has reinforced the concerns of irrational utilization. Severe shortage of IVIG products and frequent off-label use of that without adequate scientific support make its utilization under active investigation. However, unfortunately there is not sufficient data regarding its use in Iran. This clinical study attempted to evaluate the pattern of IVIG administration and find those variables associated with inappropriate IVIG utilization.

Methods: We performed a prospective study in one of the largest referral hospital in 2016 in Iran. Patients who received IVIG were randomly selected from different wards to recruit in the study. Subsequently their charts were reviewed for related clinical data to assess the pattern of IVIG administration and find variables which could predict this behavior. Indications of IVIG prescription were categorized as indications with scientific evidentiary support or those with lack of evidence for efficacy according to FDA guidance. Univariate and multivariate logistic regression was also performed to detect associations related to misuse of IVIG.

Results: We recognized 27.4% of patients had received IVIG with inadequate scientific evidentiary according to FDA guidance. All variables were analyzed to evaluate factors affecting misuse of IVIG. According to univariate analysis, a significant increase in the risk of IVIG misuse had been observed in younger population ($p < 0.001$). Hospital ward admission was also a major predictor of IVIG misuse. However, younger age and longer time to start IVIG administration from hospital admission remained statistically significant when multivariate model was developed ($p < 0.001$ and 0.002 , respectively)

Conclusion: This study highlighted inappropriate IVIG administration and showed variables which predicted this pattern. These findings could be beneficial to identify patients at risk for IVIG misuse and necessitate collaborative strategies to decrease the burden of IVIG overuse.

Keywords: Intravenous immunoglobulin, FDA, misuse, drug use evaluation.



Preparation and Characterization of Nanoliposomal Doxorubicin Targeted With Leptin-Derived Peptide and Evaluation of Its Cytotoxicity *In Vitro* in U-87MG and C-26 Colon Carcinoma Cell Lines

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Abstract

Introduction: Chemotherapy is the treatment of choice for many types of cancer; nevertheless, chemotherapeutic agents –including doxorubicin- cause severe adverse effects due to low selectivity and high volume of distribution.¹ Proper drug delivery systems, decrease the distribution of the drug in healthy organs and enhance the concentration of the agent in the tumor tissue. Among cancer drug delivery systems, PEGylated nanoliposomes have a good position.² Although liposomes improve the safety and pharmacokinetic properties of drugs, they do not sufficiently enhance the clinical efficacy of therapy. Targeted therapy can be the key to the enhancement of clinical response to chemotherapy¹. There is a growing body of evidence of an increase in the expression of leptin –a polypeptide hormone secreted by adipose tissue and targeting different parts of brain- receptor in various cancerous cells including gastrointestinal³ cancers and gliomas^{4,5}. In addition, it has been proved that leptin receptor is highly expressed in endothelial cells of cerebral capillaries; which can be of value in drug delivery to cerebral tumors including gliomas^{6,7}.

Methods: In the present study, we used a leptin-derived peptide to target PEGylated liposomes of doxorubicin. The first step was to prepare DSPE-mPEG-maleimide conjugate. Then we post-inserted the conjugate on the surface of liposomes and characterized the formulations in terms of stability, size distribution and zeta potential. Finally, *in vitro* cytotoxicity and cell uptake of the targeted formulations was assessed on C-26 (colon carcinoma) and U-87 (glioma) cell lines.

Results: Results indicate that leptin-derived peptide-targeted PEGylated liposomes have enhanced cytotoxicity and cell uptake in comparison with untargeted PEGylated liposomes.

Conclusion: Overall, it can be concluded that leptin receptor-targeting nanoliposomes of doxorubicin have more cellular uptake and less IC50 in comparison with non-targeted doxorubicin-containing nanoliposomal formulation.

This can be used to improve therapeutic efficiency and side effect profile of doxorubicin chemotherapy. However, more investigations including *in vivo* studies remain to be assessed.

Keywords: leptin, liposome, doxorubicin, glioma, post insertion.



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Physical Adsorption of Indinavir on Fullerene (C60) Surface

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Abstract

Introduction: Fullerenes are carbon allotropes similar in structure to graphene but rolled up to form closed-cage, hollow spheres. The C60 fullerene is a remarkably stable compound consisting of 60 carbon atoms with a diameter of approximately 0.7 nm and a molecular weight of 720 g/mol. Thirty carbon double bonds present in the structure, to which free radicals can easily be added. C60 has some unique physicochemical, photochemical, electrochemical and biological properties which make it a promising candidate for being used in biological studies as a carrier for drug delivery purposes (1, 2).

Methods: At first a stable water dispersion of fullerene was prepared with a concentration of 0.4 mg/ml. Afterwards, 10 mg of pure indinavir was added to the aqueous dispersion. The mixture was 20 minutes sonicated and then shaken for 12 hours in the dark (2).

Results: In order to confirm the physical adsorption, size and zeta potential of nano particle were investigated before and after adding drug. Both size and zeta potential of nano particles were changed during the process.

Conclusion: According to the obtained data, indinavir was successfully adsorbed on the surface of fullerene.

Keywords: Fullerene, Indinavir, Physical adsorption.



Novel and Efficient Method for Solid Phase Synthesis of Urea Containing Dipeptide Targeting Prostate Specific Membrane Antigen (PSMA)

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Abstract

Introduction: Nowadays, peptides are one of the most favorable drug-carriers which their low stability to hydrolysis is the key drawback concerning them. In an endeavor to overcome it, some hydrolysis resistance bonds like urea band were successfully substituted with amid band in peptide sequences. The purpose of present study is synthesis of urea containing PSMA inhibitor under solid phase with high purity targeting prostate cancer cells.

Methods: This process involves on-resin generation of isocyanate intermediate derived glutamate-bound-resin by reaction with triphosgene followed by formation of urea band via α -amine of lysine by solid phase peptide synthesis (SPPS).

Results: Here, the well-known pharmacophore of PSMA inhibitor glutamate-urea-lysine (EUK) was synthesized in solid phase. The characterization of synthetic compound was done using LC-Mass and H-NMR.

Conclusion: During this work, we take advantage of SPSS to easily prepare EUK as a PSMA inhibitor in high yield and purity and optimize consumed starting materials.

Keywords: Peptide, PSMA, Triphosgene, Urea Band, Solid phase.



Investigate the Analgesic Effect of Methanol Extracts of the Plant *Vicia Hirsuta* the Hot Plate Test and Writhing In Mice

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Abstract

Introduction: *Vicia* genus member of Papilionaceae family has 45 species in Iran. Many pharmacological activities have been reported from *Vicia* (V) genus. Flavonoid and fenolic content were found in *vicia* genus. Flavonoids has anti nociceptive effect. There is no report on *vicia hirsute*'s anti nociceptive activity. In the present study, antinociceptive effect of *vicia hirsute* has evaluated by hot plate and writhing test.

Methods: Methanolic extract of *vicia hirsuta* at doses of 100-200-400-800 mg/kg (i.p.) were tested in hot plate and writhing tests in mice. In the hot plate test, the animal is placed on a hot plate and the time it takes for the animal to respond to the stimulus of the pain that is hot is measured. If the substance has analgesic effect, this time will increase. In the test of pain induced by acidosis or writing .The drug is injected Intraperitoneally one hour before the start of the test And after 60 minutes 0.5 cc 0.6% acetic acid solution is injected intraperitoneally. 5 minutes after injection of acetic acid, pain appears (the animal kicks its hands and feet around). The number of kicking is counted from 6 to 30 minutes.

Results: In the writing test, all of test groups had significant difference in comparison with control group ($P<0.001$) and significantly decreased the numbers of writhing in mice. In hot-plate test *vicia hirsute* extract injection increased pain threshold especially after 30 minutes in comparison with control groups.

Conclusion: The results of pharmacological tests performed in the present study suggest that the methanolic extract of aerial part of *vicia hirsuta* presents anti nociceptive effects which may be attributed to its flavonoid contents.

Keywords: *vicia hirsute*, antinociceptive, hot plate test, writing test.



Isolation and Identification of Potential Phages to Attack Invasive *E.coli*

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Abstract

Introduction: *Escherichia coli* O157:H7 is one of the most important shiga toxin-producing types of *E. coli* causing hemorrhagic colitis and diarrhea (1). In recent years phages have been used successfully as a strong weapon against some pathogens especially because of increasing disaster of antibiotic-resistant bacteria since the early 1920s (2).

Methods: Different samples were collected from Vali-e-Asr hospital wastewater, soils and some streams around Fasa city. After centrifugation and precipitation, samples were filtered and added to TSB medium with 1 mL of fresh culture of *E. coli*. The tubes were incubated at 37 °C for 18 h at 80 rpm. Then the medium was filtered. After a serial dilution, concentration of phage in each tube was determined by the double-layer agar method. Among different plaques, the biggest and the clearest ones were removed from the agar and incubated in SM buffer.

Results: The purified and isolated phages from plaques were identified by transmission electron microscopy (TEM). Results of TEM showed that the target phages were belonged to the lambda family. The highest titer obtained from lambda phage after PEG precipitation was about 1.2×10^{11} pfu/ml. Obtained phages were tested on other types of bacteria. All test results were negative. Through this process, selective phages against *E. coli* O157:H7 were isolated and identified as a strong weapon against hemorrhagic colitis and diarrhea.

Conclusion: Because of host specificity, automated dose adjustment (they can reach the proper killing titer by themselves), relatively easy mass production and *in vivo* use as an alternative to antibiotics, phages are potentially good bactericidal candidates (2). This study showed that phages can be good replacement for chemical antibiotics.

Keywords: Phage therapy, *Escherichia coli*, Antibiotic resistance.



Design and Synthesis of Novel Phthalimide Derivatives as Soluble Epoxide Hydrolase Inhibitors

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Abstract

Introduction: Inhibition of a soluble epoxide hydrolase (sEH) enzyme leads to high levels of epoxyeicosatrienoic acids which are involved in the regulation of blood pressure and vascular inflammation. The most potent inhibitors reported in the literature are urea-based ones which often have poor bioavailability. In this study, a series of amide derivatives with a phthalimide ring as a novel secondary pharmacophore against the sEH enzyme were designed and synthesized.

Methods: Novel amide compounds were designed based on structure and activity relationship of soluble epoxide hydrolase inhibitors and molecular docking study was performed by Glide software. Phthalic anhydride was reacted with 4 nitroaniline to obtain N-(4-nitrophenyl) phthalimide. Then nitro group of phenyl ring was reduced to amine by SnCl₂. Finally, new amide derivatives were synthesized from the reaction of above amine with various benzoyl chlorides.

Results: The docking results revealed that the designed compounds fit in the active site pocket properly and have suitable distances for effective hydrogen binding from important amino acids of Tyr466 and Asp335. These novel compounds were synthesized in acceptable yield and their structures were confirmed by instrumental methods including IR, Mass, HNMR and ¹³CNMR spectroscopies.

Conclusion: In conclusion, some novel amide-based soluble epoxide hydrolase enzyme inhibitors with a phthalimide ring were designed, synthesized and approved by IR, NMR and Mass spectra.

Keywords: Inhibitor, soluble epoxide hydrolase, amide, phthalimide



Preparation, Physicochemical Characterization and Optimization of Posaconazole Loaded PLGA Nanoparticles: Design of Experiments Approach

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Abstract

Introduction: Poly (lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) have been extensively used as biocompatible carriers for different drugs to enhance their water solubility, sustained-release properties and decrease their adverse effects. Posaconazole (PSZ) is a poorly soluble drug which has an important role in treatment of fungal infections. The purpose of this study was to develop PSZ-loaded PLGA NPs as a novel sustained-release formulation with lower adverse effects for intravenous (IV) administration in comparison with the commercial product which contains beta-cyclodextrin as a solubilizer.

Methods: The NPs were prepared by the nanoprecipitation method. A 2-factorial design was employed in this study considering polymer to drug ratio, internal phase volume, surfactant type (TPGS or PVA) and surfactant percentage as independent variables. The responses were encapsulation efficiency (%EE), particle size and polydispersity index (PDI).

Results: The NPs were prepared in the sizes range of 122 to 1887 nm. The PDI was in the range of 0.038-0.956 and the %EE varied between 2.6 and 78.7%. NPs size and PDI were mostly affected by the amount of co-polymer whereas %EE was mostly affected by surfactant type. The optimized formulation was formulated with 60 mg PLGA, 4 mL internal phase and 1% PVA. This formulation demonstrated the particle size of 233 nm, EE of 78% and PDI of 0.220. Cumulative drug release amounts were 26% and 83% after 10 and 48 h, respectively. *In vitro* release studies showed a sustained release up to 5 days.

Conclusion: With formulation optimization and tuning preparation conditions, we obtained stable and uniform PSZ loaded PLGA NPs with sustained-release character which could provide the advantage of lower frequency administration. The PLGA NPs containing PSZ could be of clinical importance in decreasing adverse effects by eliminating beta-cyclodextrin.

Keywords: Posaconazole, PLGA, Nanoparticles, Design of experiments.



Rapid and sensitive HPLC Method for Determination of Posaconazole in Rat Plasma Using Low Sample Volume

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Abstract

Introduction: Posaconazole (PSZ) is a new antifungal drug for treatment of fungal infections.¹ Novel formulations of PSZ, such as nanoparticles (NPs) and liposomes have been under investigation to enhance its efficiency. For preclinical pharmacokinetics evaluation of these formulations, minimization of specimen volume is a desirable feature. In this study, a rapid and a convenient high-performance liquid chromatography (HPLC) method with simple liquid-liquid extraction has been developed which required small volumes of plasma (0.1 mL).

Methods: PSZ and diazepam (internal standard) were extracted from 0.1 mL rat or human plasma, using liquid-liquid extraction with 1.5 mL tert-butyl methyl ether. After evaporation of organic layer in vacuum, the dried residue was reconstituted in mobile phase and injected through PerfectSil C18 (4.6 × 250 mm, 5 μm) column. The mobile phase, consisted of acetonitrile and deionized water (60: 40, v/v), was pumped at 1 mL/min. The UV detector was set at λ=262 nm.

Results: The components eluted within 10 min and were baseline resolved with no interferences from endogenous substances in plasma. Drug peak was successfully appeared within 8 min. The method was validated with acceptable inter- and intra-assay precision and accuracy. Calibration curves were linear ($r^2=0.996$) over the range of 50–2000 ng/mL and limit of quantitation (LOQ) was 50 ng/mL. Mean recovery percentage was more than 80% for PSZ. Stability studies indicated that PSZ was stable for 2 h and 1 week in plasma samples at room temperature and 4 °C, respectively.

Conclusion: This method based on 0.1 mL of plasma was shown to be sensitive, rapid and appropriate for use in the pharmacokinetic study of 1 mg/Kg of PSZ in rat.

Keywords: Posaconazole, HPLC, UV detection, Pharmacokinetics, Small sample volume.



Effects of Phloretin on Oxidative and Inflammatory Reaction in Rat Model of Cecal Ligation and Puncture Induced Sepsis

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Abstract

Introduction: Sepsis is the debilitating systemic disease and described as a severe and irregular systemic inflammatory reaction syndrome (SIRS) against infection. As phloretin is a natural antioxidant agent, we employed a CLP (cecal ligation and puncture) model in rats to investigate an anti-inflammatory and antioxidant effects of phloretin as well as determining its protective effect on liver tissue damage caused by sepsis.

Methods: Male Wistar albino rats were randomly divided into three groups as follows: sham group, sepsis group and phloretin treated CLP group. Sepsis was induced by cecal ligation and puncture (CLP) method. Phloretin was administered intraperitoneally in two equal doses immediately after surgery.

Results: It was observed that blood urea nitrogen (BUN) and tumor necrosis factor alpha (TNF- α) level were dramatically increased in CLP operated group (43.88 ± 1.905 mg/dl, 37.63 ± 1.92 respectively) when compared to the sham group. Moreover, tissue Glutathione (GSH) and liver nuclear factor κ B (NF- κ B p65) transcription factor values were higher in CLP group whereas, the elevation was considerably reduced in the phloretin treated group. There were no significant differences in serum creatinine and creatinine phosphokinase level between groups.

Conclusions: The present study suggested that phloretin act as a natural protective agent against tissue damages induced in an experimental sepsis created model, likely caused by free oxygen radicals.

Keywords: Phloretin, Sepsis, NF- κ B, TNF- α , Oxidative stress, Antioxidants



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Application of Dispersive Liquid-Liquid Microextraction and High-Performance Liquid Chromatography for the Determination of Bupropion

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Abstract

Introduction: Bupropion (BUP), (\pm)-2-(tert-butyl amino)-1-(3-chlorophenyl) propan-1-one [1]. The drug is an antidepressant that acts as norepinephrine, dopamine reuptake inhibitor, and nicotine antagonist. Bupropion is used also for depression, smoking cessation, obesity, and attention deficit hyperactivity disorder [2].

Methods: A simple, selective, and sensitive high performance liquid chromatography (HPLC) procedure has been developed for determination of bupropion as a drug using. Sample preparation involved ultrasound-assisted solvent dispersive liquid-liquid microextraction by 1,2-Dichloroethene. The HPLC separation was performed on a ZORBAX eclipse plus C18 column (100 mm \times 4.6 mm, 3.5 Micron, Agilent, USA) with a mobile phase consisting of sodium hydrogen phosphate and ethanol (60:40, v/v) (pH adjusted to 7.5) at a flow rate of 1.0 mL/min. The peaks were detected by using UV/Vis detector at 254 nm.

Results: The calibration curves were linear over the selected concentration ranges of 5-500 ng.L⁻¹ for all analytes, with calculated coefficients of determination (R^2) of greater than 0.9975. The limits of detection (LOD) and limits of quantitation (LOQ) of the method were 8.17 and 27.5 ng.L⁻¹ respectively. The accuracy of the evaluated was expressed in term of RSD, which was less than 10%.

Conclusion: The method is accurate, rapid and sensitive, and can be used for the bupropion analysis in drug products.

Keywords: Bupropion; HPLC; liquid-liquid microextraction.



Pharmacokinetic and Biodistribution Studies of Tween 60 Based Niosomes Following IV Administration to Mice

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Abstract

Introduction: Generally, clinical success of nano-carriers correlates well with their in-vivo disposition and blood circulation residence time. The present study was aimed to investigate the biodistribution and blood kinetics of Tween 60 based niosomes after i.v. administration to mice. For *in vivo* tracking the prepared niosomes were radiolabeled with ^{99m}Tc.

Methods: In order to label niosomes with ^{99m}Tc, glutathion loaded niosomes with the composition of Tween 60 and cholesterol (60:40 %mol) were prepared by thin film hydration method. The prepared vesicles were characterized for particle size, size distribution and zeta potential. The preformed GSH loaded niosomes were incubated with the complex of ^{99m}Tc and HMPAO and the labeled niosomes were separated from any free ^{99m}Tc by Sephadex G-25 column. For *in vivo* studies, labeled niosomes and ^{99m}Tc -HMPAO complex (as control) were injected via the tail vein to mice. Animals were sacrificed at eight different time points, and the blood and tissue distribution in terms of the percent of the injected dose/gram of tissue (%ID/g) were obtained.

Results: Radiolabeled niosomes had a mean diameter of about 159.3 ± 1.2 nm and ζ -potential of about -33 mV. Results showed that niosomal formulation significantly modified the disposition profile of ^{99m}Tc -HMPAO complex. The blood AUC of niosomes was about 3.95 fold greater than the AUC of control. When compared to the free label, distribution of labeled niosomes in all tissues with exception of liver and spleen were reduced.

Conclusion: ^{99m}Tc labeled niosomes with labeling efficiency > 90% an acceptable radio-labeling stability were prepared. Niosomes carrying radionuclide were successfully applied for tracking the *in vivo* disposition of these carriers. Compared to free label, niosomal carries had markedly higher blood concentrations, longer circulation time and lower distribution in most of tissues.

Keywords: Niosomes, Pharmacokinetics, Tissue distribution, ^{99m}Tc -HMPAO



Is *E. elaterium* from the North West of Iran toxic?

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Abstract

Introduction: *Ecballium elaterium* (L.) A. Rich from Cucurbitaceae family, also called “squirting cucumber,” is a wild Mediterranean medicinal plant found abundantly in the Eastern-Azarbajejan province in Iran. This study was undertaken to examine possibility of cytotoxic effect of six different extracts of *E. elaterium* fruit.

Methods: The extracts of three different parts of the fruit of *E. elaterium* were prepared in two ways and removed their solvent. These extracts were assayed on cell line of lung epithelial called on A549 (human lung epithelial cell carcinoma) by MTT assay.

Results: The IC₅₀ values for flesh, seeds and liquid contents of fruits in ethanolic extract were 9233.706, 617.128 and 796.372 μg/ml, and in defatted ethanolic extracts were 5509.806, 644.815 and 563.735 μg/ml for A549 cell line after 24 h, respectively.

Conclusion: The results of the current study showed that the two different of three various parts of extract of *E. elaterium* fruit has various cytotoxic effect on human lung epithelia cell carcinoma cell line.

Keywords: *Ecballium elaterium*, MTT assay, IC₅₀, Defatted ethanolic extract.



Phytochemical Analysis and Antioxidant Activity of the Essential Oil of Aerial Parts of *Falcaria Vulgaris*

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Abstract

Introduction: *Falcaria vulgaris* from Umbeliferae family grows in different parts of Iran. It is variously used in folk medicine and named as "Ghaze-yaghi" because of its leaf shape. It is traditionally has been used as dry powder in west and south-west of Iran, to accelerate skin wound healing for centuries.

In this study we determined content of essential oil of aerial parts of *Falcaria vulgaris* and evaluated its antioxidant activity.

Methods: 100g of dried aerial parts of *F.vulgaris* powdered and submitted to Clevenger apparatus for hydro-distillation. Also 220g of dried powder extracted by Soxhlet method with 3 solvents: n-hexane, dichloromethane and methanol. Then the essential oil analyzed by Gas chromatography- Mass spectroscopy. Moreover antioxidant test by 2,2-dinitro phenyl-1-picrilhydrazyl(DPPH) was applied on extracts and essential oil. Total phenol and total flavonoid of methanolic extract was determined by Folin-ciocalteu and AlCl₃ reagents.

Results: 0.2 ml clear yellow oil was extracted and 22 compound were determined; which include hydrocarbon monoterpenes (3%), oxygenated monoterpenes (3%), hydrocarbon sesquiterpenes (21.2%), oxygenated sesquiterpenes (57.8%), ketones (3%), aldehydes (9%). The most common compound of oil was Spathulenol. Essential oil of aerial part showed lowest antioxidant activity and methanolic extract by RC₅₀= 0.0456±0.0002 had the highest antioxidant activity. Each gram of methanolic extract also had 68.008 mg phenol and 11.99 mg flavonoid.

Conclusion: The most determined compounds from essential oil of *Falcaria vulgaris* were oxygenated sesquiterpenes and hydrocarbon sesquiterpenes. Proper antioxidant activity of methanolic extract can be useful in treatment of diseases caused by oxidative stress and inflammation.



Chemical Composition, Antioxidant Activity, and General Toxicity of the Aerial Parts of *Ecballium Elaterium*

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Abstract

Introduction: The plants of Cucurbitacea family have been considered as valuable herbal remedies, which they mainly distributed in tropical and subtropical areas. *Ecballium* genus includes 965 species. In this study, the chemical composition and biological activities of *Ecballium elaterium* have been investigated. Regarding the importance of reported biological effects of this family, it seems to be rational to start phytochemical studies on this genus.

Methods: The aerial parts of this species were extracted using n-hexane, dichloromethane and methanol by Soxhlet apparatus. Dried methanolic extract was subjected to C18 Sep-Pak using step gradient of MeOH-Water. Further purification of the fractions by preparative reversed phase HPLC yielded 3 compounds. Structure elucidation was accomplished by using ¹HNMR and ¹³CNMR method. The essential oil was determined by GC-MS. Free-radical scavenging activity, general toxicity, total phenol and total flavonoid contents of extracts and fractions were evaluated using DPPH radicals, *Artemia salina*, Folin-ciocalteu and AlCl₃ reagents, respectively.

Results: Phytochemical study of the methanolic extract of this plant yielded two flavonoids and one naphthalen structures. The study on compositions of the essential oil yielded 17 compounds, which were mainly composed of ketones and ester of fatty acids. The MeOH extract showed strong antioxidant activity compared to the other extracts. In regards to fractions, 40%, showed the most potent antioxidant activity as well as high phenol and flavonoid contents. In brine shrimp lethality assay, the extracts didn't show any general toxicity.

Conclusion: Presence of phenolic derivatives especially flavonoids seems to be an important antioxidant compounds in methanolic extract and might be useful in inflammatory conditions, cancer prevention and oxidative stresses.

Keywords: *Ecballium elaterium*, GC-MS, Antioxidant, Total phenol, Total flavonoid, General activity.



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Effect of Different Protein-Based Vehicles on Stability and Anti-Cancer Activity of Curcumin

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Abstract

Introduction: Curcumin is a natural polyphenolic compound with anti-cancer, anti-inflammatory, and anti-oxidation properties. But, low water solubility/bioavailability and rapid hydrolytic/photonic degradation are two challenges that limit use of curcumin. In this study, the role of the native/modified forms of serum albumin, casein and β -Lactoglobulin, as food-grade biopolymers in the improvement of stability and anticancer properties of curcumin and protective potentiality of these compounds against oxidative stress induced by hydrogen peroxide were surveyed.

Methods: Proteins were modified with acetic anhydride which offers neutral acetyl groups usually at lysine side chains. Hydrolytic degradation of curcumin and its interaction with native/modified proteins were studied using UV-vis and fluorescence spectroscopy, respectively. Anti-cancer activity of curcumin was examined by methyl thiazol tetrazolium bromide (MTT) assay, which is based on the reduction of MTT by the mitochondrial dehydrogenase of live cells to a purple formazan product. Additionally, the cytotoxicity of curcumin to different cell line was

investigated in the presence of the native/modified forms of protein giving inhibitory concentration for free and complexed protein-curcumin, respectively. Also, intracellular ROS was measured by using the fluorescent dye DCFH-DA for free and protein-curcumin complexes.

Results: Upon interaction of curcumin with the native proteins, its hydrolytic/photonic degradation was significantly suppressed in the order of serum albumin>casein> β -Lactoglobulin. But, acetylation changed capability of proteins in the improvement of stability properties of curcumin in the order of β -Lactoglobulin>albumin>casein. Analyses of curcumin interaction with the proteins revealed that binding of curcumin to the hydrophobic patches of proteins increases its stability/efficacy. Also, both free curcumin and “curcumin-protein” systems showed dose-dependent cytotoxicities. Especially, at higher concentrations, the anti-cancer activity of “curcumin-casein” systems in SKNMC cells and “curcumin-casein” and “curcumin-albumin” systems in MCF7 cells was significantly higher than free curcumin, suggesting that these systems are more effective to protect curcumin and deliver it to cancer cells. Also, in the presence of native proteins (BSA and β LG), curcumin decreases ROS generation by H_2O_2 .

Conclusion: The increased stability enhances lifetime and gives an additional opportunity to intact/functional curcumin to be up taken by target cells. This poor bioavailability may be due to degradation of curcumin in gastrointestinal tract and plasma. This laboratory suggests that traditional mixing of curcumin with milk may lead to its enhanced stability, bioavailability and anticancer properties. We discussed the importance of our findings.

Keywords: Curcumin, Albumin, Casein, β -Lactoglobulin, Degradation, Stability, ROS (Reactive oxygen species)



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Medication Reconciliation on Hospital Admission in an Infectious Diseases

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Abstract

Introduction: Medical errors can cause preventable harms, mostly caused by an incomplete medication list. “Medication reconciliation is the process of creating the most accurate list possible of all medications a patient is taking and comparing that list against the physician’s orders, with the goal of providing correct medications to the patient at all transition points.(1)” This study was designed to evaluate the medication reconciliation at admission time.

Methods: Data was collected using a form, designed to take medical history and medication history (pre-admission and admission medications) shortly after admission. The study was carried out for 8 months through non-probability sampling in infectious disease setting in an academic medical center. The medication discrepancies were checked according to validated medical references. Data were analyzed using SPSS.

Results: A total of 85 patients (mean age=54.67 years) formed the study population. About 60% of patients brought their pre-admission medications to the hospital (2.48 ± 3.8 drug/person). The most common pre-admission medications were *drugs acting on the gastrointestinal system* and metabolism (24.64%). On admission 65.4% medication discrepancies were detected, resulted in changing the dose and/or dosage form, potency or administration route (18.01%) withdrawing a drug (29.86%) and replacing the medication (17.54%).

Nearly half of patients brought their pre-admission medications which gave the advantage of providing accurate medication history. In the current treatment plans, there is no integrated plan to reconcile the medications. Elderly people are often suffered from chronic diseases and taking long-term medications, increasing the risk of medication errors and drug interactions so bringing current medications to the hospital and having a coherent medication reconciliation program can prevent errors.

Conclusion: It seems that the implementation of electronic medication reconciliation is an appropriate method to decrease the current problems and to perform a better and more convenient medication reconciliation process in hospitals.

Keywords: Medication reconciliation, Medical errors, admission, Valiasr hospital, Zanjan.



Antibiotic Resistance of Isolated Gram Negative Bacteria Causing Urinary Tract Infection in Valiasr Hospital, Zanjan, Iran

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Abstract

Introduction: The world entered to post antibiotic era and antibiotic resistance has become a major global threat for humanity. One way to prevent the development of progressive antibiotic resistance is identifying common pathogens causing infections and finding out their antibacterial resistance patterns.

Urinary Tract Infections (UTI) is the most common bacterial infection. Additionally UTI is one of the most common nosocomial infections. Gram negative microorganisms are the most common causes of UTI. Due to the regional, inter-hospital and time to time variance of antibacterial resistance pattern we have designed this study to determine the susceptibility of inpatient Gram-negative urinary tract isolates to antibiotics

Methods: This study was a laboratory-based study performed on 427 isolates from UTI patients admitted to an academic medical center. The isolates, considered to be significant pathogens were included in our study. Susceptibility testing was performed using agar dilution method (using guidelines of National Committee for Clinical Laboratory Standards). Data was analyzed using SPSS.

Results: Of 427 UTI patients, 146 (%34.2) had community acquired and 281 (%65.8) had nosocomial UTI. Women were 238 (%55.8) of the UTI patients. The common pathogens cause UTI was *Escherichia coli* (%44.2), *Klebsiella* spp (%9.8) and *Pseudomona aeruginosa* (%4.9). Antibacterial resistance of *Escherichia coli* in our study were as follows: cotrimoxazole (%64), nalidixic acid (%78), ciprofloxacin (%58), imipenem (%47) and nitrofurantoin (%12). Antibacterial resistance of *Klebsiella* spp were as follows; cotrimoxazole (%75), nalidixic acid (%65), ciprofloxacin (%52), imipenem (%47), nitrofurantoin (%55) and cephalexin (%73).

The pathogens causing UTI in our study was similar to other studies in Iran but antibacterial resistance patterns in many cases were higher than other countries and in some cases were also higher than other cities of Iran.

Conclusion: In conclusion the results of this study showed that serious and urgent attention to antibiotic resistance is needed.

Keywords: Antibiotic Resistance, Urinary Tract Infection, Valiasr hospital, Zanjan



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The Study of Trigonella Foenum Graecum.L Effect on Lipid Profile and its Comparison with Atorvastatin in High Cholesterol Fed Rats

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Abstract

Introduction: Today, medicinal plants are in the focus of attention because of their roles in treatment of many diseases. The aim of this study was to determine the hypocholesterolemic effect of Trigonella Foenum Graecum.L(Fenugreek) seeds powder and its comparison with atorvastatin on high cholesterol diet fed rats.

Methods: Fourty male rats weighing 180–200g were kept under observation for about 2 weeks and then were randomly divided into four groups of 10 each: group1(fed with normal diet: ND), group2, fed with high cholesterol diet, HCD(ND mixed with 2% cholesterol+ 0.5% cholic acid), group3(fed with HCD mixed with fenugreek seeds powder, 8 g/kg body weight/day: HCD+FEN), group4 (fed with HCD supplemented with aqueous emulsion of atorvastatin, 0.5mg/kg body weight/day, administered orally via oral feeding tube: HCD+Ator).

After 6 weeks, the serum levels of triglyceride, total cholesterol, high density lipoprotein cholesterol (HDL-c), alanine aminotransferase (ALT) and aspartic aminotransferase (AST) and fasting blood suger (FBS) were assayed by enzymatic methods. Low density lipoprotein cholesterol (LDL-c) and very low density lipoprotein (VLDL-c) were estimated by Friedewald equation and triglyceride/5 equation.

Results: In groups received atorvastatin and fenugreek, the serum levels of cholesterol, triglyceride, LDL-c and VLDL-c, ALT and FBS decreased ($p < 0.001$) and serum level of HDL-c increased ($p < 0.05$) as compared to group HCD.

Conclusion: Both atorvastatin and fenugreek have hypolipidemic and hypoglycemic activities in high cholesterol diet fed rats and ameliorate high cholesterol diet induced dyslipidemia. Atorvastatin has significantly more potent hypolipidemic and hypoglycemic activities than fenugreek seeds powder ($p < 0.001$).

Keywords: Atorvastatin, Trigonella Foenum Graecum.L, Cholesterol, LDL-c



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Design, Synthesis, and Molecular Modeling Study of New Pyrazinobenzimidazole Derivatives as Selective COX-2 Inhibitors

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Abstract

Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutics, for the treatment of pain and inflammation. Classic NSAIDs act by non-selective inhibiting of cyclooxygenase enzyme (COX). Therefore, long-term use of such NSAIDs, most often has side effects on gastrointestinal tract. While selective COX-2 inhibitors may be considered as anti-inflammatory drugs which do not have side effects. For this reason novel scaffolds with high selectivity for COX-2 inhibition need to be found and evaluated for their anti-inflammatory effects. Hence, in this research based on the structure-activity relationship (SAR) of selective COX-2 inhibitors, a new group of pyrazinobenzimidazole derivatives were designed.

Methods: Preparation of designed compounds was started from the *o*-phenylenediamine. Condensation of *o*-phenylenediamine and lactic acid obtained 2-(hydroxyethyl) benzimidazole. The product was oxidized using $K_2Cr_2O_7$ to give 2-acetylbenzimidazole. 2-acetylbenzimidazole and α -bromo-4-(methylsulfonyl) acetophenone were

reacted in the presence of K_2CO_3 in acetone. The final products were obtained by reacting final intermediate and aniline derivatives in AcOH.

Results: All designed compounds were synthesized successfully and purified using different methods. Spectroscopic data such as IR, Mass and 1H NMR were applied to characterize the structure of final compounds.

Conclusion: We synthesized a new series of pyrazinobenzimidazole derivatives based of COX-2 inhibitors SAR. The molecular modeling studies indicated synthesized compounds have a binding similar to that of known COX-2 inhibitor.

Keywords: cyclooxygenase-2 inhibition, molecular modeling, synthesis, pyrazinobenzimidazole



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Meropenem Utilization Evaluation in a Referral Teaching Hospital

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Abstract

Introduction: Inappropriate use of antibiotics is associated with detrimental effects including emergence of antibiotic resistance. The high rate of empirical prescription of meropenem in hospitals will potentially increase the prevalence of bacterial resistance. This study aimed to evaluate the use of meropenem in a referral teaching hospital to detect different types of errors in its prescription.

Methods: In a prospective descriptive cross-sectional study, hospitalized adult patients who underwent meropenem prescription for any indication were randomly selected. The collected data included the indication for prescription of meropenem and its correctness, the basis of prescription (empirical or culture-based), administered dose and its correctness, duration of treatment with meropenem and its correctness, the status of demanding sample culture in the case of empirical prescription, the status of dose adjustment in the case of renal impairment, and the treatment outcome.

Results: Over the study period, 123 patients were evaluated. The most frequent indication for prescription of meropenem was pneumonia (31.7%) and skin and soft tissue infections (18.7%). Out of these prescriptions, 62.6% (77 prescriptions) were incorrect. All meropenem prescriptions were initially empirical. Furthermore, sample culture and antibiotic susceptibility test were requested for only 52% of patients (n = 66) with only 2 of these patients (3.03%) being underwent antibiotic regimen change based on the tests results. Treatment duration was correct for 53.7% of patients. Seventeen patients (13.8%) received an inappropriate dose of the antibiotic. Furthermore, of 51 patients who needed meropenem dose adjustment because of renal impairment, 17 patients (33.33%) received unadjusted dose.

Conclusion: High rate of errors exists in utilization of meropenem in our referral hospital especially in rank order of selection for treatment (indication), dose adjustment and treatment duration. Therefore, modification strategies are necessary to promote rational use of meropenem in this center.

Keywords: Drug Utilization Evaluation, Meropenem, Hospital



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Evaluation of the Effect of Chronic Administration of *Citrus Aurantium* on the Development of Tolerance to Morphine Analgesia in Male Rats

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Abstract

Introduction: Opioids as analgesic agents are used in acute and chronic pain. Long-term use of opioids can lead to development of tolerance to the analgesic effect. One of the plants which is considered in delaying tolerance to morphine, is *Citrus aurantium*. Essential oil of fruit epicarp increases the release of neurotransmitters such as glutamate, GABA, aspart and glycine (1). Also the linalool in the essence has shown anti-inflammatory and analgesic effect (2). The overall objective of this study was to evaluate the effect of chronic administration of *C. aurantium* essential oil on the development of tolerance to morphine analgesia in male rats.

Methods: Essential oil was extracted from epicarp of *C. aurantium*'s fresh fruit by steam distillation method (water and glycerol ratio of 3:1). The experiments were carried out in 5 rat groups in the weight range (225-275 g). The control group received morphine (10mg/kg) and the test groups received morphine with the different doses of essence (20, 40 and 80mg/kg) or 1ml of essence's vehicle (Kolliphor®HS15 30% in normal saline that adjusted in pH=7.4 with phosphate buffer) intraperitoneally (3). Every other day, half an hour after the injection, the hot-plate test was carried out.

Results: Morphine tolerance was complete after 5 days in the control group. The vehicle group showed tolerance on the 9th day (p-value=0.734), 20mg group on the 13th day (p-value to control=0.015, to vehicle=0.139), 40 mg group on the 15th day (p-value to control and vehicle<0.001) and 80 mg group on the 17th day (p-value to control and vehicle<0.001). According to AUC of the percentage of maximum possible effect values, essential oil may interfere in the development of morphine tolerance.

Conclusion: According to the results, the essential oil of *C. aurantium*'s epicarp can delay the developing of tolerance to analgesic effects of morphine.

Keywords: Morphine, Tolerance, *Citrus aurantium*, Analgesic effect



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Nano-structure Copper (II) Complex Coordinated by 4, 4'-Dimethoxy-2, 2'-Bipyridine: Sonochemical Synthesis, Characterization, and Binding Interactions with DNA

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Abstract

Introduction: Advances in nanomaterials science contributed to develop new biomedicine fields, such as cancer diagnosis and therapy, nanocarriers for targeted delivery of drugs and genes. Advances in nanomedicines develop to

overcome several limitations of conventional chemotherapy such as nonspecific biodistribution, poor water solubility of most common chemotherapeutic drugs and low therapeutic indices.

Methods: $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ (1 mmol) and 4, 4'-dimethoxy-2,2'-bipyridine (dimethoxybpy) (2 mmol) were dissolved in ethanol and the product was obtained by addition of NH_4PF_6 . The suspension was positioned in a high-density ultrasonic probe for 1 h. Characterization was done by CHN, FT-IR, DLS and SEM. Absorption spectra were recorded at constant DNA concentration and variable the nano-structure complex concentrations. In competitive studies with GelRed (GR), DNA was pretreated with GR ($[\text{DNA}]/[\text{GR}]=10$) for 30 min and then was excited at 520 nm. The nano-structure complex was added and its effect on the emission intensity was measured. For SEM images, 1 mL of different concentrations of DNA was added to 1 mL of aqueous suspension of nano-structure, ($[\text{nano}]: [\text{DNA}] = 1:1, 1:2$ and $1:3$), and kept 48h to construct crystalline structure of nano-structure complex–DNA.

Results: The nano-structure complex, $[\text{Cu}(\text{dimethoxybpy})_2](\text{PF}_6)_2$ was successfully synthesized with sizes of about 38 to 98 nm (the structure of the complex was characterized by CHN, FT-IR and X-ray). Upon addition of the nano-structure complex to DNA, the absorption intensity at 260 nm changed, which is indicative of strong DNA-complex interaction that may have caused a change in the conformation of DNA. The emission intensity of GR–DNA system at 597 nm significantly decreased with the addition of the nano-structure complex, which confirms the nano-structure complex binds to DNA by insertion between DNA base pairs. The SEM images of nano-structure complex–DNA exhibit a highly ordered liquid crystalline form of DNA. The results show DNA condensation depend on experimental conditions, such as the ratio of DNA to nano-structure complex [2].

Conclusion: According to results, insertion of planar nano-structure complex between DNA base pairs and positive charge may be the major driving forces in the high DNA binding affinity.

Keywords: Nano-structure Cu (II) complex, GelRed, DLS, SEM, DNA condensation



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Cytotoxicity of Bis (4, 4'-Dimethoxy-2, 2'-Bipyridine) Copper (II) Complex against Human Carcinoma Cell Lines

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Abstract

Introduction: Today, more than 30 years after discovery of cisplatin, this complex is still one of the most effective and world's best-selling chemotherapeutic drugs, but it has encountered many side effects [1]. Many new researches have been focused on the synthesis and investigation of new metal-based anticancer agents because of their advantages, such as better biological activity, better selectivity, lower toxicities, and different mechanisms of action to overcome the unresolved clinical problems of cisplatin analogues.

Methods: An ethanolic solution of 4, 4'-dimethoxy-2, 2'-bipyridine (dimethoxybpy) was added to an aqueous solution of $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ (3:1 mmol) stirred for 6 h/RT and the product was obtained by addition of NH_4PF_6 . Characterization was done by CHN, FT-IR and X-ray. The cytotoxicity against MCF-7, A-549 and HT-29 was assayed by MTT method. After cell culture, the cells were treated in triplicate with increasing concentrations of the complex and cisplatin (1, 10, 20, 30, 40, and 60 μM) and incubated for 24 h. Live cells image were acquired directly using an inverted microscope without any treatment. Then, 20 μL of the MTT solution was added and after 4 h, the medium was exchanged with 100 μL of DMSO to dissolve purple formazan crystal. The absorbance of each well converted to percentage of cell growth inhibition and the IC_{50} values were calculated [2]. The obtained results are expressed as mean \pm SEM. The differences in cell viability between the groups were determined by one-way ANOVA, followed by the Tukey test. $P < 0.05$ was considered significant.

Results: The copper (II) complex, $[\text{Cu}(\text{dimethoxybpy})_2](\text{PF}_6)_2$, was successfully synthesized in good yield (75%). Microscopic analyses show the morphological changes in the cells with increasing the concentration of the complex and also show a dose-dependent growth inhibitory effect on the cells. The IC_{50} values obtained for the complex against MCF-7, A-549, and HT-29 were found to be 31, 53, and 36 μM , respectively. These investigations demonstrate that the complex is more effective against MCF-7 and HT-29 cells than A-549 cells under the same experimental conditions.

Conclusion: These results suggest that the complex can be introduced as an effective metal-based anticancer drug and further experiments in relevance to potential anticancer activity of this complex *in vivo* can be considered.

Keywords: Cytotoxicity, Copper (II) complex, chemotherapeutic agents, Cisplatin, MTT assay



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Synthesis, Characterization, and BSA- Binding Studies of Tris (4, 4'-Dimethyl-2, 2'-Bipyridine) Nickel (II) Complex

Abstract

Introduction: Protein binding increases blood solubility of medicines and their access to targets [1]. Human serum albumin is the most important carrier protein in the blood and has multiple binding sites and is able to interact with drugs and form a stable protein-drug complex which could affect the absorption, distribution, activity and toxicity of drugs [2]. Because HSA is expensive and its production is limited, bovine serum albumin (BSA) is usually used as a less costly substitute protein source.

Methods: $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and 4,4'-dimethyl-2,2'-bipyridine (dimethylbpy) (1:3 mmol) were dissolved in ethanol, stirred for 5 h/RT and the product was obtained by addition of NaClO_4 . Characterization was done by CHN, FT-IR, UV-vis and X-ray diffraction analysis.

Absorption and fluorescence titration experiments were performed at constant BSA concentration and variable complex concentrations. The change in UV-visible absorbance at 280 nm was recorded after each titrant addition. Fluorescence spectra were recorded at temperatures 290, 300 and 310 K with excitation and emission wavelengths of 280 and 344 nm, respectively. Synchronous fluorescence spectra also, were measured at two different $\Delta\lambda$ (difference between the excitation and emission wavelengths of BSA) values such as 15 and 60 nm. In CD experiment, the [BSA]/ [complex] ratio is 1:1. The CD spectra in the absence and presence of the complex were recorded in the range of 200–260 nm. The spectrum of Tris buffer was subtracted from sample spectra.

Results: The complex, $[\text{Ni}(\text{dimethylbpy})_3](\text{ClO}_4)_2$, was successfully synthesized in good yield (70%). Upon addition of the complex to BSA, the absorption intensity at 280 nm changed, which is indicative of strong BSA-complex interaction that may have caused conformational changes or variation of the microenvironment around amino acids of BSA [3]. The results indicate that the complex has a quite strong ability to quench the fluorescence of BSA [4]. The complex shows good binding affinity to BSA giving relatively high binding constants (104–106 M⁻¹) [3]. The synchronous measurements also confirmed an effective binding. CD intensity of BSA significantly decreased (shifting to zero levels) confirming conformational changes of the protein

Conclusion: According to the result, it can be concluded that BSA could act as a carrier protein for this complex.

Keywords: Serum albumin; Nickel (II) complex, UV-visible, Fluorescence, Synchronous fluorescence, Circular dichroism



Evaluation of the Effect of Chronic Administration of *Marrubium Vulgare* on the Development of Tolerance to Morphine Analgesia in Male Rats

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Abstract

Introduction: Opioids are potent analgesics and are irreplaceable for the treatment of severe pain in anesthesia. Long term exposure of opioids caused tolerance to it. Morphine enhanced the release of IL-1 β , TNF- α , IL-6, and of NO via μ -opioid receptor-PKC ϵ signaling pathway in activated microglial cells, mediating a proinflammatory phenotype in mouse microglial cells(1). The anti-inflammatory and analgesic effect of *Marrubium vulgare* is been proven (2). The present study was designed to investigate the effect of *Marrubium vulgare* on the development of morphine-induced tolerance in male rats.

Methods: Male Wistar rats were assigned to 5 groups of morphine (10mg/kg, IP), morphine (10mg/kg, IP) in combination with three different doses of the extract (20, 40 and 80mg/kg, IP) and morphine (10mg/kg, IP) in combination with vehicle (0.25ml/rat DMSO 50% in saline, IP). Every other day nociception was examined using hotplate test (55 ± 0.5 °C).

Results: Morphine tolerance was completed after 7 days in the control group but was completed in the groups treated with three different doses of the extract (20, 40, 80 mg/kg) respectively on the 9th, 11th and 19th day. There isn't a statistically significant different between vehicle group and control one. Maybe the anti-inflammatory effect of *Marrubium vulgare* is potentially important mechanism of delaying morphine-induced tolerance.

Conclusion: The extract dose-dependently delayed morphine-induced tolerance.

Keywords: *Marrubium vulgare*, Morphine, Tolerance, Analgesic



A Dispersive Liquid–Liquid Micro–Extraction Technique for the Pre– Concentration and Quantification of Stigmasterol and B-Sitosterol in Milk Samples Using A HPLC Method

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Abstract

Introduction: Phytosterols are plant sterols with chemical structures similar to that of cholesterol representing potential roles in reducing blood cholesterol and preventing some cancers. Therefore, in recent years, fortification of foodstuffs with phytosterols has gained the important position in food industry. In present study, a dispersive liquid-liquid micro-extraction (DLLME)-HPLC-UV technique has been described for the detection and simultaneous quantification of phytosterols including stigma sterol and β -sitosterol in milk products.

Methods: A DLLME procedure was utilized to extract stigmasterol and β -sitosterol from milk samples, where acetonitrile (2 ml) and carbon tetrachloride (200 μ l) were used as disperser and extracting solvents, respectively. Then, the obtained extract was analyzed with a HPLC method using the mobile phase of methanol / water (95:5 % v/v) with flow rate of 1.0 mL/min and stationary phase of C₈ column (250 mm \times 4.6 mm, 5 μ m) at 30 °C, equipped to a UV detector set at 205 nm.

Results: The obtained results illustrated that, the method was linear for the quantification of stigmasterol and β -sitosterol in the concentration ranges of 5.0 to 20 μ g/ml and 2.5 to 30 μ g/ml, correspondingly. The LOQ of the method was 2.72 μ g/ml for stigmasterol and 1.87 μ g/ml for β -sitosterol. The method was accurate (83.4 % \leq accuracy % \leq 106.5 %) and precise (0.9 % \leq RSD% \leq 9.7 %) for the simultaneous determination of stigmasterol and β -sitosterol in milk samples.

Conclusion: By taking the obtained results into the account, it can be concluded that the developed method could be applied as a feasible and reliable technique in food quality control laboratories to inspect the amount of phytosterols in milk samples.



Design and Synthesis of Novel Amide Derivatives of 1, 3, 4-Oxadiazole as Soluble Epoxide Hydrolase Inhibitors

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Abstract

Introduction: Soluble epoxide hydrolase is a member of the α/β hydrolase fold family of enzymes that involved in the metabolism of endogenous mediators such as epoxides of arachidonic acid, linoleic acid, and other lipid epoxides. By inhibition of sEH enzyme, epoxyeicosatrienoic acids (EETs) which are known as modulators of blood pressure and inflammation accumulate. Since the most potent sEH inhibitors reported in literature have limited pharmacokinetic profile, new scaffolds are needed for the therapeutic applications.

Methods: Based on structure and activity relationship of soluble epoxide hydrolase inhibitors and by using Glide software, new amide-based compounds were designed. 4-nitrobenzoyl chloride was reacted with hydrazine hydrate to obtain corresponding hydrazide which treated with benzoyl chloride and triphenylphosphine to close 1,3,4-oxadiazole ring. Then nitro group was reduced to amine by SnCl_2 . Finally, new amide derivatives were synthesized from the reaction of above amine with chloroacetylchloride and followed by reacting with various amines.

Results: Docking studies on the designed sEH inhibitors confirm that the amide groups of the analogues fit properly in the active site of sEH and have a suitable distance from the amino acids of Tyr466 and Asp335 for effective hydrogen bonding. These novel compounds were synthesized in appropriate yield and their structure was approved by instrumental methods including IR, Mass, HNMR and ^{13}C NMR spectroscopies.

Conclusion: In conclusion, some novel amide-based soluble epoxide hydrolase enzyme inhibitors with a 1,3,4-oxadiazole scaffold were designed, synthesized and approved by IR, NMR and Mass spectra.

Keywords: Inhibitor, soluble epoxide hydrolase, amide, oxadiazole



Performance the Guideline of Prescribing Albumin and Its Effect on Reducing Budget in a Teaching Hospital

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Abstract

Introduction: Medication studies are especially important for drugs with narrow therapeutic index, specific indication, high costs for drugs with widespread use. Albumin20% always ranked among the topmost costly drugs in Booali Sina Hospital. Considering the fact that widespread and inappropriate use of this drug is considered as a concern in hospitals all over the world rather than being a regional problem, we decided to establish a guideline for Albumin20% in our hospital and evaluate its administration pattern both before and after establishing the guideline.

Methods: This is an experimental study (clinical trial) performed at the Booali Sina Hospital, on 1626 selected patients receiving Albumin20% infusion during a 24-month period (12 months before and 12 months after codification and establishing guideline). We used predesigned data collection forms to collect the related information to determine compliance with the guidelines.

Results: The results show that the established guideline and educational programs on using guidelines can help reducing Albumin usage and treatment costs. The standardization of practice led to a financial saving of over 3,096,600,000 Rials in a year. From the total number of serum albumin orders, there are only 24% prescribed with rational dose and duration under appropriate indications. The most frequent inappropriate prescribing motives are hypoalbuminemia (75.6%), nutritional support (42.5%), and edema (24.4%).

Conclusion: Despite the current valid guidelines defining the appropriate prescribing of albumin this study demonstrates the extensive inappropriate use of this expensive medicine in hospitals in Iran. We conclude establishing the guideline is successful in reducing the overall rate of Albumin20% the administration and its related costs. The result indicates prospective monitoring and intervention by pharmacists and specific guideline of using this agent should be independently set in each hospital.

Keywords: albumin, guideline, budget, teaching hospital



A Comparative Kinetic Study on Drug Release Phenomenon from Polymeric Nanoparticles

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Abstract

Introduction: Swellable polymeric nanoparticles have been frequently used in controlled drug release systems. Generally, the drug release phenomenon acts as a major determinant influencing pharmacological effect in such formulations and evaluation of drug release kinetics, turns out to be very useful on approach to find the best model applicable to release profile. For this purpose, the current study provide a comparative release analysis and identify the most convenient model well defined the release behavior.

Methods: To study the release kinetics of various drug molecules from the swellable polymeric nanoparticles, the extracted data from literature were fitted to eight conventional models. Coefficient of determination (R^2) and absolute percent error (E%) were calculated for each set as well as the overall error (OE), the number of error (NE) and the akaike information criterion (AIC) for all sets. The accuracy of R^2 was assessed employing Sum square of errors (SSE), sum square of regression (SSR) and sum square of total variation (SST).

Results: The model associated with the highest R^2 and the number of the error, as well as the lowest overall error (OE) and akaike information criterion (AIC) is regarded as giving the best fit out of the models. Among the models, Weibull (W) model produced R^2 and OE values of 0.93 and 8.79, respectively. Also, the number of errors less than 5% was 46.15 percent of a total number of data set and akaike information criterion of this model is -34.93 which the smallest value of all is.

Conclusion: Drug release kinetics is a predominant of importance in recognition of release determinants, mechanism and finding the ideal set of conditions leading to the desired release profile *in vivo*. The results represent that Weibull model describes the release pattern with the major applicability.

Keywords: Drug release, Kinetic analysis, Swellable polymeric nanoparticles, Weibull model.



Optimization of 5-Fluorouracil Loaded Chitosan - Dextran Microparticles Intended for Colon Delivery

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Abstract

Introduction: Polymeric hydrogels especially carbohydrate polymers are receiving considerable interest as promising devices in drug delivery systems. Among them, dextran, which can be degraded by microbial enzymes presented in colon, offers specific characteristics in colon selective drug delivery via oral route of administration. In the current study a particulate colon specific drug delivery system based on chitosan-dextran loaded by 5-fluorouracil (5-Fu) have been prepared and the properties of resulting particles were investigated.

Methods: Hydrogel microparticles containing 5-Fu were obtained upon an ionic gelation technique. The preparation process was optimized by a systematic multi-objective optimization approach in terms of the particle size and loading efficiency of the resulting microparticles. A series of *in vitro* characterization tests were carried out on the optimum formulation. The *in vitro* drug release profile was determined under 5 different pH media simulated to GI tract condition. Although to define the final formulation effect on colorectal cancer cells in comparison with free drug solution, Mtt test were performed on SW742 cell line.

Results: According to the analysis of variance procedure, the P value of < 0.0001 and 0.0001 for size and loading efficiency analysis, determined the final quadratic model terms were significant and the "Lack of Fit F-value" of models implied the Lack of Fit was not significant relative to the pure error. Under the condition studied, the molecular weight of chitosan and 5-Fu concentration is identified as significant parameters controlling particle size and loading efficiency, respectively. The optimum particles had good spherical geometry with the final particle sizes, loading efficiency, and loading capacity of 51.33±0.95µm, 13.12±0.65 and 26.96±0.38%, respectively. The *in vitro* drug release profile characterized by a Higuchi model and the Mtt results confirmed the higher effect of studied formulation on cell eradicating compare to free drug.

Conclusion: The formulation and surface characterization of particles was successfully performed the appropriate properties of particles have provided a potential means for colon drug delivery system via oral administration.

Keywords: 5-fluorouracil, Colon delivery, colorectal cancer, Drug release, Hydrogel.



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Molecular Modeling Studies and Synthesis of 9-Alkyl/Aryl-3-(5-Mercapto-1,3,4-Oxadiazol-2-Yl) -7, 8, 9, 10-Tetrahydrobenzo [H] Quinolin-4 (1H) -One Derivative as Inhibitors of HIV Replication

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Abstract

Introduction: The causative agent of acquired immune deficiency syndrome (AIDS) is the human immunodeficiency virus type 1 (HIV-1). During the past three decades, the combination of antiretroviral drugs with HAART (highly active antiretroviral therapy) regimens has transformed the management of HIV infection from a fatal disease to a manageable chronic condition. However, Resistance to marketed anti-HIV drugs is increasing at an alarming rate. Thus, there is a need to improve existing agents and develop new agents which work by different mechanisms. HIV-1 integrase as one of the key enzymes for HIV-1 replication represents a crucial target for antiretroviral drugs, because it has no counterpart in mammalian cells. In this research, aimed at the discovery of new compounds as anti-HIV-1 agents, the HIV-1 integrase inhibitors were selected as a lead to design new analogues.

Methods: Preparation of novel compounds was started from the 5, 6, 7, 8-tetrahydro-1-naphthylamine. The Gould–Jacob cyclization reaction was the main method to form the core structure. Condensation of 5, 6, 7, 8-tetrahydro-1-naphthylamine with ethoxy methylene malonate diethyl ester (EMME) produced methylene malonate intermediate. This compound was converted to an ester intermediate in diphenyl ether containing catalytic 2-chlorobenzoic acid at high temperature. The ester was subsequently treated with Hydrazine with absolute ethanol to form the

corresponding hydrazide intermediate. Hydrazide intermediate reacted with CS₂ with alkali absolute ethanol to give 3-(5-mercapto 1, 3, 4-oxadiazol-2-yl) -7, 8, 9, 10-tetrahydrobenzo [h] quinolin-4 (1H) -one derivative. This compound was treated with different alkyl and aryl halides in the presence of CH₃COONa in absolute ethanol to give final products.

Results: Final compounds were synthesized and purified using different crystallization and chromatography methods. The structure of the synthesized compounds was confirmed by IR, LC-MS (ESI), and ¹H-NMR. A molecular modeling study using the later crystallographic data available for PFV (prototype foamy virus) integrase was performed to explain the probable mechanism of action of synthesized compounds.

Conclusion: We synthesized a novel series of 9-alkyl/aryl-3-(5-mercapto-1, 3, 4-oxadiazol-2-yl) -7, 8, 9, 10-tetrahydrobenzo [h] quinolin-4 (1H) -one derivative based on HIV-1 integrase inhibitors pharmacophores. The molecular modeling studies suggested that the anti-HIV activity of these compounds might involve a metal chelating mechanism. According to HIV-1 integrase inhibitors structure activity relationship, carbonyl group and N atom of oxadiazole ring play as a chelate motif. The anti-HIV activity of novel compounds is under investigation.

Keywords: Synthesis, Anti-HIV activity, Modeling, tetrahydrobenzo [h] quinolin-4 (1H) -one.



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Design, Synthesis, and Docking Studies of Carboxamide and Carbothiamide Derivatives of 8-Methyl-4-Oxo-1, 4-Dihydroquinoline as Anti-HIV Agents

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Abstract

Introduction: Human Immunodeficiency Virus (HIV-1) causes Acquired Immune Deficiency Syndrome (AIDs). AIDS is one of the most serious health problems in the world. Marketed anti-HIV drugs can fail to control HIV due to lack of therapy adherence, occurrence of side effects, loss of drug effectiveness over time caused by development of resistance. It is therefore essential to continue to develop new antiretroviral drugs. HIV-1 integrase, the enzyme responsible for the integration of viral DNA into the host genome, provides many potential targets for therapeutic

intervention. It has no counterpart in mammalian cells. In this research, it is used of integrase inhibitors as designing base for achieving to new structures with anti HIV effect.

Methods: New compounds were prepared starting from the o-toluidine in 4 steps. O-toluidine was converted to ethyl 1, 4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate based on Gold-Jacobs reaction. The obtained ester was subsequently reacted with hydrazine hydrate in DMF to form the corresponding hydrazide intermediate. In order to synthesize final products, hydrazide intermediate reacted with phenyl isocyanates and phenyl isothiocyanates derivatives in DMF as solvent.

Results: Target compounds were synthesized and purified using different crystallization and chromatography methods. The structure of synthesized compounds was confirmed by IR, LC-MS (ESI), ¹H-NMR and ¹³C-NMR. A molecular modeling study using the later crystallographic data available for PFV (prototype foamy virus) integrase was performed to explain the probable mechanism of action of synthesized compounds.

Conclusion: We designed and synthesized a novel series of carboxamide and carbothiamide derivatives of 8-methyl-4-oxo-1, 4-dihydroquinoline derivatives based on HIV-1 integrase inhibitors pharmacophores. Docking study revealed that the anti-HIV activity of these compounds might involve a metal chelating mechanism. According to HIV-1 integrase inhibitors structure activity relationship, carbonyl groups play as a chelator motif. The anti-HIV activities of synthesized compounds are under investigations.

Keywords: Synthesis, anti-HIV activity, 8-methyl-4-oxo-1,4-dihydroquinoline, docking study.



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The Impact of a Pharmacist Based Patient Educational Program on the Knowledge, Awareness and Beliefs of Parents Who Had a Patient with Growth Hormone Deficiency and Receiving GH in an Educational Community Pharmacy

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Abstract

Introduction: The community pharmacists are the key members of the multidisciplinary team caring for patients with growth hormone deficiency (GHD) in pharmacotherapy monitoring; the potential benefits of pharmacist patient education may be the more accurate medication, less failure and better tolerance. The objective of this study was to assess the effect of a pharmacist based patient education program on the knowledge and awareness of parents. In which the ultimate goal is to support their decision-making, care, independent empowerment with health problems and less failure to treat psychosomatic consequence of GHD.

Methods: We prepared a questionnaire consisted of 32 items to assess the patients' knowledge of correct using of growth hormone (GHD). After testing the questionnaire validity and reliability based on the opinions of the members of a pharmacotherapy panel, 26 items remained. Parents of 70 patients with our inclusion criteria responded the questionnaire before and after the pharmacist educational program.

Results: Patients' achieved scores before and after receiving the educational program were 12.01 ± 2.0 and 25.55 ± 1.89 respectively. The results show that most participants have not satisfiable knowledge about GH, although they have administered this medication for their child, and also after they received the educational program their knowledge and awareness significantly rise ($P < 0.01$).

Conclusion: There are few studies evaluating the role and potential impact that community pharmacists can have on patients with GHD. Our results showed that pharmacists' intervention could improve the pharmacotherapeutic knowledge and awareness of patients, and it may provide important contributions to the consequence of GHD.

Keywords: Community Pharmacy, Patient counseling, Patient education, growth hormone deficiency (GHD).



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Preparation and Modification of Surface Methotrexate-Loaded Mesoporous Silica Nanoparticle Intended for Brain Delivery

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Abstract

Introduction: Many nanoparticles have been employed as a carrier to deliver the CNS drugs across the BBB. Recently, mesoporous silica nanoparticles (MSNs) have gained special attention in the biomedical research field due to its great advantages such as large surface areas and pore volumes, tunable pore/particle size, controllable morphology and excellent biocompatibility. Methotrexate (MTX) is a hydrophilic small molecule anticancer agent ($\log P -1.8$) widely used in the CNS malignancies as is poor drug permeability through the BBB(1). In the study, we investigated controlled release of interaction MSN and MSN-NH₂ between MTX as anti cancer drug.

Methods: First, MSN was synthesized by thermal method (2). Next, MSN was modified by post-synthesis method with amino group using APTES (MSN-NH₂).

Results: The results indicate that the X-ray patterns are very similar with a very intense peak assigned to reflections at 2θ of 2.34° (100) and two additional peaks with low intensities at 2θ of 3.96° (110) and 4.69° (200) reflections at MSN. The FT-IR spectra further indicated the successful grafting of various functional groups onto the surface of MSN and MSN-NH₂. The typical Si-O-Si asymmetry stretch bond around 1075.6 , 811.55 cm^{-1} for Si-O-Si symmetry stretching vibration and 408.84 cm^{-1} for Si-O-Si bending vibration (MSN). For MSN-NH₂, the 1565.99 cm^{-1} bending vibration, 3126.21 cm^{-1} stretching vibration for NH₂ group and 1495.46 cm^{-1} bending bond for CH₂ group.

Conclusion: Surface modification of these mesoporous silica nanoparticles can play an important role in CNS controlled release them. Furthermore, the surface-modified mesoporous silica nanoparticles showed acceptable release performance *in vitro*.

Keywords: Mesoporous Silica Nanoparticles, Drug Delivery, Methotrexate, Controlled Release.



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Preparation of Oral Solid Formulation from Chicory and Turmeric Hydro Alcoholic Extracts for Treating Fatty Liver Patients

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Abstract

Introduction: Nonalcoholic fatty liver disease is a common disease among the patients specially the obese ones. Due to inefficiency and lack of the prescribed chemical medicines, herbal drugs with proven effects are prescribed like *Curcuma longa*, *Gingiber officinale*, *Silybum marianum*, *Chicorium intybus* and etc. The hepatoprotective and antioxidant effects of turmeric and chicory have been previously shown. Since there isn't any standardized dosage form of these herbs the aim of this study is the preparation of oral solid formulation from chicory and turmeric hydro alcoholic extracts.

Method: The maceration method was used to obtain hydro alcoholic extracts of the seed, root and stem of chicory to clarify which part has the more hepatoprotective effect. The hydro alcoholic extract of the seed, root and stem of chicory was standardized by total phenol as well as total flavonoids tests. The extract of turmeric was standardized by some methods written in herbal pharmacopeia of Iran.

Conclusion: The seeds of chicory showed more phenolic compounds than other parts of the plant. So the extract of seeds would be used in formulation. The future steps will be standardization of turmeric extract and formulation of the mentioned extracts as a solid dosage form.

Keywords: Nonalcoholic fatty liver, *Curcuma longa*, *Chicorium intybus*, hydro alcoholic extract .



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Synthesis of New Naphtoquinone Derivatives as Antiplatelet Aggregation and Evaluation of their Activity

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Abstract

Introduction: According to a statistics in 2016, cardiovascular diseases are one of the most important reasons of global mortality and a lot of people will die because of them. Also 50 percent of all deaths in Iran are due to cardiovascular diseases. One of the leading causes of these problems is forming clots and thrombosis in vessels, causes decreasing blood flow to vital organs such as heart and brain, and lead to serious problems including heart attack, embolia, stork and etc. One of the useful routs to treat or prevent of these diseases is using antithrombotic agents that can be used for prevention and treatment of blood clot. Antithrombotic drugs are classified into 3 groups such as anticoagulants, antiplatelets and fibrinolytics. In this research, according to structure-activity relationship of antiplatelet substances, we designed and synthesized new naphtoquinone derivatives.

Methods: For the synthesis of different derivatives, first the tri methoxy benzaldehyde and naphtoquinone and anilines were dissolved in water and the ZnCl₂ catalyst was added to the mixture. The reaction mixture was refluxed and stirring for 3-8h monitoring through TLC. After cooling, the precipitated solid was filtered and washed with chloroform/water and after purified by column chromatography the product, their structure was confirmed by IR, LC-MS and NMR spectrums.

Results: After confirming their structure, antiplatelet activity of these compounds and their mechanism of action have been evaluated by using platelet aggregating agents in 2 methods. Some of the compounds have a good activity on platelet aggregation.

Conclusion: The obtained data indicated that some of our synthesized compounds possess potent antiplatelet activity. However, further studies are needed to confirm the exact mechanism of action of antiplatelet aggregation.

Keywords: antiplatelet, naphtoquinone derivatives, trimethoxy benzaldehyde.



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Evaluation of Total Antioxidant Capacity and Lipid Peroxidation Level in Semen and Serum Samples in Farmers of Karafs Region, Hamadan, Iran

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Abstract

Introduction: Recent studies have shown that organophosphorus compounds can be associated with infertility in human. In the present study, changes of oxidative stress biomarkers were investigated in serum and semen samples, in farmers of Karafs region, Hamadan, Iran.

Methods: In this study, thirty male infertile farmers and thirty healthy men were considered as the case and control groups, respectively. After sampling, serum cholinesterase activity in serum and total antioxidant capacity and lipid peroxidation for both semen and serum samples were determined.

Results: our findings showed that serum cholinesterase enzyme activity in farmers was significantly lower than control group. In addition, a significant decrease in semen total antioxidant capacity was observed in comparison with control group. In addition, remarkable increase in lipid peroxidation level was detected for both serum and semen samples of farmers compared to the control group.

Conclusion: Occurrence of oxidative stress may be associated with decreasing of semen quality and also infertility, in farmers of Karafs region, Hamadan, Iran.

Keywords: Organophosphorus, Infertility, Oxidative stress, lipid peroxidation.



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Biodegradable Nanofiber as Intrapocket Drug Delivery System for Treatment of Periodontitis

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Abstract

Introduction: The purpose of the study was to formulate biodegradable intrapocket dental nanofibers, which could be easily placed into the periodontal pocket, and be capable of delivering therapeutic concentrations of clindamycin and dexamethason with lower dose, hence obviating lower side effects.

Methods: Nanofiber was prepared using chitosan, Zein, Poly (vinyl alcohol). Solutions of 4 w/v chitosan and 1% w/w zein and 2% polyvinyl alcohol were prepared, and the nanofibers were produced by electrospinning technique. Scanning electronmicroscopy (SEM) was used to investigate the morphology and average diameter of the electrospun nanofibers. The device was optimized on the basis of evaluation parameters such as weight variation, content uniformity, surface pH, and *in vitro* release studies. *In vitro* drug release studies in phosphate buffer solution showed that the drug release rate was affected by the drug/polymer ratio.

Results: *in vitro* release studies showed that drug concentrations were maintained above the MIC value for the period of the release studies. Growth inhibition of bacteria was obtained from clindamycin containing nanofibers.

Conclusion: The drug was released locally and had a high benefit to low risk ratio as compared to systemic administration which is unacceptable due to, low benefit to high-risk ratio. Hence low-dose site-specific nanofibers present a better alternative.

Keywords: Biodegradable Nanofiber, intrapocket drug delivery, Chitosan, Zein.



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Investigation of the Effect of Biodegradable Polymeric Electrospun Nanofiber as Biological Dressing for Vitiligo Treatment

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Abstract

Introduction: Vitiligo is a common hereditary chronic disease, which melanocytes are systemically damaged, especially in parts of the skin, mucous membranes, the eyes and the inner ear. About 1% of the world's populations are infected which affect all races and both sexes equally and can develop at any age. There are several treatments for this disease such as physical, surgical, and systemic therapy. Various surgical techniques are usually used in patients who have failed medical treatment and physical response. One of the most effective of surgical techniques involves the creation of a blister under the epidermis of the skin graft donor site. Herein we introduce a new biocompatible nano bandage, helpful for vitiligo wound healing after surgical therapy.

Methods: Biocompatible nanofiber of polyvinyl alcohol and Chitosan with various ratios as 30:70, 50:50 and 70:30 were prepared. Different voltage such as 8, 16 and 22 kV was applied. The optimum fiber was characterized by FTIR, XRD, and SEM. The fibrous bandage was sterilized by plasma. The blisters were made on the surface of the healthy skin which becomes ready by suction and making method. Using a laser, scratches were created on vitiligo lesions. The epidermis containing the extracted melanocyte cells was placed on the lesion. The biological and ordinary dressings were placed in an area of the patient's body. The size of the lesions was monitored at deferent times by taking images of the lesions.

Results: Nanofibres were prepared with a diameter of 196 nm. FTIR and XRD results showed the chemical bonds between polymeric molecules. Clinical data analysis presented a significant improvement (at 3 months) of the vitiligo lesions treated by nano bandage in compare with ordinary bandages.

Conclusion: The biocompatible nanofibrous bandage of CS and PVA as a dressing for vitiligo lesions was significantly better than an ordinary one.

Keywords: Vitiligo, electrospun, Chitosan, Biological dressing.



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Preparation and Characterization of Polymer- Peptide Conjugation as A Targeted Carrier

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Abstract

Introduction: Recently, nanomedicine has emerged as a medical application of nanotechnology. Nanotechnology derived drug delivery can cause the drug to remain in blood circulation for a long time, thereby leading to lesser fluctuations in plasma levels and therefore, minimal side effects (1, 2). By this kind of carriers, the systemic cytotoxicity of cancerous drugs decreased (3). Cancer targeting by peptides as ligands for targeted delivery of anticancer drugs or drug carriers have a potential that significantly enhance the selectivity and the therapeutic benefit of current chemotherapeutic agents. Considerable preclinical data have shown remarkable success in the application of tumor targeting peptides (4).

Methods: In brief, 100 mg of hyaluronic acid (HA) was dissolved in 100 ml phosphate buffer saline pH 7.4, 0.1 M, and mixed with 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (7–20 mg, 2 molar equivalents to HA) and N-hydroxysuccinimide (4–12 mg, 2 molar equivalents to HA) for activation. After activation, the specified weight of amino acid was added to the solution for coupling. The obtained product lyophilized by freeze dryer and investigated by FT-IR and PCS. Finally, for carrier further investigation, polymer was loaded by Idarubicin as an anticancer drug.

Results: The FTIR results showed that the complete coupling of polymer occurred by amino acid. Therefore, the amide bond was detected in 3500-3700 cm^{-1} . Also, the free amine groups of amino acids were detected in 3300-3500 cm^{-1} with broad spectrum. The PCS results showed that nanoparticles size was 150 nm with acceptable PDI of 0.265. Further size investigation with SEM proved the spherical shape of NPs obtained with sonication.

Conclusion: Hylaronic acid was modified successfully by amino acid as proved by analysis technique. Obtain formulation could have an application in targeted drug delivery and as well as cancer therapy. A polymeric nanoparticle as a drug carrier represents a marvelous avenue for cancer therapy

Keywords: Targeted drug delivery, Amino Acid, Hyaluronic acid, Carbodiimides.



Evaluation of Ginseng Extract and Vitamin B5 Effects on Hair Regeneration Cycle

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Abstract

Introduction: If the ratio of Anagen to Telogen in hair growth's cycle is below 4, a person has alopecia. Four factors play the main roles in Androgenic Alopecia: genetic changes, hormonal changes, lack of nutrition and seborrhea. Glucoside is a polyphenol which enable hair follicle's stem cells division, while preserve their properties, protect stem cells against apoptosis, and lead them to Anagen phase, then enhance the metabolism of papilla dermal fibroblast so, cause repair and renewal of hair growth. In this study, we investigate the effects of ginseng extract that rich with phenolic compounds for reproduction rate of hairs.

Methods: The ability to liberate peptide products and absorb the combination of ginseng and vitamin B5 on healthy and damaged hair with fluorescein reactions after extraction were measured in two different conditions: high temperature (50 ° C) and high ionic strength (0.5 mol sodium chloride). Protocol of work is to evaluate strength and durability of hair in two groups; normal hairs washed by water once and another time put it under treatment of ginseng extract and vitamin B5 10% by amount of 30 ml for 1h, then wash by standard way. Finally, absorption rate of phenolic compounds was measured by Folin sioculto method and the results states by milligrams of extract. Folin sioculto method is one of the most common methods of phenolic compounds measurements.

Results: when the hair loss occur indeed Telogen phase prolonged and make harder the transmission to Anagen phase then hair become gradually thinner and increase percentage of transmission to Telogen phase. This problem is due to the fact that the follicle stem cells are less active. Therefore, fibroblasts located in skin papillae are less effective in communicating with stem cells, which means that the matrix is not reconstructed like before. Hair growth stimulants such as peptides, special proteins such as Lupine hydrolyzed proteins, and various amino acids such as tyrosine derivatives, arginine, ornithine, citruline, and amino saccharides: Glucosamine; to enhance the extracellular matrix in the papilla and hair's onion does not only stimulate hair growth, but also improves the nutrition and respiration of the root-cell-forming cells, increasing the strength and thickness of the head hair. The ingredients in the Ginseng Extract cause hair loss in people to normal levels and stimulate cell metabolism and hair rejuvenation as well as hair health

Conclusion: The results of the release of peptide products from normal and damaged hair showed that with the combination of ginseng extract and vitamin B5 10%, 7 mg of this compound per gram of normal hair and 16.6 mg of this

compound per gram of Damaged hair is absorbed and shows a significant difference between the two groups ($P < 0.05$).

Keywords: Ginseng extract, Dexpanthenol, Androgenic alopecia, Hair regrowth



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The Usage Pattern of Herbal Products, and Herb-Drug Interactions among Patients with Chronic Kidney Disease

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Abstract

Introduction: Chronic Kidney Disease (CKD) is a global public health problem with an increasing incidence, which is accompanied by a lot of complications. Like the other chronic disease, patients with CKD also may benefit from complementary and alternative medicine (CAM). One of the prevalently used CAM is herbal products. In this study, we planned to determine the usage prevalence of herbal products and herb-drug interactions in CKD patients.

Methods: A cross sectional study was conducted on 800 CKD and post-transplant patients in Isfahan, Iran. Patients were subjected to an interview in order to fill the related checklist. Demographic and clinical characteristics of the patients, as well as the drugs or herbs used by the patients were recorded. The mentioned data were analyzed with regard to their relationship with the use of herbal products and significant herb-drug interactions.

Results: This study included 800 patients (554 males and 246 females). Hypertension (35.2%) was the most common cause of kidney failure where the diabetes mellitus (13%) took the second place. The most frequently used unformulated herb was cowslip (*Echium amoenum*) (15.3%), while the most frequently used formulated herb was anti-cough and mucolytic syrup based on *Thymus vulgaris* (24.3%). Eighteen patients used herbs with unknown sources and contents. In our study, Ginseng had the most possible interactions with prescription drugs (18 interactions).

Discussion: The present study provided the possible list of the most frequent herb-drug interaction in CKD patients. Usage of herbal products in patients with chronic illness, while numerous prescription and non-prescription drugs are taken, could lead to fluctuations in the main drug effects, which finally may affect on disease progression. This can be more highlighted in kidney-grafted patients, where a herbal product may affect the immunosuppressive

agent's serum concentration and graft survival. Due to the possibility of important interactions occurrence in this population, health care team should play an active role to inform the patients about herbal products safety, adverse effects and possible interactions.

Keywords: Complementary and alternative medicine, herbal products, herb-drug interaction, chronic kidney disease



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Study of Effect of Silymarin (Livergol) on Copper and Zinc Serum Level in Patients with Rheumatoid Arthritis

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disease, which can lead to joint destruction and disability. Inflammatory factors increase in rheumatoid arthritis. Silymarin and its biologically active component are strong antioxidant and have chelating activities. Numerous studies have indicated the association between Copper (Cu) concentrations in pathogenesis of RA.

Methods: In clinical trial study we evaluated the effects of silymarin tablet (Livergol®) on Serum levels of copper and zinc in Forty-four participants with chronic rheumatoid arthritis Disease. Venous blood sample was obtained from all fasting patients at both beginning as well as at the end of the study. All patient were treated with total, 420 mg of silymarin daily, divided in, three doses for a 3-month.

Results: Silymarin significantly increased Cu serum level in 44 RA patients after 90 days (118 ± 11.58 versus 127 ± 18.96 , $p=0.02$). The Zn concentration was also higher in serum of RA patients after 90 days (130 ± 19.34 versus 137 ± 43.24 , $p=0.3$). During the inflammatory process, the production of cytokines is increased. Both IL-1 and IL-6 are responsible for hepatocytes stimulation to increase the synthesis and secretion of Ceruoplasmin to the blood serum. Ceruoplasmin transfers Cu from hepatocytes to the blood serum. Copper ion is a very powerful catalyst in

oxidation processes which accelerates oxidation reactions. Silymarin, with chelating effect on copper reduces Oxidation.

Conclusion: It seems that the 'copper and Zn serum level in patients with RA is correlated with presence of the inflammatory process. That could serve as a useful marker for the diagnosis of this disease.

Keywords: Rheumatoid arthritis, Silymarin, chelating activities



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Preparation and Evaluation of Lipophilic Methotrexate Prodrugs Based on Fatty Acids

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Abstract

Introduction: Prodrugs are described as inactive or less active bio reversible derivatives of active drug molecules, which undergo enzymatic or chemical biotransformation before eliciting their pharmacological effects. The major goal in prodrug design is to overcome the various physicochemical, pharmaceutical, biopharmaceutical and pharmacokinetic limitations of parent drug, which otherwise would hinder its clinical use (1, 2). Methotrexate (MTX) is one of the most widely used chemotherapy drugs for the treatment of a number of cancers including: breast, head and neck, leukemia, lymphoma, lung, osteosarcoma bladder, and trophoblastic neoplasms. As an analogue of folic acid, MTX can be utilized not only as a drug but also as a potential targeting agent (3). The aim of this study was to design and develop an amidation method to synthesize the prodrugs of methotrexate and also to find out the detailed chemical characteristics of these products.

Methods: Methotrexate was conjugated with Fatty acids by an amidation reaction. A solution of fatty acid (1 mmol), DCC (1.1 mmol) and methotrexate (0.5 mmol) in anhydrous N, N-Dimethylformamide (2 mL) as a solvent were stirred mechanically at room temperature until amidation was complete. The N, N-dicyclohexylurea was

filtered off and the solvent was removed under reduced pressure to give the products which were chromatographed over a column of silica gel using chloroform-methanol as eluent.

Results: A series of lipophilic methotrexate prodrugs were successfully prepared by an amidation reaction between carboxyl group of fatty acid and amino groups of methotrexate. The synthesized prodrugs were characterized using IR, ¹H NMR and ¹³C NMR spectroscopy.

Conclusion: In conclusion, a proper method for amidation of methotrexate and Fatty acids was developed. Lipophilic folic acid prodrugs were successfully synthesized and the structures of compounds were characterized.

Keywords: Amidation reaction, Methotrexate, Prodrug, Fatty acid



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Evaluation of Cyproheptadine Administration in Prevention of Sleep Disorders Induced by Methylphenidate in Attention Deficit Hyperactivity Disorder Children

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Abstract

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in childhood. Stimulants are first line therapy for this disorder. Methylphenidate which is the best choice for therapy has a few side effects (1). The most common one is loss of appetite. The adverse effects may limit optimal dosing and patients' compliance and lead to treatment discontinuation. This research evaluated the effects of cyproheptadine on appetite problems induced by methylphenidate in children with ADHD (2).

Methods: During this pilot, randomized, double-blinded, placebo-controlled clinical trial, the effect of cyproheptadine 4mg daily in two divided doses for eight weeks, on loss of appetite occurrence induced by methylphenidate was assessed. Forty patients, that fulfilled the inclusion criteria assigned to the cyproheptadine or placebo group. Patient' weight and ADHD rating scale scores were recorded at baseline and weekly during these 8weeks. Rate of growth was evaluated weekly for each patient.

Results: There were no significant differences between cyproheptadine and placebo groups regarding weight and rate of growth in weekly assessments. In addition, there were no significant differences between two groups in response to therapy based on ADHD rating scale scores.

Conclusion: Cyproheptadine does not have considerable effect on appetite problems induced by methylphenidate in ADHD children. Moreover, cyproheptadine has no negative impact on patients' response to methylphenidate.

Key words: Attention Deficit/ Hyperactivity Disorder-loss of appetite-methylphenidate-cyproheptadine



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Urine Neutrophil Gelatinase Associated Lipocalin as an Early Marker of Acute Kidney Injury in Hematopoietic Stem Cell Transplantation Patients

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Abstract

Introduction: Acute kidney injury (AKI) is common in hematopoietic stem cell transplantation (HSCT) patients with an incidence of 21–73%. Prevention and early diagnosis reduces the frequency and severity of this complication. Predictive biomarkers are of major importance to timely diagnosis. Neutrophil gelatinase associated lipocalin (NGAL) is a widely investigated novel biomarker for early diagnosis of AKI. However, no study assessed NGAL for AKI diagnosis in HSCT patients.

Methods: We performed further analyses on gathered data from our recent trial to evaluate the performance of urine NGAL (uNGAL) as an indicator of AKI in 72 allogeneic HSCT patients. AKI diagnosis and severity were assessed using Risk–Injury–Failure–Loss–End-stage renal disease and AKI Network criteria. We assessed uNGAL on days –6, –3, +3, +9 and +15. Time-dependant Cox regression analysis revealed a statistically significant relationship between uNGAL and AKI occurrence. (HR = 1.04 (1.008–1.07), p = 0.01).

Results: There was a relation between uNGAL day+9 to baseline ratio and incidence of AKI (unadjusted HR = 1.047 (1.012–1.083), p < 0.01). The area under the receiver-operating characteristic curve for day+9 to

baseline ratio was 0.86 (0.74–0.99, $p < 0.01$) and a cut-off value of 2.62 was 85% sensitive and 83% specific in predicting AKI.

Conclusion: Our results indicated that increase in uNGAL augmented the risk of AKI and the changes of day +9 uNGAL concentrations from baseline could be of value for predicting AKI in HSCT patients. Additionally uNGAL changes preceded serum Cr raises by nearly 2 days.

Keywords: Acute kidney injury, hemtopoietic stem cell transplantation, neutrophil gelatinase associated lipocalin, nephrotoxicity, receiver-operating characteristic curve



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Investigating the Effect of Vitamine D on Stress Oxidative Biomarkers of Hippocampus in the B-Amyloid Peptide Induced Model of Alzheimer's Disease in Rat

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Abstract

Introduction: Vitamin D3 (1, 25-dihydroxyvitamin D3) is a steroid molecule whose concentration in the body depends on exposure to the sun and diet. There is growing evidence that Vitamin D3 (1, 25-dihydroxyvitamin D3) is involved in brain development. Vitamin D intoxication has been shown to generate oxidative stress due to the production of free radicals and alter the antioxidant defense system. Major pathological hallmarks of AD include amyloid beta-peptide (A β)-rich plaques, neurofibrillary tangles (NFTs), synapse loss, and brain atrophy especially in those areas of the brain associated with memory and higher executive function.

Methods: In this study 36 male rats were equally separated in to 6 groups (6 rats each Group). I (control),II (Sham solvent group), III (Sham surgery group), while Group IV was given Vitamin D (37.5 ng /kg/day) for 14 days , V (Alzheimer Group) , VI (Alzheimer group received Vitamin D) . 24 hours after treatment, hippocampus was isolated. Then MDA, TTG, TAC, DNA Damage, Vitamine D were measured by spectrophotometer.

Results: Results were expressed as the Mean \pm SE for all animals in each group. Statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by post hoc Tukey test. Results were considered

significantly different if $p < 0.05$. An decrease in MDA and DNA damage in ALZ group was observed compared with control group. Also, the results showed that Vitamin D could decrease liver toxicity rats through reduction of ROS. The results suggested that Vitamin D could ameliorate Alzheimer rats through reduction of inflammation.

Conclusion: In the present study, the protective effect of vitamin D has been carried out against neurotoxicity in the rat hippocampus and remarkable oxidative damage was also observed.

Keywords: Vitamin D, Hippocampus, Oxidative stress, Alzheimer, Rat



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Poly (Lactide-Co-Glycolide) Acid Cryoprotected Nanoparticles in Active Drug Delivery

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Abstract

Introduction: Folate is essential for the production and maintenance of new cells. Many cancer cells have higher demand for folic acid (1). Poly (lactide-co-glycolide) acid (PLGA) is widely used for preparation of nanoparticles, injectable depots, films, scaffolds and as a bulk implant for drug delivery systems designing due to low toxicity and tunable biodegradability (2). PLGA with tunable functional group could be modified with targeting agents and were used in targeted drug delivery. The dispersion of freeze-dried formulations is so important in intravenous drug delivery. For this purpose, cryoprotective agents were used in powder preparation.

Methods: Idarubicin has been encapsulated in PLGA nanoparticles using the emulsification/solvent evaporation technique. In continue the folic acid coupled to nanoparticles (NPs) by carbodiimides activation. The different concentration of monosaccharide used as a protecting agent in freeze-drying. Prepared NPs were characterized using PCS, FT-IR techniques and *in vitro* release of Idarubicin from targeted and non-targeted NPs evaluated.

Results: The FT-IR spectra proved the complete conjugation of targeting agent on the shell of PLGA NPs. The average size and encapsulation efficiency of the prepared PLGA – folic acid NPs were found to be around 150 nm and 66%, respectively. The entrapment efficiency slightly decreased after coupling due to the drug leakage in the coupling reaction. The PCS analysis showed a slightly change in particle size after three months storage. *In vitro* release profile indicated that up to 90% of the drug was released in 24 h.

Conclusion: A cryoprotectant is a substance used to protect biological tissue from freezing damage. Active drug delivery by ligand mediated targeting used in cancer therapy. In this study the monosaccharide-protected folic acid, conjugated PLGA nanoparticles prepared and proved the positive effect of sucrose on the NPs dispersing followed dehydration.

Keywords: Poly (lactide-co-glycolide), Idarubicin, Folic acid, Active drug delivery, Cryoprotective agent



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Optimization of the Extraction Process of *Rebaudioside "C"* from *Stevia* Plant

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Abstract

Introduction: In this study, a new method named optimized "Bubble Column Extraction with Ultrasonic Bath (BCE-UB)" was used to extract Rebaudioside "C" from the *Stevia Rebadiana* leaves. This substance is diterpene glycoside named Steviol that is 350 times sweeter than sucrose (sugar) and does not increase the blood glucose.

Methods: For the qualitative and quantitative analysis of extracted Steviol glycosides, High-Performance Liquid Chromatography (HPLC) with UV detector and NH₂ column was used. Several parameters including extraction time, liquor to material ratio, air flow, extraction solvent, and particle size of samples were taken into account. Among them, the first three parameters were control parameters that were stabilized in their most optimized form.

Recognized as the most important parameters in the amount of extraction, the three others are signal parameters that were optimized by the method of Design Of Experiments (DOE).

Results: The most optimized condition for the highest extraction amount of Rebaudioside “C” was achieved by water solvent (pH 7) as extraction solvent, the mesh size 45, temperature of 343 K, a liquor to material ratio of 123 ml.g⁻¹, an extraction time of 58 min, and an air flow of 1.5 L/min.

Conclusion: By this new extraction method compared to other methods, highest efficiency of Rebaudioside “C” was achieved and process of extraction of Rebaudioside “C” from Stevia plant was optimized.

Keywords: Rebaudioside “C”, HPLC, Diabetes, Bubble Column Reactor, DOE, Stevia Plant



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Evaluation of Antimicrobial Activities of Different Extracts from Some Plants Are Used in Traditional Medicine in Iran

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Abstract

Introduction: During the last two decades, the development of drug resistance as well as the appearance of undesirable side effects of certain antibiotics has led to the search of new antimicrobial agents mainly plant extracts with the goal to discover new chemical structures which overcome the above disadvantages. In this investigation we choice some plants from *Apiaceae*, *Asteraceae*, *Brassicaceae* and *Cucurbitaceae* families to evaluate their antimicrobial effects.

Methods :The aerial parts of *Anthriscus nemorosa*, *Artemisia marschalliana*, *Eryngium billardieri*, *Eryngium caeruleum*, *Eryngium thyrsoideum*, *Lepidim vesicarium* and also seeds of *Ecballium elaterium* were extracted by soxhlet method using n-hexane, dichloromethane and methanol solvents. Antimicrobial activity of the extracts

against four gram positive strains (*Bacillus subtilis*, *Listeria monocytogenes*, *Staphylococcus aureus* and *Staphylococcus epidermidis*), two gram negative strains (*Escherichia coli*, and *Salmonella typhi*) as well as a fungi (*Candida albicans*) were screened by disc diffusion method. Among the extracts, Potent extracts selected for further investigation (fractionation and MIC calculation).

Results: From 21 plants samples in 4 families, 13 samples showed antimicrobial activity at least against one of the bacterial species. Extracts with high activity were n-hexan extract of *Eryngium caeruleum* against *Staphylococcus aureus* and *Staphylococcus epidermidis* also n-hexan extract of *Eryngium thyrsoideum* against *Staphylococcus epidermidis*. The amount of MIC for n-hexan extract of *Eryngium caeruleum* against *Staphylococcus aureus* was 1.56 mg/ml.

Conclusion: The N-hexane extracts of *Eryngium caeruleum* and *Eryngium thyrsoideum* possess high antibacterial activity against the tested organisms. These findings can be the basis for further studies to isolate active compounds, elucidate the structures, and also evaluate them against wider range of bacterial strains with the goal to find new therapeutic principles.

Keywords: *Eryngium caeruleum*, *Eryngium thyrsoideum*, Antimicrobial, traditional medicine



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A Review on Biological Activity of *Nepeta* Genus Essential Oil

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Abstract

Introduction: Aromatic plants are at present widely studied for their large therapeutic potential and benefits. The genus *Nepeta*, one of the largest genera of the Lamiaceae family, belongs to the subfamily Nepetoideae and tribe Menthae. Several *Nepeta* spp. are used in folk medicine as diuretic, diaphoretic, antitussive, antispasmodic, anti-asthmatic, febrifuge, emmenagogue, and sedative agents, and for the antiseptic and astringent properties as topical remedy in children with cutaneous eruptions, and for snake and scorpion bites. Most importantly, a number of compounds from *Nepeta* species have been found to possess potent bioactivities

Methods: The present study was carried out based on the literature review of the essential oil composition of *Nepeta* species. The data presented in this paper were collected using all scientific data come from encyclopedias, books, journals, articles and websites including PubMed, Scopus, Web of science, Science Direct and Google Scholar.

Results: Biological Activities:

Activity on Central Nervous System

Antibacterial, Antifungal, and Antiviral Activities

Trypanocidal activity

larvicidal activity

Antioxidant Activity

Antinociceptive, Analgesic, and Anti-Inflammatory Activities

Cytotoxic Activity

Acetylcholinesterase inhibitory effect

Spasmolytic and Bronchodilatory Activities

Feline-Attractant and Insect-Repellent Activities

Conclusion: The genus *Nepeta* comprises ca. 300 species contained aromatic plants, which tend to accumulate monoterpenoid-rich essential oils. Many of them have been used as traditional herbal medicines and have revealed that many components of oils from this genus exhibit significant bioactivities. Nevertheless, there are still many *Nepeta* species that have received no or only little attention; in the future, to search for more potential bioactive essential oil components, much more phytochemical and biological studies should be carried out on this genus.

Keywords: Lamiaceae, *Nepeta*, biological activity, essential oil



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Association between Interlukin-6 (IL-6), Interlukin-10 (IL-10), and Depression in Patients Undergoing Hematopoietic Stem Cell Transplantation

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Abstract

Introduction: The release of pro-inflammatory cytokines is responsible for the variety of behavioral, neuro-endocrine and neuro-chemical alterations in psychiatric condition. In this study we evaluate relation between depression and IL-6 and IL-10 in patients undergoing hematopoietic stem cell transplantation (HSCT).

Methods: 66 patients in this cross-sectional study from July 2013 until August 2014 for HSCT interred the study and were assessed for depression using Hospital Anxiety and Depression Scale (HADS). Serum interleukin (IL)-6, (IL)-10 and high sensitive C-reactive protein (hs-CRP) were assessed on the same time. Association between these biomarkers with depression was evaluated using SPSS version 20.

Results: A total of 66 patients with the mean age of 41.18±13.92 and 41.95±12.35 years old in non-depressed and depressed group respectively were enrolled in this study. Patients with depression showed significantly higher levels of serum IL-6 and the IL-6-to-IL-10 ratio compared to patients without depression ($p<0.001$). There was no statistically significant association between IL-10 and hs-CRP with depression in this group of the patients.

Conclusion: High IL-6 level has significant association with depression in patients undergoing HSCT. In conclusion, since IL-6 can affect the outcomes after HSCT and depression was associated with increased serum IL-6 level, early identification of depression can be beneficial in these patients.

Keywords: Depression, Hematopoietic stem cell transplantation, hs-CRP, Inflammatory cytokines, IL-6



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Evaluation and Comparison of Antioxidant and Anti Lipid Peroxidation Activity Methanolic and Hydrolyzed Extract of Cuttle Fish (*Sepia Pharaonix*) of Persian Gulf

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Abstract

Introduction: Cuttlefish belong to the class cephalopoda and their muscle tissue, skin and ink showing different therapeutic effects such as significant antioxidative ones. Given that free radicals are the cause of several degenerative diseases such as cardiovascular diseases, cancer, Alzheimer, etc. This study was designed and conducted for evaluation and comparison of antioxidant activity of aqueous and methanolic extract of cuttle fish.

Methods: Blue swimming crab was fished and kept on freezing condition until extracting. Aqueous, methanolic, and hydrolyzed by pepsin extractions were done with maceration method. To evaluate the antioxidant activity methods of TEAC, FRAP, DPPH, and hydroxyl radical scavenging were used and pro-oxidant effect was determined by bleomycin method. Inhibition of lipid peroxidation in the brain, liver, kidney, and lungs of rats was performed in a laboratory setting.

Results: in DPPH, FRAP, and ABTS tests the antioxidant activity of aqueous extract was more than other extract. Also aqueous extract have a greater impact on inhibit lipid peroxidation in the brain, liver and lungs. By comparing hydroxyl radical scavenging with and without the presence of EDTA was observed that this extract can directly inhibit the hydroxyl radical. Bleomycin assay results showed that pro-oxidant effect increases with increasing concentration.

Conclusion: the result showed that all extract have acceptable antioxidant power. Better effects of aqueous extract could be due to proteins compounds and water-soluble vitamins in it.

Keywords: cuttle fish (*Sepia pharaonis*), DPPH, FRAP, ABTS, hydroxyl radical scavenging, antioxidant capacity.



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Concurrent Inflammation Augments Antimalarial Drugs-Induced Liver Injury

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Abstract

Introduction: Accumulating evidence suggests that drug exposure during a modest inflammation induced by bacterial lipopolysaccharide (LPS) might increase the risk of drug-induced liver injury. The current investigation was designed to test if antimalarial drugs hepatotoxicity is augmented in LPS-treated animals.

Methods: Rats were pre-treated with LPS (100 µg/kg, i.p). Afterward, non-hepatotoxic doses of amodiaquine (25, 50 and 100 mg/kg, oral) and chloroquine (25, 50 and 100 mg/kg, oral) were administered.

Results: Interestingly, liver injury was evident only in animals treated with both drug and LPS as estimated by pathological changes in serum biochemistry (ALT, AST, LDH, and TNF- α), and liver tissue (severe hepatitis, endotheliitis, and sinusoidal congestion). An increase in liver myeloperoxidase enzyme activity, lipid peroxidation, and protein carbonylation, along with tissue glutathione depletion were also detected in LPS and drug co-treated animals.

Conclusion: Antimalarial drugs rendered hepatotoxic in animals undergoing a modest inflammation. These results indicate a synergistic liver injury from co-exposure to antimalarial drugs and inflammation.

Keywords: Drug-Induced Liver Injury; Hepatotoxicity; Inflammation; Lipopolysaccharide; Malaria



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Study of Antinociceptive Activity of the Hydroalcoholic Extract of *Potentilla Reptans* L. in Male Mice

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Abstract

Introduction: *Potentilla* species (Rosaceae) are perennial and herbaceous plants. This genus traditionally have been used for various diseases such as diarrhea, wound healing and especially anti-inflammatory and analgesic agents in Iran and other parts of the world. The aim of this study was investigation of antinociceptive effect and preliminary phytochemical screening of *P. reptans* L. (popularly called creeping cinquefoil) which has a wide distribution in the North of Iran.

Methods: The present study investigated the antinociceptive activity of hydroalcoholic extract prepared from the aerial parts of *P. reptans* L. using the acetic acid-induced writhing, hot plate and rotarod test in male mice. Also we applied qualitative and quantitative assay for detection of phytochemicals such as terpenoids, saponins, alkaloids, flavonoids and phenolic compounds and determination of Total phenol, tannin and flavonoid contents in *P. reptans* L. aerial parts.

Results: Oral administration of the hydroalcoholic extract of *P. reptans* L. (100, 300, and 500 mg/kg) dose-dependently reduced the number of writhings induced by acetic acid and increased reaction time in hot-plate test. The antinociceptive effects were significantly antagonized by naloxone (4 mg/kg; i.p.) in writhing test that be comparable with normal saline. In rotarod test none of the extract doses affected locomotor activity. The phytochemical screening of the *P. reptans* L. aerial parts revealed the presence of high concentration of flavonoids, saponins, tannins and penta-cyclic triterpenoids. Content of total phenol and tannins was calculated 247.7 mg/g and 101.7mg/g expressed as tannic acid respectively. Flavonoids content was 24 mg/g as quercetin equivalents in dry extract.

Conclusion: In this study suitable antinociceptive effect from hydroalcoholic extract of aerial part of *P. reptans* L. observed in hot plate and writhing test and didn't exhibit neurotoxicity in oral administration. Analgesic effect of the extract could be mediated via opioid receptors and inhibition of prostaglandins synthesis.

Keywords: antinociceptive, *Potentilla reptans* L., hot plate, writhing test, rotarod test.



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Investigation of the Binding Ability of Anti-Tnf α Scfv J₄₈ Antibody by Using ELISA and Estimating Possible Interactions by Docking Studies

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Abstract

Introduction: TNF α is an inflammatory cytokine, which have different physiological and pathological functions. In this context, using antibodies with smaller size and stronger binding affinity is one of the common strategies to inhibit TNF α activity in chronic disease (1). In past works, we produced and purified the ScFv J₄₈ antibody which had been identified by Phage display technique (2). Now we aimed to examine binding ability of J₄₈ to TNF α by ELISA and evaluate the possible interactions among them by docking studies.

Methods: The purified ScFv antibody (i.e.J₄₈) in various concentrations from 0.012µM to 1µM was prepared and added to the TNFα coated wells. Then anti-6His and HRP conjugated goat anti mouse antibodies were used for ScFv J₄₈ detection. For docking studies, the Tree-dimensional structure of J₄₈ antibody was modeled in Swiss model website. Next, the modeled structure was docked to TNFα by using Z dock. To estimate the possible interactions between J₄₈ and TNFα, the docked complex was analyzed in PIC website.

Results: Analyzing of ELISA results showed that J₄₈ has a relatively high binding affinity to TNFα. And docking results revealed that the hydrogen bond, hydrophobic bond, π-cation interactions were involved in the interactions between TNFα and J₄₈.

Conclusion: According to the results of the ELISA and docking studies, J₄₈ has a good inhibition activity on TNFα. Therefore, J₄₈ can be a suitable candidate for clinical trials or may be used for designing a new stronger anti- TNFα medication.

Keywords: TNF-α, ScFv, ELISA, Docking studies



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***In Vitro* Cytotoxic Activity of a *Lactococcus Lactis* Antimicrobial Peptide against Breast Cancer Cells**

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Abstract

Introduction: Nisin, an effective natural food preservative, is an antimicrobial peptide produced by *Lactococcus lactis*. Although it has been mainly studied and developed as potential alternatives for antibiotics, other pharmacological effects of nisin including cytotoxic and anti-tumor activity have been attracted many attentions. Here, we aimed to evaluate *in vitro* cytotoxic activity of nisin against breast cancer cells.

Methods: The effect of temperature, pH and chemical composition of medium on the yield of nisin production by *L. lactis* was evaluated. The anti-proliferative effect of nisin against a breast cancer cell line (MCF7) and a non-cancerous cell line (HUVEC) was determined using MTT assay. Furthermore, potential synergistic effect of nisin on doxorubicin cytotoxicity was evaluated.

Results: The survival of MCF-7 cells was significantly inhibited by nisin and the IC₅₀ value of 17 µg/ml was found. Nisin exhibited lower level of cytotoxicity for a normal cell line, HUVEC, with an IC₅₀ value of 64 µg/ml. This four-fold difference in nisin cytotoxicity against MCF-7 over HUVEC cells was showed to be statistically significant in MTT assay (P < 0.05). It was showed that co-incubation of nisin, increased cytotoxicity of doxorubicin. This synergic effect was more significant in lower concentration of doxorubicin and against MCF-7. Approximately, three-fold higher cytotoxicity was observed when MCF-7 cells were incubated with combination of nisin (10 µg/ml) and doxorubicin (6 µg/ml) compared with doxorubicin alone (P < 0.01).

Conclusion: In conclusion, our study reported effective cytotoxic effects of nisin against MCF-7, a breast cancer cell line. Furthermore, nisin exhibited a selective toxicity against cancerous cells in comparison to HUVEC, a normal cell line. Most importantly, combination of nisin with doxorubicin led to synergetic anticancer effect. It could be suggested that nisin either alone or in combination with other chemotherapeutic agents can be a potential treatment for breast cancer.

Keywords: nisin, breast cancer, cytotoxicity, Lactococcus lactis, antimicrobial peptide



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Selective Toxicity of Chrysin on Isolated Mitochondria Obtained from Liver Hepatocytes of Hepatocellular Carcinoma Induced Rat

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Abstract

Introduction: Chrysin is a natural flavonoid currently under investigation due to its important biological anti-cancer properties. Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death. In patients

with HCC current treatments show poor tolerance and low efficacy. So, alternative therapies with good efficacy are urgently needed. The aim of this research was to evaluate the selective apoptotic effects of chrysin on mitochondria obtained from the liver of HCC rats.

Methods: In this study, HCC induced by diethyl nitrosamine (DEN), as an initiator, and 2-acetylaminofluorene (2-AAF), as a promoter. After confirmation of liver cancer, rat liver mitochondria for evaluation of the selective cytotoxic effects of chrysin were isolated, and mitochondrial parameters related to apoptosis signaling were then determined.

Results: Our results showed that chrysin was able to induce increased in reactive oxygen species (ROS) level, mitochondrial swelling, mitochondrial membrane permeabilization (MMP) and cytochrome c release only in cancerous but not in untreated normal hepatocyte mitochondria.

Conclusion: Finally, our finding underlines chrysin as a promising therapeutic candidate against HCC and recommends the compound for further studies.

Keywords: Hepatocellular Carcinoma, Chrysin, Mitochondrial Targeting, Apoptosis



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A Survey of Effects of Nanoceria for Potentiation of Anticancer Effect of Doxorubicin and Inhibition of Doxorubicin-Induced Cardiotoxicity in Human Ovarian Cancer in Nude Mice

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Abstract

Introduction: Nowadays combination therapy by different mechanism and synergetic effect is one of the main procedures in cancer treatment [1]. Doxorubicin is an anthracycline antibiotic that its usage is limited due to its cardiotoxicity [2]. Nanoceria (Nano particle of cerium oxide) showed anti-oxidant effects [3] and in this study we evaluated effect of nanoceria for potentiation of anticancer effect of doxorubicin and also attenuation of doxorubicin cardiotoxicity.

Methods: In first step, we growth SKOV3 cell line in RPMI medium and then injected it to Nude mice for tumor growth. After 2 month and rising of tumor we began drug and Nano ceria injection to inhibit tumor growth. We had four group that first group just get doxorubicin 2mg/kg (G1), second group just get Nano ceria 100mg/kg (G2), third group get both of them (G3) and control group that didn't get anything (G4). After 14 days tumor had been exit, its size and apoptosis markers had been study. Hearts tissue had been exit too and oxidative stress markers such as Lipid peroxidation and Glutathione were measured. Also, pathological changes in both tumor and heart tissue was done

Results: Tumor growth during of 14 days especially in last days had been stabilized. For example tumor size in one mouse in G3 after rising from 0.7 to 1 mm, in last day was 0.9 mm. Pathology samples showed wide and focal necrosis especially in G3. Evaluation of oxidative stress markers showed nanoceria inhibited doxorubicin induced oxidative stress in heart tissue.

Conclusion: Our data showed that synergic anticancer effect of doxorubicin and nanoceria and protection effect of nanoceria against doxorubicin induced cardiotoxicity.

Keywords: Nano ceria, Doxorubicin, Ovarian cancer, Nude mice, Cardiotoxicity.



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Invivo Anti-Inflammatory Activity of Citrus Aurantifolia Peel Essential Oil

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Abstract

Introduction: *Citrus aurantifolia* popularly named lime, is a native plant in Iran and is distributed in some part of the world. The *C. aurantifolia* essential oil (EO) has been reported to have antioxidant (2), antimicrobial (1), antifungal activities (1) and treatment of drug-induced obesity (2). In this study we were prompted to investigate the anti-inflammatory property of the peel EO of *C. aurantifolia* collected from Iran.

Methods: The EO from peels of *C. aurantifolia* was obtained by hydro distillation using a Clevenger apparatus. The examined EO was analyzed by gas chromatography/mass spectrometry (GC/MS) to determine the possible active components. Anti-inflammatory activity was investigated by inflammatory paw edema in rat.

Results: The EO significantly reduced carrageenan-induced paw edema at the time 120min in all tested dose as compared to the vehicle group ($p < 0.001$). The major components of the oil were characterized as limonene (40.4 %) and -pinene (16.4 %).

Conclusion: These results clearly showed the anti-inflammatory effect of *C. aurantifolia* EO. Further studies are suggested to clarify the mechanism of tested EO for the observed pharmacological effects.

Keywords: *Citrus aurantifolia*, essential oil, anti-inflammatory.



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Preparation of Biodegradable Self-Assembled MPEG-PCL Micelles of

Indinavir: *In Vitro* Characterization

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Abstract

Introduction: Indinavir (IDV) is a potent protease inhibitor of the human immunodeficiency virus (HIV) widely used in the treatment against the acquired immune deficiency syndrome (AIDS) and prescribed in combination with other protease inhibitors, nucleoside analogues or reverse transcriptase inhibitors [1]. Nanotechnology provides an

effective method to improve the water solubility of hydrophobic drug. In this work, Indinavir was encapsulated into monomethoxy poly (ethylene glycol)-poly (ϵ -caprolactone) (MPEG-PCL) micelles through a single emulsion method, creating Indinavir-loaded MPEG-PCL (IDV/MPEG-PCL) micelles.

Methods: monomethoxypoly (ethylene glycol)-poly(ϵ -caprolactone) (MPEG-PCL) -block copolymer were synthesized by ring-opening polymerization using stannous octoate [Sn(Oct)₂] as catalyst [2]. MPEG -PCL copolymer was characterized *in vitro* by FTIR and GPC techniques. A single emulsion method was used to prepare MPEG-PCL di-block copolymer nanoparticles [3]. The resulting nanoparticles were characterized by various techniques such as particle size analyzer (DLS) and Zeta potential.

Results: GPC and FT-IR analysis were used to confirm the structure of copolymer. The size and surface characteristics of of MPEG-PCL diblock copolymer nanoparticles was also investigated by dynamic light scattering (DLS), Scanning electron microscopy (SEM) and Atomic-force microscopy (AFM) techniques. The size and PDI of MPEG-PCL diblock copolymer nanoparticles were found to be 220 nm and 0.232, respectively. The encapsulation efficiency of Indinavir was 60 % and the loading of Indinavir was 5%.

Conclusion: The results indicate the successful formulation of Indinavir loaded M-PEG/PCL micelles.

Keywords: Indinavir, MPEG-PCL, copolymer, Nanoparticles.



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Preparation of Inclusion Complexes Composed of Hydroxy propyl β -cyclodextrin and Poly Vinyl Prolidone (PVP) for Improvement of Aqueous Solubility of Tadalafil as a Poorly Soluble Drug

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Abstract

Introduction: Solubility and dissolution rate are the most important factors in oral bioavailability of drugs. Tadalafil is a Phosphodiesterase 5 inhibitor, which is used for treating erectile dysfunction and benign prostatic hyperplasia.

Methods: Tadalafil is second class of the classification biopharmaceutical system (BCS), that its poor water solubility leads to low bioavailability. The purpose of this study is dissolution enhancement of Tadalafil by

preparation of solid dispersion, kneading, Lyophilization, co-solvent evaporation method using PVP k25 and Cyclodextrin as hydrophilic carriers. Calibration curve of this study for 5, 10, 20, 50,100, 150, 200 µg/ml Concentration of Tadalafil in Acetonitrile illustrated and $r^2=0.993$.

Results: Different ratio (1:1, 1:3, 1:5) of Tadalafil and PVP or CD was prepared. Saturation solubility, high performance liquid chromatography, Fourier Transforms Infra-Red (FTIR) spectroscopy and dissolution studies in phosphate buffer (pH=6.8) mediums were performed. Raw Tadalafil after 180 minutes in phosphate buffer had maximum 6 percentages of solution as well as in the same situation for solid dispersion 1:3 ratio of Tadalafil and VP was 95% and for solid dispersion 1:3 ratio of Tadalafil and CD was 35%. Therefor Dissolution studies of Tadalafil in solid dispersion samples with PVP are 15 folds higher than raw Tadalafil.

Conclusion: The obtained results indicate that inclusion complexes prepared from poly vinyl pyrrolidone by kneading method, posed the greatest enhancement in aqueous solubility of Tadalafil as a poorly soluble drug.

Keywords: Tadalafil, Solubility, Inclusion complexes, HydroxyPropyl β-cyclodextrin, Poly Vinyl Pyrrolidone (PVP), Kneading method, Lyophilization, common solvent method.



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Fulvic Acids-Anionic Linear Globular Dendrimer G2 Nano-Conjugate:

Synthesis and Anti HCV Assessment

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Abstract

Introduction: Hepatitis C virus (HCV) is a leading cause of cirrhosis and liver cancer worldwide known as the ninth cause of mortality in the West and other countries are developing. Universally in the United States, due to chronic liver disease and cirrhosis 25 thousand people lose their lives in the year. It seems HCV, plays such a major role (about 40%) in these cases. Preventive vaccine does not exist for this disease and conventional therapies (interferon and Ribavirin) was effective in only 40 to 80 percent of infected people and are often associated with side effects.

Today's the plants and natural drugs have an important role in treatment of diseases as well as being interested as research target for HCV treatment. Shilajit is a natural pale-brown to blackish-brown exudation, of variable consistency, exuding from layers of rocks in many mountain ranges of the world. It is a potent and very safe dietary supplement, restoring the energetic balance and has the ability to prevent several diseases. Fulvic acid is the most bioactive part of shilajit which have wonderful effects.

Methods: In the current study, a novel structure of fulvic acids nanoparticle conjugated to anionic linear globular dendrimer was synthesized, characterized and then assessed against HCV replication pathway *in vitro* as well.

Results: The results of the present study are indicating to the role of fulvic acid derivatives as anti HCV principles of the Shilajit. Conjugation of the fulvic acids with the G2 dendrimer enhanced the inhibition of the HCV expression, significantly.

Conclusion: According to the present data, fulvic acid conjugated to anionic linear globular dendrimer may have a promising future to inhibit replication of HCV virus in clinical practice.

Keywords: Shilajit, HCV, Fulvic acids, Liver, Antiviral activity.



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Essential Oil Analysis of *Nepeta Menthoides* Boiss. & Bohse. and its Leishmanicidal Activity

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Abstract

Introduction: Leishmaniosis is a parasitic disease caused by *Leishmania* spp. and transmitted to human via sandflies. It has three major clinical forms *i.e.* cutaneous, visceral and mucosal. During the last decade, there has been an extensive epidemic form of this disease around the world. Treatment is based on the use of chemical drugs like glucantime and amphotericin B but severe side effects, the high expense and the prevalence of drug-resistant species urge the need to new drugs. *Nepeta menthoides* Bioss. & Bohse. (Lamiaceae) is a native medicinal plant of Iran with different biological and pharmacological activities. Since several essential oils of Lamiaceae family have shown anti-leishmanial activity in previous reports, we decided to analyze the essential oil of *N. menthoides* and evaluate its leishmanicidal activity [1].

Methods: *N. menthoides* was collected from Ardabil, Iran in June 2015. The essential oil was prepared using hydro-distillation method and its constituents were analyzed using GC/MS. A standard strain of *L. major* was obtained from Pasteur Institute, Tehran, Iran (MRHO/IR/75/ER). The leishmanicidal activity of the essential oil was evaluated using MTT assay based on a previously reported method. DMSO and amphotericin B were used as negative and positive controls, respectively.

Results: The essential oil of *N. menthoides* was a pale yellow liquid and its major constituent was 1,8-cineole (70.06%). Different concentrations of the essential oil (0.125-1 µl/ml) showed a range of leishmanicidal activity and the IC₅₀ value was 0.366 µl/ml (IC₅₀ value of amphotericin B: 1.2 µM). The considerable anti-leishmanial activity of the essential oil can be related to the presence of 1,8-cineole and its ability to increase the lipid dynamic and fluidity of plasma membrane in *L. major* [2].

Conclusion: *N. menthoides* essential oil and 1, 8-cineole can be considered as promising candidates in future investigations of anti-leishmanial drugs.

Keywords: *Nepeta menthoides*, *Leishmania major*, 1, 8-cineole, essential oil



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The Protective Effects of Propofol on Lung Oxidative Damage in Rat Subacute Poisoning with Cisplatin

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Abstract

Introduction: lung cancer is the most common cause of cancer related death in men and women in world wide. Cisplatin is a chemotherapy drug, used to treat variant tumors and it has oxidant effect on lung tissues. Propofol (2,6-di-isopropyl phenol) used as an injection for the induction and maintenance of anesthesia. The purpose of this study was to investigate the protective effects of propofol on the toxic oxidant effect on lung tissues in subacute poisoning with cisplatin in rats (1).

Methods: In this study, 20 male Wistar rats weighing 180-250g were randomly divided into four groups. A control group received normal saline and a group of toxic cisplatin with dose of 7 mg /kg/day, IP, a group received propofol 10 mg /kg/day, IP and fourth group poisoned with cisplatin that received propofol for 7 days. Then in lung tissues homogenate biomarker of antioxidant capacity (TAC) was done by FRAP, Catalase (CAT) activity and Lipid peroxidation (LPO) was done by colometric method (2,3). The data were analyzed by spss V:16 software and statistical variance test was OneWayANOVA. Significant level of $p < 0.05$ was considered.

Results: TAC in lung tissues homogenate in cisplatin group has significant decreased comparing control group. Also TAC in propofol group has significant increase in comparing cisplatin and the group cisplatin and propofol. LPO in cisplatin group has significant increased comparing to propofol and propofol cisplatin group. CAT activity didn't show significant difference between groups.

Conclusion: According to these results, it seems that propofol as an antioxidant drug could modulate the toxic effect of cisplatin in lung tissues (4).

Keywords: Cisplatin, Propofol, Antioxidant, Catalase, Lipid peroxidation:lung



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Identification, Characterization and Investigation the Antimicrobial Activities of Lactic Acid Bacteria Isolated From Iranian Traditional Sourdoughs

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Abstract

Introduction: Lactic Acid Bacteria (LABs) represent the prevailing microflora of sourdoughs. Fungal and bacterial growth is the major cause of spoilage in baked products. The aims of this study were Isolation, identification and characterization of LABs isolated from Iranian traditional sourdoughs and evaluation of their antimicrobial and antifungal activities.

Methods: Several kinds of traditional Iranian sourdoughs were collected. Colonies were isolated from MRS agar plates then were checked for morphology, gram staining, catalase test, TSI media and SIM semi solid media and carbohydrate fermentation test.

Four pathogenic microorganisms including *E. coli*, *S. aureous*, *penicillium* and *A. flavus* were used in this study. Isolated LABs were applicated for agar spot test and inhibition zones were measured.

Among LAB's, *L. casei* was selected for further experiments. 20 ml of supernatant of *L. casei* (T7) were added to 100 ml of SCDB and to SDB in the same manner, then 1ml of pathogenic microbial suspension were added to SCDB and SDB and were incubated. Every 2 hours the optical density (OD) was measured against the distilled water as blank.

Results: After performing identification procedures, one genus (Lactobacillus) and three different species (*L.Plantarum*, *L.Casei* and *L.Alimentarius*) were identified. The inhibition zones of each pathogen in presence of isolated lactobacillus were measured. According to these results *Lactobacillus casei* was selected as superior anti pathogenic LABs for carrying out future experiments. The optical density of pathogen's culture media against distilled water (as a blank) was measured. These data have suggested that *L.casei* can inhibit the growth of both pathogenic fungi and bacteria for a period of 24 hours.

Conclusion: Addition of some Iranian traditional sourdoughs to baked goods, may exert natural, safe and reliable preservation via the bio-preservative action against the most common pathogenic organisms and prevention of early bread staling and spoilage.

Keywords: sourdoughs; Lactic Acid Bacteria; antibacterial and antifungal effects



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Evaluation the Cytotoxic Effects of Aerial Parts and Rhizome's Extract of *Ecballium Elaterium* (L.) on Cancerous and Normal Cells

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Abstract

Introduction: *Ecballium elaterium* (L.) known as wild cucumber belongs to cucurbitaceae family, is distributed in Ardebil and Gilan and like many other members of its family is a source of terpenoids (cucurbitacins). This work has been investigated the cytotoxic effects of aerial parts and rhizomes of *Ecballium elaterium* (L.) on cancerous and normal cells.

Methods: 100 g of dried powder from each of the organs was extracted by Soxhlet apparatus with n-hexane, dichloromethane and methanol, respectively. The extracts are then dried by the Evaporator. The cytotoxic effect of each of the six extracts (Three solvents and two organs) was evaluated by the MTT assay. And also, at this stage, the effects of each of the extracts on cancer cells and normal cells were compared. Finally, the cytotoxic effects of fractions of the most effective extract on cancer cells were evaluated and results were compared with normal cells.

Results: After monitoring several cancer cells, the best result was observed on the MCF7 (breast cancer cell line). The highest IC₅₀ observed for n-Hexane extracts and the comparison of the results of total extract and fractions with the results of normal cells indicated a difference in cytotoxic activity on normal cells and cancerous cells.

Conclusion: The results show that the highest amount of cucurbitacins was introduced into the N-hexane extract.

Keywords: *Ecballium elaterium* (L.), MTT assay, cucurbitacin, Soxhlet apparatus, MCF7, IC₅₀



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Effect of Glycerin and Polyethylene Glycol400 on the Dissolution Rate of Naproxen from Liquisolid Compact Systems

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Abstract

Introduction: Among various techniques to overcome the solubility issue, several researchers reported that the formulation of liquisolid tablets is one of the most promising techniques for promoting drug dissolution (1-3). In the

present study, an attempt is made to enhance dissolution rates of naproxen using liquisolid tablet technique and dissolution rates of the liquisolid tablets were compared with conventional tablets.

Methods: glycerin and polyethylene glycol 400 were used as non-volatile liquid vehicles in the liquisolid systems containing naproxen and the effect of several amounts of them on the dissolution behavior of naproxen was investigated. To evaluate any interaction between naproxen and the other components in liquisolid formulations, the differential scanning calorimeter (DSC) and FTIR was used.

Results: The results showed that the liquisolid formulations exhibited significantly higher drug dissolution rate in comparison with directly compressed tablet. The results showed more dissolution rate in liquisolid compacts containing PEG400 in comparison with tablets containing glycerin, ($p < 0.001$) in more formulation. The DSC and FTIR evaluation showed no interaction between drug and excipients. The amorphous portion of drug was increased in systems containing vehicles.

Conclusion: The liquisolid compacts technique can be a promising alternative for the formulation of water insoluble drugs, such as naproxen in to rapid release tablets.

Keywords: Naproxen, Liquisolid system, Dissolution rate, PEG 400, Glycerin



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Flexible Docking and Molecular Dynamics Study of a 2-Hydroxyiminoethanone Derivative as a Selective Cyclooxygenase-1 Inhibitor

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Abstract

Introduction: P-glycoprotein is an efflux protein with 1200 amino acids (170kDa) expressing on cell membranes. Over-expression of this trans-membrane glycoprotein has been found as a multi drug resistance protein in tumor cell membranes for instance liver, lung and colon cancer. P-gp is one of the main parts of blood-brain barrier and controls the transport of compounds across the BBB. Defining effective strategies with drugs which inhibit this protein may present better solutions in drug design for experts. [1]

Methods: In this study 3D structure of this human protein was predicted based on crystallographic data via determining initial similarity in BLAST and then based on 3D structure of mucin protein (mus musculus, PDB: 3G61) using Modeller9.14 [2]. After determining of molecular dynamic structure and solvation of protein with GROMACS5 and also determined the amount of electric charge and minimization of energy for ligand molecules in order to simulation *in vivo* conditions with MOE. The binding energy for interaction of 80 ligands from different types of drug groups with receptor binding site with consideration these amino acids M36, F39, F46, F70, Y84, Q162, Y274, F281, F303, L306, F310, F699, F695, I703, Y920, F924, F945 as flexible residues were checked and determined by Autodock vina 4 with 3 methods: Rigid, blind flexible and non-blind flexible docking. At the end we chose 8 ligands for final molecular dynamics that were available for *in vitro* studies in Iran and then calculated the mean binding, electrostatic, VanderWaals and polar solvation energies using APBS and GROMACS.

Results: Our docking result presented in prerequisite file no1. Mean binding, electrostatic, VanderWaals and polar solvation energy calculations presented in prerequisite file no2 which were calculated by *g_mmpbsa* script employing APBS and GROMACS engines.

Conclusion: It seems dockings results and molecular dynamic are correlated in wide range. Furthermore referring to previous studies shows that more affinity to specific site of p-gp binding site improves conditions for binding and create inhibitory effect. Continuing this study by *in vitro* methods can make data more optimized in this regard.

Keywords: p-glycoprotein, molecular dynamics, GROMACS, autodock, docking



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Combined Virtual Screening, MMPBSA, Molecular Docking and Dynamics Studies against Deadly Anthrax: An In Silico Effort to Inhibit Bacillus Anthracis Nucleoside Hydrolase

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Abstract

Introduction: Anthrax is a deadly disease caused by *Bacillus anthracis*, a dangerous biological warfare agent employed for both military and terrorist purposes [1]. A critical selective target for chemotherapy against this disease is nucleoside hydrolase (NH), an enzyme still not found in mammals [2].

Methods: In the current study, we have performed molecular docking and dynamics studies (MD), aiming to propose the new potent inhibitors of *B. anthracis* NH among National Cancer Institute (NCI) Diversity Set. We also analyzed the principal interactions of proposed compounds with the active site residues of NH and the relevant factors to biological activity. Additionally, the physic-chemical properties of free and inhibitor bound NH (totally three systems) were evaluated and discussed.

Results: Temporal RMSD calculations showed all three systems reached to equilibration. RMSF values showed that upon inhibitor binding, the flexibilities of Asp 9 and Asp 13 were decreased. On the other hand, in the presence of the inhibitor, the flexibility of some residues like Lys 75 was increased via interruption of a hydrogen bond between this residue and Met 79. Our data showed that compound NSC79887 is a good candidate to inhibit NH and also for biological tests and further development. However, Rg of all systems remained unchanged indicates constant compactness of NH during MD simulations

Conclusion: Molecular docking, MD simulations and ADMET prediction revealed that all physic-chemical parameters are within the acceptable range defined for human use. So, NSC79887 could be a potential inhibitor of therapeutic targets of deadly anthrax, and further analysis can be carried out through various experimental studies.

Keywords: Anthrax- Docking and dynamics studies- Nucleoside hydrolase- Compound NSC79887- Inhibitor bound.



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Synthesis and Antimicrobial Evaluation of Some 1, 3, 4-Oxadiazole

Compounds Derived From Ethyl Mandelate

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Abstract

Introduction: Although deaths from bacterial and fungal infections have declined in the developed countries, these infections are still major problem in undeveloped territories. One of the attractive backbones for scientists in production of new therapeutic agents is oxadiazole structure. There are four known isomers of this five-membered heterocycle including: 1,2,4-, 1,2,3-, 1,2,5-, and 1,3,4-oxadiazole. However, 1,3,4-oxadiazole is more important because of its remarkable biological activities. Compounds containing 1,3,4-oxadiazole structure possess various pharmacological effects including antibacterial, antifungal, anti-tubercular, anti-inflammatory, cytotoxic, and insecticidal activities.

Methods: Ethyl mandelate was treated with hydrazine hydrate to yield the corresponding acylhydrazide. Some of the 2,5 disubstituted 1,3,4-oxadiazoles derivatives were prepared from acylhydrazide using three different procedures. In the first procedure, acylhydrazide was reacted with nitro or chloro acrolein to afford a diacylhydrazide which was cyclized to 2, 5-disubstituted 1,3,4-oxadiazole in the presence of phosphoryl chloride as dehydrating agent. In the second procedure, furan-oxadiazole derivative was directly prepared from carboxylic acids and acylhydrazide in one step. In the third procedure, acyl hydrazide was condensed with 5-nitrofurfuraldehyde to yield 5-nitrofuran-2-yl) methylene)-2-phenyl acetohydrazide intermediate which was cyclized to form the nitrofuran-oxadiazole derivative by acetic anhydride as dehydrating agent. All the newly synthesized compounds were screened for their antibacterial and antifungal activities.

Results: The structures of these compounds have been elucidated by spectral IR and $^1\text{H-NMR}$ analysis.

The results of antibacterial screening showed that compounds (furan and nitro furan derivatives) had the highest activities against *S. aureus* and *E. coli*. Presence of a para-substituted-phenyl group (chlorine or nitro) at position 5 of oxadiazole may be responsible for fungistatic and fungicidal activities against *C. albicans* in comparison with furan derivative of oxadiazole.

Conclusion: According to the antimicrobial results, furan-derivatives of oxadiazoles showed potential antibacterial activities and a para-substituted phenyl derivatives of oxadiazole exhibited significant antifungal activities.

Keywords: Oxadiazole; Mandelate; Antibacterial, Antifungal



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Synthesis, Antimicrobial Activity Evaluations, and Molecular Docking Studies on Thioredoxin Reductase of Novel Gold (I) Complexes Containing Thiolate Ligands

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Abstract

Introduction: Gold complexes are emerging as a new class of metal complexes with outstanding cytotoxic properties. Recently we have witnessed a revival of gold complexes in medicinal chemistry and new results have demonstrated that gold complexes are promising antimicrobial drug candidates. It was observed that many of the gold complexes inhibit the thioredoxin reductase (TrxR) enzyme with high specificity and potency and this target is the biological main target of gold complexes.

Methods: Here, some novel phosphine gold (I)-thiolate complexes were synthesized and fully characterized by X-ray and NMR spectroscopy. Their antimicrobial properties against gram-positive bacteria (*P. aeruginosa*, *E. coli*), gram-negative bacteria (*S. aureus*, *B. subtilis*), fungi (*C. albicans*) and yeast (*S. cerevisiae*) were evaluated. Molecular docking studies of them on TrxR were also performed by means of AutoDock 4.2. The 3D X-ray structure of TrxR was taken from the protein data bank (PDB) encoded 4CBQ.

Results: The synthesized compounds exhibited minimum inhibitory concentration (MIC) values in the 1 µg/mL–100 µg/mL range. The most active of the series, has MIC of 3.89 µM, 3.15 µM, 4.36 µM, 5.44 µM, 6.13 µM, and 8.37 µg/mL against *P. aeruginosa*, *E. coli*, *S. aureus*, *B. subtilis*, *C. albicans*, and *S. cerevisiae* respectively. The results were compared with Aunofin and Ciprofloxacin.

Conclusion: Computer-aided molecular docking computations were employed to discover the probable binding conformations of the Au (I) compounds with the active site of the TrxR. The main binding sites on TrxR is interaction of Au (I) with Cys286. The interaction of sulfur group with Thr269 was also observed. There exists an arene-hydrogen interaction between the phenyl group with residue Thr269. The antimicrobial activity results showed that these gold (I) compounds have good inhibitory effect on all studied microbial agents.

Keywords: Molecular Docking, Gold (I) complexes, antimicrobial activity, synthesis, thioredoxin reductase.



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Design of the Valid-Reliable Questionnaire for Evaluation of Knowledge, Attitude, and Practice of Pharmacists Regarding Renal Dose Adjustment

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Abstract

Introduction: Chronic kidney disease (CKD) is a worldwide public health problem with poor outcomes and high cost. For assessing the knowledge, attitude, and practice of the pharmacists about drug dosing adjustments in chronic kidney disease, we designed a valid and reliable questionnaire.

Methods: To carry out this study, a questionnaire was designed which contains three sections of knowledge, attitude, and practice of the pharmacist. Respectively, the number of questions in each section of the initial questionnaire was 17, 10, and 12. To assess the necessity of the questionnaire, options "essential" or "useful but non-essential" and "non-essential" were used. The collected data were used for calculation of Content validity ratio (CVR). As well as to assess the Content validity index (CVI) of the questionnaire options "relevance" and "clarity" and "simplicity" were used. The questionnaire has been completed manually and online by 15 experienced professors. The assessing of the questionnaire reliability involves administering the same measures to the same groups including 30 students selected randomly from the sixth year, under the same conditions on two different times with two week intervals. Cronbach's alpha was used for assessing the internal consistency reliability.

Results: According to the limit level of CVR, 0.49, for 15 respondents, residual questions after the calculation of CVR equation were 31. If the calculated CVI for each question higher than 0.79 was acceptable. The final questionnaire contained 26 questions. The Cronbach's alpha coefficient was calculated for the questionnaire 0.7 that finally confirmed the validated and reliable 20-item questionnaire.

Conclusion: The pharmacists' role as a member of the medical team to improve the treatment of patients with chronic renal failure is very important. In this study, we designed valid and reliable questionnaire for evaluation of the knowledge, attitude, and practice of the pharmacist about renal dose adjustment.

Keywords: Chronic kidney disease, pharmacists' role, questionnaire, validity, reliability



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Effect of Epigallocatechin Gallat on Metabolic Disorders Induced by Olanzapine

Abstract

Introduction: Atypical antipsychotics particularly olanzapine are associated with obesity and serious metabolic disturbances (1). As green tea (*Camellia sinensis*) is generally associated with beneficial effects on obesity and other metabolic disturbances (2), this study was undertaken to evaluate the effect of epigallocatechin gallat (EGCG), green tea polyphenol, on olanzapine induced weight gain and metabolic abnormalities in rat.

Methods: Male Wistar rats were divided into eight groups: Control, olanzapine (5 mg/kg/day, IP.), EGCG (10, 20 and 40 mg/kg/day, IP.) plus olanzapine and EGCG (10, 20 and 40 mg/kg/day, IP.). Treatments were continued for 11 days. Body weight gain, average food and water intake were measured during the experiment. Plasma lipid, glucose and leptin levels, mean systolic blood pressure and total locomotion were evaluated at the end of experiment.

Results: This study demonstrated that olanzapine caused 4.15% weight gain in rats compared to the control group. Olanzapine also caused a 35% increase in food consumption, changed lipid profile (25.2% increase in LDL-C, 78.9% in TG, 27.19% in total cholesterol, and 17.9% decrease in HDL-C), 6.10% increase in blood glucose, 3.1-fold increase in leptin serum levels, and 28.37% increase in systolic blood pressure compared to the control group. Total locomotion decreased 86.6% compared to the control. EGCG plus olanzapine induced weight loss, decreased food consumption, improved lipid profile, decreased blood glucose and systolic blood pressure in comparison with olanzapine.

Conclusion: EGCG could exert protective effects against olanzapine induced obesity partially due to its lowering effect on leptin. EGCG improved other metabolic abnormalities including dyslipidemia, hyperglycemia and hypertension induced by olanzapine in rat.

Keywords: Olanzapine; epigallocatechin gallat; green tea; metabolic syndrome; weight gain; leptin.



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Conventional Surfactants as an Alternative to Simulated Intestinal Fluid for Evaluation of Lamotrigine Solubility in Gastrointestinal Tract

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Abstract

Introduction: The simple aqueous buffer typically used for dissolution testing does not illustrate all possible circumstance in the gastrointestinal tract. However, simulation of gastrointestinal conditions i.e. fed state simulated intestinal fluid (FeSSIF) and fasted state simulated intestinal fluid (FaSSIF) is necessary to forecast *in vivo* behavior of solid oral dosage forms. These media are expensive and this can restrict their routine application. The aim of this study is to investigate the possibility of use of conventional surfactants as an alternative medium to simulate biorelevant media.

Methods: Lamotrigine was used as a poorly soluble drug in this study. The simulated intestinal fluid composed of phosphatidylcholine and sodium taurocholate and aqueous solutions with varying concentration of surfactants (sodium dodecyl sulfate and Tween 80) were prepared. Excess amount of drug powder added into certain volume of different media and they were shaken at 150 rpm for 48h at 37 °C. Then, the solutions were filtered and assayed by UV- spectrophotometry.

Results: The results demonstrated that the solubility of lamotrigine with conventional surfactants could be matched with biorelevant media.

Conclusion: Selected media containing surfactants can be used to replace with biorelevant media in gastrointestinal tract. These media are uncomplicated and inexpensive and they are a great potential in solubility and dissolution testing of drugs and oral solid formulations.

Keywords: Lamotrigine, Simulated intestinal fluid, Solubility, Surfactant



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Physical Adsorption of Indinavir on Fullerene (C60) Surface

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Abstract

Introduction: Fullerenes are carbon allotropes similar in structure to graphene but rolled up to form closed-cage, hollow spheres. The C60 fullerene is a remarkably stable compound consisting of 60 carbon atoms with a diameter of approximately 0.7 nm and a molecular weight of 720 g/mol. Thirty carbon double bonds present in the structure, to which free radicals can easily be added. C60 has some unique physicochemical, photochemical, electrochemical and biological properties which make it a promising candidate for being used in biological studies as a carrier for drug delivery purposes. (1, 2)

Methods: At first a stable water dispersion of fullerene was prepared with a concentration of 0.4 mg/ml. Afterwards, 10 mg of pure indinavir was added to the aqueous dispersion. The mixture was 20 minutes sonicated and then shaken for 12 hours in the dark.(2)

Results: In order to confirm the physical adsorption, size and zeta potential of nano particle were investigated before and after adding drug. Both size and zeta potential of nano particles were changed during the process.

Conclusion: According to the obtained data, indinavir was successfully adsorbed on the surface of fullerene.

Keywords: Fullerene, indinavir, physical adsorption



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Preparation and Physicochemical Characterization of Topical Quercetin Loaded Liposome

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Abstract

Introduction: Quercetin (3, 3', 4', 5, 7-pentahydroxy flavone) is found in many dietary regimes include onions, apples potatoes (1). Quercetin has shown pharmacological effects such as antioxidant, anti-inflammation and wound healing effects (2). Liposomes were first used as topical therapy by Mezei. Comparison of liposomal and conventional forms indicate that concentration of liposomal drug in the skin and subcutaneous tissue is more than conventional forms, but its distribution in plasma and other tissues is lower (3). The purpose of this study is preparing quercetin loaded liposome by fusion method and characterizing their physicochemical properties.

Methods: Liposomes prepared by fusion method. Briefly, the lipid components consisted of Soybean phosphatidyle choline, cholesterol, quercetin, propylene glycol, vit E melted at about 75°C. HEPES buffer was heated separately and added up to 100% to the previously heated melted lipids, and the mixture was homogenized (Ultra-Turrax IKA T25) for 5 min at 12,000 rpm and allow it to cool down to room temperature. The physicochemical properties of the formulations were investigated.

Results: In this study it was observed that the particle sizes of liposomes were in the range of 8.68 to about 39.4 nm. Incorporation efficiency of liposomes was over 80% drug release test is in 60-70 percentage.

Conclusion: According to the results of the study, it is concluded that liposomes may be successfully used for topical delivery of quercetin.

Keywords: liposome, quercetin, fusion, topical



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Effect of Freeze-Drying on Bioactivity of Medicinal Herb Extracts: A Review

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Many studies established to investigate the effects of different drying methods on chemical components and bioactivity of medicinal herb extracts. These results show that thermal treatment (air drying, vacuum-oven drying and vacuum-microwave drying) and non-thermal treatment (freeze-drying) have significant different effects on chemical composition (volatiles, phenolics, flavonoids and carotenoids), physical properties as colour and bioactivities (antioxidant capacity).[1, 2]

This research review finds several results of related studies suggested high temperature process can reduce the power of scavenging of free radicals and antioxidant properties. Also, degradation of chemical component and

pigment decomposition was less affected in freeze-drying method. Therefore, freeze-drying can be the appropriate and effective methods for obtaining bioactive compound such as polysaccharide, flavonoids and phenolics constituents) in medicinal herb extracts, due to preserve bioactive components.[3, 4]

Keywords: Drying treatment, Freeze-drying, Antioxidant properties, physicochemical properties.



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Synthesis of Polyelectrolyte Complex Nanoparticles Based on Electrostatic Interaction of Alginate and Poly (3-Acrylamidopropyl) Trimethylammonium Chloride

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Abstract

Introduction: The interaction between two or more opposite charged polyelectrolytes in solution leads to complexes that are called as polyelectrolyte complex (PEC). Polymers used for PEC formation are classified on the basis of origin as natural and synthesis. PECs have many advantages such as high biodegradability, excellent biocompatibility, non-toxicity, low cost, low energy requirement for their production [1]. In the present study, self-assembled polyelectrolyte complex (PEC) nanoparticles were prepared by electrostatic interactions between alginate (Alg) and poly (3-Acrylamidopropyl) trimethylammonium chloride (p (APTMACl)). The effect of pH, ionic strength, polymer concentration and polymers mixing ratio on the formation of polyelectrolyte complexes between Alg and p (APTMACl) was investigated. The formation of complexes was confirmed by the UV-visible spectra (turbidity), FT-IR spectroscopy, dynamic light scattering and zeta- potential.

Methods: p (APTMACl) and its copolymers with acrylamide were prepared by solution polymerization technique in the presence of ammonium persulfate initiator. Then the nanoparticles were prepared by *complexing* the

synthesized cationic polyelectrolyte (0.1%, w/v) and alginate (0.1%, w/v) as an anionic polymer in different conditions by simple mixing.

Results: FT-IR spectra of the synthesized PEC revealed the presence of both polymers. The PECs formed using Alg (0.1% w/v) and p (APTMACl) (0.1% w/v) (Alg/p(APTMACl) ratio (1:1 v/v)), were turbid with particle size of 100 nm. With increasing the Alg concentration to (7:1 v/v), the particle size increased and the turbidity decreased. Effect of pH on the complex formation was confirmed using UV-visible spectra. The absorbance peak at 220 nm is directly proportional to the electrostatic interactions between two polymers. The absorbance intensity increased as a function of the electrical charge of the polymer chains in pH=7. In the presence of NaCl, the intensity of the electrostatic interaction between the polymers reduced due to the screening of polymer charges by the microions [2]. PEC preparation with high polymer concentration resulted in rising turbidity [3].

Conclusion: Cationic polymer was formed by the solution polymerization method. PECs having size in nanometer range, were prepared by the simple mixing of Alg and p (APTMACl). These polyelectrolyte complex nanoparticles can be used for the encapsulation and delivery of proteins and drugs.

Keywords: Polymer, Polyelectrolyte, Polyelectrolyte complex, Nanoparticle, Alginate



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Pharmacokinetic and Efficacy Evaluation of Gemcitabine Loaded Nanoparticles in Animal Model

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Abstract

Introduction: Gemcitabine (Gem) is an anticancer nucleoside analogue active against various solid tumors. Unfortunately, this potent drug possesses important drawbacks such as limited biological half-life and rapid enzymatic degradation to the inactive metabolite, following intravenous (IV) and oral administration. With the

objective of overcoming the above drawbacks and improving the oral absorption and increased efficacy of Gem, we designed a new nanocarrier for delivering anticancer drugs to the targeted malignant tumor cells.

Methods: Chitosan nanoparticles (Gem NP) were produced based on the ionic gelation method. The optimum loaded nanoparticles were evaluated by *in vitro* cytotoxicity and *in vivo* antitumor activity in breast tumor xenografted Balb/c compared to free drug.

Results: The cytotoxicity experiment showed that the nanoparticles were effective equal to free drug in 4T1 and MDA-MB-231 cell lines. Furthermore, the final tumor size of mice receiving the Gem NP was significantly reduced compared to the solution of free drug, Nano-Control and untreated models after IV administration.

Conclusion: The animal model of the artificial heterogeneous tumor showed that the nanotherapeutic was preferentially cytotoxic to 4T1 cells compared to the *in vitro* model. In this preclinical relevant study, the antitumor efficacy of Gem was found to be significantly increased as loaded in chitosan nanocarrier.

Keywords: Preclinical study, Gemcitabine, Chitosan nanoparticles, xenograft tumor model, target drug delivery



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Herbal Hydrogel as Novel Adhesion Prevention after Peritoneal Administration

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Abstract

Introduction: Peritoneal adhesions are pathological fibrotic bands developing after mesothelial damage which causes different problems in the patients. The aim of this study was to compare the anti-adhesion efficacy of a herbal structure made from Psyllium seeds with a commercially available formulation named Pluronic both in the form of hydrogel in a rat cecum abrasion model.

Methods: The rat model utilized a cecal abrasion and abdominal wall insult surgical protocol. Psyllium hydrogel treatment was applied by syringe to coat both the cecal and the abdominal wall insults, while other animals were treated with Pluronic applied to the cecal injury. Control animals did not receive any treatment. Animals were sacrificed after 21 days of laparotomy and adhesion severity was quantitatively graded according to macromorphological characteristics. Histological analysis was also performed for all animals.

Results: Psyllium treated animals showed significantly lower adhesion scores than other groups ($P < 0.05$), while Pluronic did not demonstrate any noticeable results.

Conclusion: Psyllium hydrogel showed a significantly decreased adhesion score compared with the Pluronic and control groups. However, Psyllium compared with all adhesion formulations and barriers offer natural structure as well as ease of application and ability to conform to complex tissue geometries that could provide surgeons with another prophylactic treatment for preventing abdominal adhesions.

Keywords: Peritoneal adhesion, Psyllium hydrogel, Herbal formulation



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Evaluation of Antimicrobial Activity of *Eucalyptus Camaldulensis* Essential Oil on the Growth of Drug-Resistant Bacteria

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Abstract

Introduction: Due to bacterial resistance to common antibiotics and because of irrational consumption of antimicrobial drugs by general public and also high rates of allergies and side effects to the chemical remedies, it is essential to find antimicrobial compounds with minimal side effects. The purpose of this research was to evaluate the activity of essential oil extracted from leaves of *Eucalyptus camaldulensis*, the major *Eucalyptus* species cultivated in south of Iran, Khuzestan on the growth of drug resistant bacteria.

Materials: The extraction of essential oil from leaves was performed by hydro distillation method using Clevenger apparatus. Constituent of the essential oil was determined by gas chromatography connected to mass spectrometry

(GC-MS). Antimicrobial activity of essential oil was assayed using disk diffusion method. Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) were determined using macro dilution techniques.

Results: Isolation and identification of the main components in essential oil identified, 1,8-Cineole (55.2%) as the main component. *Eucalyptus* essential oil was able to control the pathogenic resistant bacteria. The most effect of essential oil was evaluated on *klebsiella pneumoniae* bacteria with 35 mm diameter of inhibitory zone and MIC and MBC of 500 and 1500 ppm, respectively, whereas the lowest effect was on *salmonella infantis* and *Salmonella enteritidis* bacteria with 11mm diameters of inhibitory zones and MIC and MBC of 6000 and 8000 ppm, respectively.

Conclusion: Essential oil of *E. camaldulensis*, myrtaceae grown in Iran possesses a significant activity against some gram-positive and gram-negative bacteria. *E. camaldulensis* is beneficial as antibacterial and bactericidal agent in treating infectious illness.

Keywords: Antimicrobial Agents, *Eucalyptus camaldulensis*, Essential oil, GC-MS, *Klebsiella pneumonia*, *Salmonella infantis*, *Salmonella enteritidis*



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Evaluation of Antimicrobial Activities of Different Extracts from *Phlomis Tuberosa*, *Abutilon Fruticosum*, and *Nepeta Transcaucasica*

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Abstract

Introduction: Considering the resistance development and side effects of conventional antibiotics, use of plants has been recognized as promising alternative treatments. Based on previous studies, plants of *Nepeta*, *phlomis* and *Abutilon* genus showed remarkable antimicrobial activity.

Methods: Aerial parts of *Abutilon fruticosum*, *Nepeta transcaucasica* and *Phlomis tuberosa* were extracted by maceration method using petroleum ether, chloroform, ethyl acetate (EtOAc) and ethanol solvents. Antimicrobial activity of the extracts against seven gram positive strains (*Staphylococcus aureus*, *Bacillus cereus*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Staphylococcus epidermidis*, *Micrococcus luteus* and *Bacillus subtilis*),

three gram negative strains (*Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi*) and a fungi (*Candida albicans*). Potent extracts were subjected to fractionation and MIC calculation.

Results: The chloroform extract of *N.transcaucasica* and EtOAC extract of *A.fruticosum* were the most active extracts. *S. aureus* was the most sensitive bacteria against chloroform extract of *N.transcaucasica* (17mm, MIC 3.125 mg/ml), whereas *Listeria monocytogenes* and *B.subtilis* were the most sensitive bacteria against EtOAC extract of *A. fruticosum* (13mm, MIC 0.78 mg/ml and 13mm, MIC 0.39 mg/ml, respectively) in comparison with positive control (Amikacin, 42mm, 15mm and 17mm for *S.aureus*, *Listeria monocytogenes* and *B. subtilis*, respectively). Other extracts showed weak to moderate activity against different bacteria. Fractions 10% and 80% (EtOAC in n-hexane) of chloroform extract *N. transcaucasica* and all the fraction of *A.fruticosum* revealed the potent activity. The most potent antimicrobial activity was seen by all the fractions of *A.fruticosum* against *Listeria monocytogenes*, *Staphylococcus epidermidis* and *B.subtilis* with MIC ranging from 0.39 to 0.78 mg/ml.

Conclusion: The increasing prevalence of multidrug resistant strains of bacteria and the recent appearance of strains with reduced susceptibility to antibiotics raise the specter of untreatable bacterial infections and add urgency to the search of new infection-fighting strategies and the natural sources is the best choices for this purpose.

Keywords: Antibacterial, *Abutilon fruticosum*, *Phlomis tuberosa* and *Nepeta transcaucasica*



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Iatrogenic Underfeeding in Critically Ill Patients: a Clinical Prospective Study

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Abstract

Introduction: Widespread iatrogenic underfeeding of critically ill patients during ICU stay causes adverse consequences. Unfortunately there is limited data about the prevalence of iatrogenic underfeeding in different geographic regions of the world. Therefore this study was designed to assess underfeeding rate of critically ill patients in one of the largest referral center in Iran and find associated outcomes.

Methods: This prospective clinical study was conducted in 150 critically ill patients admitted to the ICU ward during 6 months in one of the largest teaching hospital in Iran, in 2016. Patients were randomly selected during first 24 hours of ICU admission to recruit in the study and followed for 10 days to evaluate final outcomes. Percent of nutrition intake was measured based on ASPEN guideline for nutrition support therapy in adult critically ill patients. Eighty percent of target measured calories and protein were considered adequate for patients in this study.

Results: Enteral nutrition was begun in 71% of patients with average 28.3 h after ICU admission, also 28% of patients received supplemental parenteral nutrition during the study. Underfeeding have occurred in 74% of patients and 49% of patients failed to receive adequate protein. Prealbumin and BMI significantly decreased after ending follow up in patients who did not meet adequate intake of calories or protein ($p < 0.001$). Moreover lower mortality rate was associated with adequate protein intake ($p = 0.029$). However underfeeding was also related to higher mortality rate but it was not statistically significant ($p = 0.062$).

Conclusion: According to this study high percent of critically ill patients failed to receive adequate nutrition support and were being nutritionally at risk during ICU stay which is related to adverse clinical outcomes. Therefore intervention strategies must be designed to optimize nutrition support in these patients.

Keywords: Intensive care unit, nutrition, underfeeding, prealbumin



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Coenzyme Q10 Supplementation Effects on Serum Levels of Lipid Profile in Women with Type 2 Diabetes Mellitus

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Abstract

Introduction: Diabetes mellitus is a chronic metabolic disorder that causes disruption of lipids metabolism. Coenzyme Q10 or CoQ10 is a non-enzymatic antioxidant that improves the metabolism of lipids. The purpose of this study was to determine the effects of CoQ10 supplementation on serum levels of lipid profile in women with type 2 diabetes mellitus.

Methods: This randomized double-blind placebo-controlled trial (IRCT 2016011325949N2) was conducted in Amirmomenin Hospital in Arak. 68 women with type 2 diabetes (30-65 years old) were consciously enrolled after age, BMI and type of medication matching. Individuals were randomly divided into two groups of Q10 and placebo (n = 34) (daily oral administration of one capsule of 100 mg of Q10 or placebo for 12 weeks). Serum levels of triglyceride, total cholesterol, HDL-C and LDL-C were measured at the beginning and the end of the intervention.

Results: This study showed that daily consumption of 100 mg of CoQ10 supplementation in women with type 2 diabetes for 12 weeks, caused a significant increase in serum levels of HDL-C (p=0.004) and a significant decrease in total cholesterol (p=0.006) and LDL-C (p=0.006), but does not have a significant effects on serum levels of triglyceride (p>0.05). The positive effects of CoQ10 on lipid metabolism occurs by increasing the oxidation of fatty acids and increasing PPAR α expression (1). Increasing the expression of PPAR α can activate the genes responsible for beta-oxidation of fatty acids and inhibit the enzymes responsible for the synthesis of lipids in the liver and skeletal muscles (2).

Conclusions: The results of this study confirmed the positive effects of CoQ10 supplementation on serum lipid profile in women with type 2 diabetes. It is recommended that more studies be done with larger sample sizes to confirm the results of this study.

Keywords: Type 2 diabetes, Coenzyme Q10, lipid profile, triglyceride, total cholesterol



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Quantitative Analysis of Celecoxib and Carboxyl Celecoxib in Human Urine by Using HPLC-UV Detector: Application to a Pharmacokinetic Study in Iranian Healthy Volunteer

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Abstract

Introduction: Celecoxib (Celebrex) is a cyclooxygenase (COX) inhibitor that exhibits *in vitro* and *in vivo* selectivity for COX-2 over COX-1. Celecoxib possesses anti-inflammatory, analgesic and antipyretic activities. The drug has similar efficacy as conventional nonsteroidal anti-inflammatory drugs (NSAIDs) in improving the symptoms of osteoarthritis and rheumatoid arthritis, but it is associated with a lower incidence of gastrointestinal ulceration and complications [1]. This promising gastrointestinal safety profile, together with sustained symptomatic pain relief, places celecoxib as an alternative to the conventional NSAIDs in the treatment of rheumatoid diseases, particularly in patients at high risk of developing gastrointestinal problems. The chemo-preventive effect of celecoxib on colon cancer and its clinical effects on blood platelets renal, hepatic and pancreatic was studied [2].

Methods: A simple, selective, and sensitive high performance liquid chromatography (HPLC) procedure has been developed for determination of celecoxib in human urine. Sample preparation involved ultrasound-assisted solvent dispersive liquid-liquid microextraction by chloroform. The HPLC separation was performed on a ZORBAX Eclipse Plus C18 column (100 mm × 4.6 mm, 3.5Micron, Agilent, USA) with a mobile phase of methanol/0.01 % perchloric acid(Gradient: initial 40/60(3min) to final 0/100 at 2 min) at a flow rate of 1.0 mL/min. The peaks were detected by using UV/Vis detector at 255 nm.

Results: The extraction recovery was 80.6–90.4% and the method was over the concentration range of 25.0–1000 ng/mL with a lower limit of quantitation (LLOQ) of 32.0 ng/mL using 300 L of urine. The intra- and inter-day accuracy of the method at three concentrations ranged from 97.8% to 105.2% for celecoxib with precision of 5.9–8.7%.

Conclusion: This validated method was successfully applied to a pharmacokinetic study enrolling one Iranian volunteer administered a single oral celecoxib extended-release tablet of 200 mg.

Keywords: Celecoxib; HPLC; Pharmacokinetic study; liquid-liquid microextraction



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Quantitative Analysis of Ofloxacin in Human Urine by Using HPLC-UV Detector: Application to a Pharmacokinetic Study in Iranian Healthy Volunteer

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Abstract

Introduction: Ofloxacin (OFL), (\pm)-9-fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, a synthetic broad-spectrum antimicrobial fluoroquinolone (FQ) that exhibits wide spectrum of bactericidal activity against both Gram-positive and negative bacteria, is used for the treatment of urinary tract infections, respiratory tract infections, and osteomyelitis [1,2]. This compound belongs to a class of FQs that possess similar chromophore core units that are responsible for their UV activities [3].

Methods: A simple, selective, and sensitive high performance liquid chromatography (HPLC) procedure has been developed for determination of Ofloxacin in human urine. Sample preparation involved ultrasound-assisted solvent dispersive liquid-liquid microextraction by chloroform. The HPLC separation was performed on a ZORBAX Eclipse Plus C18 column (100 mm \times 4.6 mm, 3.5Micron, Agilent, USA) with a mobile phase of methanol/2-propanol/0.04 % phosphoric acid (pH adjusted to 3.0) (18:2:80, v/v) at a flow rate of 1.0 mL/min. The peaks were detected by using UV/Vis detector at 294 nm.

Results: The extraction recovery was 72.6–88.3% and the method was over the concentration range of 10.0–1486 ng/mL with a lower limit of quantitation (LLOQ) of 23.0 ng/mL using 300 L of urine. The intra- and inter-day accuracy of the method at three concentrations ranged from 96.7% to 104.2% for ofloxacin with precision of 2.9–9.7%.

Conclusion: This validated method was successfully applied to a pharmacokinetic study enrolling one Iranian volunteer administered a single oral ofloxacin extended-release tablet of 300 mg.

Keywords: Ofloxacin; HPLC; Pharmacokinetic study; liquid-liquid microextraction



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Formulation and Physicochemical Characterization of Rapamycin Loaded Nanostructured Lipid Carriers: Effect of Process Variables

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Abstract

Introduction: Rapamycin, as a hydrophobic macrolide antibiotic, has a wide pharmacological actions (i.e. immunosuppressant, anti-cancer, anti-fibrosis) but the undesired physicochemical properties and the low bioavailability restrict the various pharmaceutical formulation and different clinical use of the drug (1). This study designed to prepare nanostructured lipid carriers (NLCs) of rapamycin to overcome the formulation challenges related to the drug instability and hydrolysis against different conditions (2).

Methods: Solubility of rapamycin in different solid and liquid lipids was measured. Rapamycin-NLCs (Rapa-NLCs) were prepared by the solvent diffusion-evaporation method (3). Effects of process variables (i.e. sonication time and power, lipid concentration, surfactants ratio, drug concentration) were studied on particle size, poly dispersity index (PDI), zeta potential (ZP) and drug encapsulation efficiency (EE) of NLCs. Shape and surface morphology of the NLCs were evaluate by scanning electron microscopy (SEM). Crystallinity of the nanoparticles was analyzed by differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). Moreover, stability study of optimized formulation was also done.

Results: The solubility study demonstrated that rapamycin has the highest solubility in precirol® ATO5 (as solid lipid) and capryol® PGMC (as liquid lipid). Process variables showed significant influence on NLCs characteristics. Optimized NLCs with 157 ± 14 nm size, 0.31 ± 0.02 PDI, $+18 \pm 2.5$ mV ZP and 97 ± 0.6 % EE was prepared based on the appropriate formulation conditions. SEM study showed spherical particles with smooth surface. DSC and PXRD studies confirmed the amorphous form of drug in the lipid matrix. Furthermore, Rapa-NLCs were stable for 1 month at 4°C.

Conclusion: Rapa-NLCs were successfully produced regarding to optimized process variables with appropriate formulation characteristics and stability. Based on our finding, the formulated Rapa-NLCs could be introduced as novel drug carrier for different topical, peripheral and parenteral prescription routes.

Keywords: Rapamycin, nanostructured lipid carriers, process variables, stability.



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Changes in 3-Year Antimicrobial Sensitivity Pattern of Gram-Positive Bacteria at the Nephrology Ward of a Referral Hospital in Shiraz

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Abstract

Introduction: Infectious diseases are considered as one of the most important causes of mortality worldwide. Knowledge about the most common causative microorganisms and their resistance pattern can be exploited to help clinicians in selecting an optimized antimicrobial agent for empirical therapy. The main purpose of this study was to determine the pattern of antimicrobial sensitivity of gram-positive bacteria during 3 consecutive years at the nephrology ward of a referral hospital in Shiraz.

Method: During a 3-year period from 2013 to 2015, data of all biological samples (e.g., blood, urine, wound drainage, synovial fluid, sputum, and cerebrospinal fluid) of patients at the adult nephrology ward of Namazi hospital sent to the central laboratory for identification of gram positive microorganisms and subsequently, their antimicrobial susceptibility testing by Kirby-Bauer disc diffusion method were analyzed in a retrospective manner. According to the size of inhibition zone, isolated microorganism was determined to be resistant, intermediately resistant, or sensitive to the certain antimicrobial agent.

Results: Coagulase-negative Staphylococci (38.5%), *Staphylococcus aureus* (25.4%), and Enterococci (23.8%) were the most common isolated gram positive bacteria from samples of the cohort. The rate of coagulase-negative Staphylococci (CONS) sensitivity to vancomycin in 2013, 2014, and 2015 was 97.87%, 98.08%, and 93.55%, respectively. Regarding *S. aureus*, sensitivity rate to oxacillin in 2014 and 2015 was 19.05% and 45.45% and to vancomycin was 93.33% and 84.62%, respectively. There was no documented data about the sensitivity of *S. aureus* to oxacillin and vancomycin in 2013. Enterococci sensitivity to vancomycin decreased from 34.37% in 2013 to 13.64% in 2015. The rate of Enterococci sensitivity to gentamicin in 2013, 2014, and 2015 was 10%, 3.45%, and 7.14%, respectively. In 2014 and 2015, the sensitivity of Enterococci to ampicillin was determined to be 32.14% and 33.33%, respectively. Data regarding the sensitivity of Enterococci to ampicillin in 2013 was unknown.

Conclusion: The rates of oxacillin-resistant *S. aureus*, vancomycin-resistant enterococci, and aminoglycoside-resistant CONS as well as Enterococcus spp. in our clinical setting were considerably high and concerning. Regular and periodic surveillance of antimicrobial sensitivity pattern of gram-positive bacteria seems necessary and strongly recommended.

Keywords: Resistance pattern, Antibiotic, Gram-positive microorganisms, Nephrology ward



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Preparation and *In Vitro* Evaluation of Naproxen-PEG Conjugate

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Abstract

Introduction: Naproxen is a steroidal anti-inflammatory drug (NSAID's) that has side effects, including digestive and stomach problems [1]. In this regard, polymeric carriers can be used to improve the therapeutic properties of this drug. Poly (ethylene glycol) (PEG) is the most used polymer and also currently the most used polymer in the biomedical field of drug delivery [2]. This contribution presents a new conjugated nanoparticle drug carrier for naproxen to get benefit from both conjugate and nanoparticle characteristics for the purpose of improvement in the drug efficacy [3-5].

Methods: A conjugate of naproxen with PEG₆₀₀₀ was synthesized in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine. The naproxen-PEG₆₀₀₀ conjugate was characterized with different techniques including ¹HNMR, FTIR, and DSC. Then, the naproxen-PEG₆₀₀₀ conjugate nanoparticles were obtained by solvent evaporation method. The resulting nanoparticles were characterized by measurement of hydrodynamic sizes, polydispersity index and zeta potentials, and release kinetic in different pH.

Results: DLS measurement of naproxen conjugated PEG₆₀₀₀ nanoparticle revealed a unimodal size distribution with an average diameter of 159±5 nm and low polydispersity index (0.24 ± 0.02). Also, for nap-PEG₁₅₀₀ conjugated is 176 and low polydispersity index is (0.19 ± 0.02). The percentages of naproxen released from prepared conjugate after 24h at pH 1.2, 6.8 and 7.4 were 8.3, 23.5 and 16.0%,

Conclusion: The findings reveal that naproxen conjugated micelles seems promising in terms of achievement of both improvements in EPR effect, and pH sensitivity which provide the possibility to enhance the drug release and accumulation inside inflammatory sites.

Keywords: Naproxen, Conjugation, Polyethylene glycol, Steroid anti-inflammatory drugs, Polymer nanoparticles



Preparation of Electrospun Nanofiber Scaffold Containing Silver Sulfadiazine as Wound Dressing in Topical Scarring

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Abstract

Introduction: Silver sulfadiazine is a widely used topical antibiotic which is active against certain bacteria growing in environment of wounds or scarring. This drug is used for treatment of skin infections and burns, impetigo and also in wound healing. For achieving proper antibacterial effect, it is necessary to provide continuous high concentrations around wound area. Nanofibers can act as a reservoir for drug delivery to topical area and release drug content for long time with steady high concentration. Purpose of this study was to prepare PVA/PVP/CHITOSAN silver sulfadiazine loaded nanofiber blends as wound dressing using electrospinning method as wound dressing.

Methods: PVA/PVP/CHITOSAN nanofiber fabricated by electrospinning process. silver sulfadiazine has been loaded on nanofiber mats. Surface morphology of the nanofibers was observed on scanning electron microscope (SEM). Drug release was determined by Franz diffusion cells and compared to existing silver sulfadiazine ointments in market. Antibacterial activity was tested against staphylococcus aureus in bacterial culture.

Results: SEM showed uniform and conformable structure of nanofibers. Drug loading was $\geq 95\%$. Release test showed expected better release due to reduction in size of drug particles in comparison to common ointment forms. Electrospun scaffold showed great antibacterial activity in bacterial culture. The scaffold maintained its antibiotic activity throughout the processes of electrospinning and gas sterilization.

Conclusion: PVA/PVP/CHITOSAN blends were successfully prepared by electrospinning process, showed better antibacterial activity due to controlled release and reduction in drug particle size. Therefore, according to the results, nanofibers containing silver sulfadiazine probably have greater potential to be used as dressings in wound healing.

Nanofibers containing drugs are promising field in optimum effectiveness of topical antibiotics in wound dressing and showed appropriate characterizations of an ideal drug delivery system.

Keywords: Nanofiber, Electrospinning, Silver Sulfadiazine, Wound Dressing



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Effect of Oral Selenium Supplementation on Hair Health of Patients with Beta Thalassemia Major

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Abstract

Introduction: Beta thalassemia major is an inherited disease which needs repeated blood transfusion for survival. Iron overload induced by numerous transfusion lead to oxidative stress and tissue injury. Iron chelating agents which are used to decrease iron overload complications can also bind and reduce the level of other trace elements such as zinc and selenium. Previous studies showed that selenium functions as an antioxidant helps rid body of the harmful effects that result from exposure to the sun and the environment.

Methods: In this randomized clinical trial 34 patients with beta thalassemia major who were older than 12 years were enrolled in this study. Patients with renal failure, other supplement intake, any change in blood transfusion and chelating agent were excluded from the study. All patients received selenium tablet 200 µg daily for one month. Hair loss questioner was administered at baseline and one month after supplementation.

Results: From 34 patients, 9 (26.47%) were female and 25(73.52%) men. In addition, 88.88% of females and 28% of men suffered from hair loss. Our data demonstrated that, 44.11% of patients complain about thinner hair and hair loss at baseline. After one month supplementation with selenium 93.32% of patients experienced improvement in hair thickness as well as their hair loss.

Discussion: Thalassemic patients are prone to trace elements deficiency due to the life style and their chelators. Selenium deficiency leads to hair loss and related complications. Supplementation with selenium can improve hair

related complaint. Further studies are needed to measure the serum selenium concentration in order to assess the relationship between selenium concentration and hair problems.

Key Words: Beta thalassemia major, Selenium, Iron chelating agent, hair loss



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The Association between Cancer and Drug Resistance

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Abstract

Introduction: Today, cancer is known as one of the main reason of mortality in worldwide so that mortality related to cancer is increasing in current years. This problem can burden high expenditure to health field in order to treatment and management of cancer. Although, it have been suggested many drug to treat cancer but many cancers resist to chemotherapy drugs during treatment and it have been proposed various mechanisms in connection with drug resistance.

Methods: In this review, mechanisms of drug resistance were described through searching related keywords in reliable databases

Results: High expression of ATP-dependent membrane proteins as a family of ATP binding cassette are one of the main reasons for drug resistance so that P-glycoprotein (a member of this family) plays an important role in drug resistance. In addition, multidrug resistance associated protein as other membrane of this family is involved in drug resistance. These proteins have property of endogenous substrates transferring. Over-expression of these proteins in cancer cells is most important obstacle to treat cancer. However, drug resistance can occur through other ways such as anti-cancer drugs associated with metabolism purines and pyrimidines or microtubules dysfunction.

Discussion: Finally, we concluded despite advances in cancer treatment by chemotherapy, protective mechanisms of cells against cytotoxic compounds are a major obstacle to overcome cancer treatment. Increase of information about drug resistance mechanisms, can be useful to design promising strategies to overcome drug resistance. Some obtained findings about drug resistance reveal new mechanisms in association with drug distribution in body. These findings can be helpful to improve patients with cancer. In addition, we suggest that in order to overcome this problem design and perform further studies.



Comparison between the pattern of General practitioners and Pediatricians prescriptions for children based on the WHO prescription indicator

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Introduction: WHO prescribing indicators measure the performance of healthcare professionals in several key dimensions related to the appropriate use of drugs including polypharmacy, the number of prescribed antibiotics and injectable drugs and Percentage of drugs prescribed from essential drugs list or formulary. Internal medicine specialists are a major part of private practitioners. This study was designed to the evaluation of the pattern of prescription by internists and general practitioners based on the WHO prescription indicators.

Methods: In this study, prescriptions of internal specialists and general practitioners were collected from private pharmacies in the city of Ahvaz during three months. The number of prescribed drugs, antibiotics, injections, drug interactions has been compared in both groups. SPSS 20 software was used for analysis of data.

Results: We randomly evaluated 63 prescription of internists and 63 prescriptions of general practitioners, in the internists orders the average number of drugs was 2.75 ± 1.58 with a range between 1 and 8 (optimal ≤ 3). An antibiotic was prescribed in 21% of prescription (optimal $\leq 30\%$) in which 10% contains more than one antibiotics. Also 13.6% of prescriptions contain at least one injectable drug (optimal $\leq 10\%$). Almost all drugs prescribed by internists and general practitioners were on the essential drug list of Iran.

Discussion: Given that the only item that was prescribed more than desired was the number of injectable drugs, it seems that the prescribing practices of internal specialists are appropriate in comparison with WHO indicators. For better judgment, it seems that it is necessary more detailed study be conducted with larger sample size.

Keywords: Prescribing pattern, prescribing indicators, antibiotic, injection



Evaluation of Ibuprofen Release from Various Concentrations of PCL In Collagen-Based GTR

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Abstract

Introduction: Guided Tissue Regeneration (GTR) is a widely used method in dental surgical procedures that utilizes a barrier membrane to exclude migration of epithelium and ensure repopulation of periodontal ligament cells at the site having insufficient gingiva. The aim of the present study is investigating the evaluation of ibuprofen release from collagen/PVA and PCL polymeric fiber in three concentrations of PCL.

Methods: Hybrid nanofibers were fabricated from two different spinable solutions contain 3, 5, 10 %wt of PCL in chloroform and PVA/Collagen (50/50) in acetic acid 2 % w/v. a constant amount of ibuprofen was loaded in the fiber mats. Chemical and physical characterizations were carried out with FTIR, XRD, TG-DTA and SEM. Release behavior calculated by full immersion method, identified by UV spectroscopy.

Results: Increasing the PCL concentration lead to increasing the fiber diameter from 200 to 1500 nm. Also, the morphology of the fiber changed from smooth to porous. A controlled release profile was obtained for ibuprofen in 72 h with three formulations. The effect of the fiber size on release profile was investigated. FTIR result did not show any undesirable interaction of PCL and ibuprofen. In addition, no polymer degradation occurred after applying high voltage during e spinning. Mechanical strength was about 7.5kpa.

Conclusion: The mat considered helpful as GTR membrane due to high mechanical strength, non-toxic effects, and controlled release profile.

Keyword: GTR, Ibuprofen, Nanofiber, Electrospinning.



The Comparative Effect of Oral Evening Primrose Oil versus Black Cohosh on Menopausal Hot Flashes: A Randomized Clinical Trial

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Abstract

Introduction: Hot flashes are undesirable experiences which affect the quality of life of menopausal women. The aim of this study was to compare the efficacy of evening primrose with black cohoshon reducing the menopausal hot flashes and improvement of quality of life.

Methods: In an 8-week randomized clinical trial, a total of 80 menopausal women who referred to hospital with complaint of hot flashes were included. The participants were randomly divided to two groups (black cohosh and primrose oil). Primrose oil group took one capsule contain 1 gram primrose oil per day and black cohosh group took one capsule contains 20 mg per day for continuous 8 weeks. Then, the frequency, duration of hot flashes and quality of life which was assessed by MENQOL Questionnaire compared between two groups at baseline, after 4 and 8 weeks.

Results: Results the mean age of women was 52 ± 3.4 years. The mean frequency score of hot flashes from baseline was significantly lower in cohosh group compared to evening primrose oil after 4 weeks and after 8 weeks respectively ($P = 0.04$) and ($p=0.001$). The mean+SD score of quality of life were significantly different between black cohosh and primrose oil after four and eight weeks of intervention ($P<0.001$).

Conclusion: Consumption of both evening primrose oil and black cohosh compared with placebo decreased the number and duration of hot flashes. However, the frequency and duration of menopausal related symptoms ameliorated more among black cohosh group compared to evening primrose oil group.

Keywords: Evening primrose oil; Black cohosh; menopausal women; hot flashes.



***Salvia macrosiphon* mucilage assessment as a tablet excipient**

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Abstract

Introduction: *Salvia macrosiphon* is one of the medicinal plants that have high levels of mucilage. The mucilage previously studied as a pharmaceutical suspensions excipient. In this study the possibility of using the mucilage has been investigated as a tablet excipient.

Methods: The mucilage is prepared from Seeds of *salvia macrosiphon*. Solubility studies were performed in water, acetone, alcohol and chloroform. Swelling index and pH of 1% solution was measured in water. Total ash, insoluble ash in acid, sulfate ash, weight loss on drying and percentage of carbon, hydrogen, nitrogen and oxygen of mucilage were determined precisely. Acetaminophen tablets were prepared with different percentages of the mucilage and microcrystalline cellulose by direct compression method. The drug dissolution test, tablet disintegration time and their physical properties were evaluated and compared with microcrystalline cellulose or crospovidone containing pills.

Results: Evaluated parameters of the extracted mucilage were well within the limits. The disintegrating performance of isolated mucilage was slightly weaker than crosspovidone. The hardness, friability, % drug content, wetting time and dissolution of the tablet which containing 4% mucilage were Comparable with tablets that containing 2% of crosspovidone as disintegrator.

Conclusion: Mucilage extracted from *Salvia macrosiphon* has the necessary physicochemical and purity properties for use as a pharmaceutical excipient. It is recommended to use this substance as a tablet superdisintegrant, because of its high swelling effect due to water absorption.

Keywords: *Salvia macrosiphon*, mucilage, tableting, disintegrator



Preparation of Erythromycin Microparticles with Eudragit S100 Polymer by Using Emulsion Method for Taste Masking

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Abstract

Introduction: Erythromycin is effective against gram-positive organisms. Erythromycin is generally safe in those who are allergic to penicillin. The drug of choice was in the treatment of neonatal respiratory chlamydia infections, eye infections bacteria and corynebacterium. Due to the bitter taste of erythromycin little acceptance among children and elderly leads to better acceptance in these cases is to modify the taste of erythromycin

Methods: Microspheres of erythromycin with pH-dependent polymer (such as Eudragits S100) were prepared by the emulsion solvent diffusion method (O1/O2). The effect of different polymer–drug ratios on the taste masking and the characteristics of the microspheres were investigated. In the current study formulations with different polymer/drug ratio were prepared and were characterized by drug loading, loading efficiency, yield, particle size, bitter taste threshold, x-ray diffraction (XRD), fourier transform spectroscopy (FTIR) and differential scanning calorimetry (DSC). The *in vitro* release studies were performed in pH 1.2 and 7.4.

Results: The best polymer to drug ratio in microparticles were E1 (1:1 polymer to drug ratio) which showed 26.93%, 53.86% entrapment, loading efficiency, respectively and mean particle size of 426.62 μm . The FTIR, XRD and DSC showed the stable character of erythromycin in the drug-loaded microspheres and revealed an amorphous form. The results showed that microparticles prepared with pH-dependent polymer (Eudragit S100) were faster release than the commercial suspension ($p < 0.05$). The results demonstrated that Eudragit S100 could for masking the unpleasant taste of erythromycin investigated.

Conclusion: The results indicated that the microsphere formulation could be a promising drug carrier for masking the bitter taste of erythromycin.

Key words: Erythromycin, Eudragit S100, Taste masking, Microsphere, Emulsion method.



Preparation and Physicochemical Characterization of Topical Quercetin Loaded Liposome

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Abstract

Introduction: Quercetin (3, 3',4',5,7-pentahydroxy flavone) is found in many dietary regimes include onions, apples potatoes (1). Quercetin has shown pharmacological effects such as antioxidant, anti-inflammation and wound healing effects (2). Liposomes were first used as topical therapy by Mezei. Comparison of liposomal and conventional forms indicate that concentration of liposomal drug in the skin and subcutaneous tissue is more than conventional forms, but its distribution in plasma and other tissues is lower (3).The purpose of this study is preparing quercetin loaded liposome by fusion method and characterizing their physicochemical properties.

Methods: Liposomes prepared by fusion method. Briefly, the lipid components consisted of Soybean phosphatidyle choline, cholesterol, quercetin, propylene glycol, vit E were melted at about 75°C. HEPES buffer was heated separately and added up to 100% to the previously heated melted lipids, and the mixture was homogenized (Ultra-Turrax IKA T25) for 5 min at 12,000 rpm and allow it to cool down to room temperature. The physicochemical properties of the formulations were investigated.

Results: In this study it was observed that the particle sizes of liposomes were in the range of 8.68 to about 39.4 nm. Incorporation efficiency of liposomes was over 80%. drug release test is in 60-70 percentage.

Conclusion: According to the results of the study, it is concluded that liposomes may be successfully used for topical delivery of quercetin.

Keywords: liposome, quercetin, fusion, topical



Preparation, Box-Behenken Statistical Optimization, and *In Vitro* Characterization of a Self Nano-Emulsifying Drug Delivery System (SNEDDS) for Oral Delivery of Budesonide as a Poorly Soluble Drug

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Abstract

Introduction: Self nano-emulsifying drug delivery systems (SNEDDS) can be used to improve oral bioavailability of lipophilic drugs. The aim of this study was preparation and characterization of a SNEDDS for oral delivery of budesonide as a poorly soluble drug.

Methods: For preparation of SNEDDS, budesonide (20 mg) was dissolved in the mixture of liquid paraffin, Tween 80 and propylene glycol. The box-behenken response surface methodology was used for statistical optimization. Prepared mixtures were then diluted in simulated intestinal fluid (SIF) and their physico-chemical characteristics were studied. Then, SNEDDS were evaluated morphologically using TEM. Finally, *in vitro* release profile of budesonide from nano-droplets was determined in SIF.

Results: The size, PdI, zeta potential and entrapment efficiency of statistically optimized SNEEDS were reported as $146 \pm 37\text{nm}$, 0.211 ± 0.06 , $+3.6 \pm 0.84\text{mV}$ and $94.3 \pm 6.58\%$, respectively. TEM images revealed spherical nano-droplets. The release profile of budesonide from nano-droplets exhibited $33.81 \pm 1.67\%$ of drug release in SIF during 360 min of incubation at 37°C indicating sustained drug release.

Conclusion: The obtained data revealed that SNEDDS could be regarded as a good candidate for oral delivery of budesonide as a poorly water soluble drug exhibiting high first pass metabolism.

Keywords: Budesonide, Poorly water soluble drugs, Self Nano-Emulsifying Drug Delivery System (SNEDDS), Oral delivery, Lymphatic absorption, Statistical optimization.



Oral Self Nano-Emulsifying Peptide Drug Delivery Systems: Impact of Lipase on Drug Release

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Abstract

Introduction: It was the aim of this study to evaluate the impact of lipases on the release behavior of a peptide drug from oral self-nano-emulsifying drug delivery systems.

Methods: Octreotide was ion paired with the anionic surfactants deoxycholate, decanoate, oleate and dodecylsulphate. The lipophilic character of these complexes was characterised by determining the n-octanol/buffer pH 7.4 partition coefficient. In the following the most hydrophilic complex was incorporated in a likely lipase degradable self-nanoemulsifying drug delivery systems (SNEDDS) formulation containing a triglyceride (olive oil; Pharm.Eur.) and in a likely not lipase degradable SNEDDS containing lipids and surfactants without any ester bonds. After 1:100 dilutions in artificial intestinal fluid (AIF), the lipid droplets were characterised regarding size distribution. With these SNEDDS, drug release studies were performed in AIF with and without lipase.

Results: Results showed that the most hydrophobic complex can be formed with deoxycholate in an octreotide: anionic surfactant ratio of 1:5. Even $73.1 \pm 8.1\%$ of it could be quantified in the n-octanol phase. SNEDDS containing octreotide | olive oil | cremophor EL | propylene glycol (2|57|38|3) and octreotide | liquid paraffin | Brij 35 | propylene glycol | ethanol (2|66.5|25|5|1.5) showed after dilution in AIF, a mean droplet size of 232 ± 53 nm and 235 ± 50 nm, respectively. Drug release studies showed a sustained release of octreotide out of these formulations for at least 24 h, whereas $> 80\%$ of the drug was released within 2 h in the presence of lipase in the case of the triglyceride containing SNEEDS. In contrast the release profile from ester-free SNEDDS was not significantly altered ($p < 0.05$) due to the addition of lipase providing evidence for the stability of this formulation towards lipases.

Conclusion: According to these results, SNEDDS could be identified as a useful tool for sustained oral peptide delivery taking an enzymatic degradation by intestinal lipases into considerations.

Keywords: Hydrophobic Ion pairing, *in vitro* release, Lipid digestion, Oral peptide delivery, Self Nano-emulsifying Drug Delivery system (SNEDDS)



Preparation and Characterization of Self Nano-Emulsifying Drug Delivery System (SNEDDS) for Oral Delivery of Heparin Using Hydrophobic Complexation by B-Cyclodextrin

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Abstract

Introduction: The aim of this study was the preparation of a self nano-emulsifying drug delivery system (SNEDDS) for oral delivery of heparin. Preparation of hydrophobic complexes between heparin as the hydrophilic macromolecule and β -cyclodextrin (β CD) was considered for preparation of orally administered SNEDDS in which the drug incorporated in internal oil phase of O/W nano-droplets.

Methods: Hydrophobic complexes of heparin- β CD were prepared. The lipophilic feature of complexes was characterized by determining their partition co-efficients. SNEDDS prototypes were prepared by mixing liquid paraffin, Tween 80, propylene glycol and ethanol, diluted 1:100 in an aqueous medium. Central composite response surface methodology was applied for statistical optimization. Independent variables were the amount of liquid paraffin and the amount of Tween 80, while responses were size and poly dispersity index (PDI). Optimized SNEDDS were studied morphologically using transmission electron microscopy (TEM). *In vitro* release of heparin was studied in the simulated gastric and simulated intestinal media.

Results: The data revealed that in molar ratio 1:3 (heparin: β CD), the n-octanol recovery was maximized and reached $67.6 \pm 11.86\%$. Size, PDI, zeta potential, EE% in gastric medium and EE% in intestinal medium for optimized nano-droplets were reported as 307 ± 30.51 nm, 0.236 ± 0.02 , $+2.1 \pm 0.66$ mV, 90.2 ± 0.04 and $96.1 \pm 0.73\%$, respectively. Microscopic images revealed spherical nano-droplets. The obtained data revealed no burst release of heparin from nano-droplets.

Conclusion: The obtained results indicate that SNEDDS could be regarded as a good candidate for oral delivery of heparin as the hydrophilic macromolecule.

Keywords: Heparin, β -cyclodextrin (β CD), Hydrophobic complexation, Self Nano-Emulsifying Drug Delivery System (SNEDDS), Oral Delivery



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15th IPSC Proceeding

Preparation, Formulation, and Characterization of Solid Lipid Nanoparticles Containing Tramadol as a Hydrophilic Drug for Transdermal Drug Delivery System

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Abstract

Introduction: Tramadol Hydrochloride, a synthetic opioid of the amino-cyclohexanol group, is centrally acting analgesic with opioid agonist properties due to its active metabolite (M1) and with a high frequency of administration. In order to reduce the frequency of administration and the opioid-like properties, followed by improving the patient compliance, tramadol Hydrochloride loaded Solid Lipid Nanoparticles (SLN) have been designed and developed.

Methods: In this study, SLN were prepared using double emulsion- solvent evaporation technique. Central composite response surface methodology was applied for optimization of nanoparticles. The independent variables were GMS/Lecithin ratio and the amount of drug. Dependent variables were size, zeta potential, PdI and EE%. Statistically optimized nanoparticles were prepared experimentally for five times. The morphology of nanoparticles was studied using SEM microscopy. *In vitro* release study was performed in a phosphate buffer with the pH of 5.4 using dialysis bag diffusion technique.

Results: Obtained data revealed that the size, Zeta potential, PdI and EE% optimized nanoparticles were 230 ± 24.5 nm, $+8.5\pm 2.38$ mV, 0.241 ± 0.004 and $86.5\pm 5.7\%$. SEM images revealed spherical nanoparticles with no sign of aggregation. *In vitro* release profile revealed sustained release of tramadol from nanoparticles $68.4\pm 9.3\%$ of entrapped drug was shown to release after 24 h of incubation.

Conclusion: According to the findings, it is believed that the prepared SLN nanoparticles can be a good candidate for transdermal delivery of tramadol as the hydrophilic drug.

Keywords: Tramadol hydrochloride, solid lipid nanoparticles, doubles emulsion- solvent evaporation technique, Central composite response surface methodology



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Mechanism and the Effect of Electroconvulsive Therapy in Control of Depression

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Abstract

Introduction: Depression is part of a vicious cycle involving poor health status, isolation, sedentary lifestyle, and worsening health status, resulting in the development of a reactive depression. In pharmacotherapy of depression used the selective serotonin reuptake inhibitors (SSRIs) and 2 antidepressant classes having broader neuroreceptor activity—the tricyclic antidepressants (TCAs) and the serotonin–norepinephrine reuptake inhibitors (SNRIs). After some time the use of these drugs can cause tolerance, so we should look for alternative therapies for treatment of depression such as Electroconvulsive therapy (ECT). ECT is considered to be the most effective for treatment of major depression, mania and catatonia. The aim of this study is to evaluate mechanism and the effect of ECT in improved depression and invited to increase use of alternative therapies in treatment of disease.

Methods: We searched following electronic databases with use of keywords such as depression, electroconvulsive therapy, tryptophan and serotonin in search engine such as sciencedirect, pubmed, google scholar. We included some studies of depressed patients that receiving ECT where cognition was assessed using standardized tests.

Results: The result indicate that the ECT increased the plasma levels of most amino acids such as tryptophan continues to 2–24 h after it administration, in the otherhand, tryptophan is involved in the synthesis of serotonin; and increased serotonin improves depression.

Conclusion: ECT is effective in treatment of depression and probably using it can reduce the use of chemical drugs, their adverse effect and tolerance to drugs.

Keywords: Electroconvulsive therapy, depression, tryptophan



Preparation and Evaluation of Microparticles Containing Tadalafil Loaded Polymeric Nanoparticles for Treatment of Pulmonary Hypertension

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Abstract

Introduction: Inhalable dry powders containing PLGA nanoparticles (NPs) were developed for the delivery of Tadalafil (TAD) in treatment of life treating pulmonary arterial hypertension.

Methods: Taguchi design was employed to evaluate the effects of different formulation variables on the physicochemical characteristics of NPs prepared using emulsion solvent evaporation method. Inhalable PLGA NPs of TAD were successfully prepared by co-spray drying the NPs with inert carriers. Physicochemical characteristics and *in vitro* deposition of the aerosolized drug were also evaluated

Results: The optimized formulation was prepared using 7.5 mg of PLGA, 2.5 mg of TAD, sonication time of 6 min and 2% PVA as the stabilizer. The optimized aqueous/oil phase ratio for NPs preparation was 10:1. Polymer/drug ratio was the most effective parameter on the release efficiency. Encapsulation efficiency, zeta potential and particle size of NPs were more affected by aqueous/organic phase ratio. The spray dried powders containing NPs had a mass median aerodynamic diameter in the range of 1.4–2.8 μm that was suitable for TAD delivery to deep region of lung. The presence of L-leucine in mannitol containing formulations decreased the interparticulate forces between particles and resulted in remarkable increase of yield as well as FPF of particles.

Conclusion: The results indicated that prepared dry powders containing TAD loaded PLGA NPs were suitable for inhalation and had potential for the treatment of pulmonary arterial hypertension.

Keywords: Pulmonary hypertension, Tadalafil, PLGA nanoparticles, Emulsion-solvent evaporation method, Spray drying, dry powder inhaler



Design, Molecular Modeling and Synthesis of Piperidyl-1, 2, 4-Triazole Derivatives as Cholinesterase Inhibitors

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Abstract

Introduction: Alzheimer's disease (AD) is a degenerative disorder of the nervous system caused by decrease in cholinergic neurotransmitters such as acetylcholine (Ach). Cholinesterase inhibitors can increase the level and duration of action of Ach by inhibition of cholinesterase enzyme. Among cholinesterase inhibitors, donepezil like compounds that have benzyl piperidine moiety are much considered due to more significant efficacy and less side effects in comparison with tacrine, the first FDA approved anti-AD drug. In this study novel cholinesterase inhibitors, that have benzyl piperidine fragment of donepezil, were designed and synthesized.

Methods: Ethyl-4-piperidine carboxylate was N-alkylated with benzyl bromide in absolute ethanol at room temperature for 24 hours. Then, the reaction was treated with hydrazinehydrate to obtain corresponding hydrazide. Finally, novel 1, 2, 4-triazole analogues were achieved by reaction of hydrazide and some benzonitrile derivatives in presence of catalytic amount of copper iodide.

Results: Based on the structure activity relationship (SAR) of the cholinesterase inhibitor, some novel compounds containing benzyl piperidine designed, synthesized and structurally elucidated by IR, NMR and Mass spectra. Docking studies confirmed that these compounds fit properly in active site with favorable affinities.

Conclusion: In this research, piperidyl-1, 2, 4-triazole derivatives as novel cholinesterase inhibitors were designed, synthesized and approved by IR, NMR and Mass spectra. Docking studies showed that the designed compounds had good affinity to the active site of cholinesterase enzyme.

Keywords: Alzheimer's disease, Cholinesterase inhibitor, 1, 2, 4-triazole, Synthesis.



Evaluation of Knowledge, Attitude, and Practice of General Physicians about Rational Prescribing and Use of Drug and Related Factors in Tehran

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Abstract

Introduction: Precision and appropriate expertise are the essential factors that must be applied by general physicians (GPs) due to their important role in preventing irrational prescribing. The present study was designed to evaluate the knowledge, attitude, and practice of GPs in terms of rational prescribing and use of drug and related factors.

Methods: This cross-sectional study assessed the knowledge, attitude, and practice of 135 GPs about rational prescribing in Tehran during second half of 1390. A questionnaire was developed to examine the level of knowledge and attitude of GPs and a check list was employed to evaluate the level of their practice. Some stimulated patients and questioners trained and sent to the office of physicians. Data analysis was done by using SPSS software.

Results: 79.3% of GPs had high and very high knowledge, 45.9% had positive attitude and 50.4% had good and very good practice. Results showed that sex of physicians influenced on practice of them ($P=0.03$). Age and job history of physicians influenced on knowledge of them ($P=0.05$, $P=0.06$ respectively) and practice area influenced on knowledge, attitude and practice of GPs ($P=0.01$).

Conclusion: GPs in Tehran have a good knowledge about rational prescribing but they don't have good attitude and they show average practice. It is necessary that some interventions were done to promote the attitude and practice of GPs.

Keywords: Rational Prescribing and Use of Drugs, Knowledge, Attitude, Practice, General physicians



Evaluation of the Effect of Vitamin E in the Prevention of Vancomycin-Induced Nephrotoxicity: A Randomized Controlled Clinical Trial

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Abstract

Introduction: Vancomycin is a glycopeptide antibiotic that has the major role for treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) (1); however, its use may be associated with nephrotoxicity. The proposed mechanism of nephrotoxicity is indirect production of reactive oxygen species (ROS) and oxidative stress (2). The purpose of this study was to investigate the effectiveness of vitamin E as an antioxidant agent in prevention of vancomycin-induced nephrotoxicity.

Methods: In a randomized controlled trial, patients who received vancomycin for any indication were randomly assigned to experimental (Vitamin E; n=30) and control (n=56) groups. The patients in experimental group received 400 units of oral vitamin E per day for 10 days started concurrently with vancomycin, while the patients in control group received vancomycin alone. Serum levels of creatinine (Cr) and blood urea nitrogen (BUN), creatinine clearance (ClCr), and 12-hour urine output were determined and recorded before the start of interventions, every other day during therapy, and 12 hours after the last dose of vancomycin dose in 10th day of therapy for all patients. Also, the rate of acute kidney injury (AKI; defined as ≥ 0.5 mg/dl or $\geq 50\%$ increase of serum creatinine from baseline value) in the two groups was recorded. Finally, the mean values of the measured parameters were compared between the groups.

Results: Vitamin E had no significant effect on serum Cr, ClCr, and 12-hour urine output compared to control group; however, it significantly reduced serum BUN after the 5th day of treatment compared to control group. Also, 10 cases of vancomycin-induced AKI were observed in the control group (17.86 %), while no case was reported from the experimental group.

Conclusion: Vitamin E has the potential for reducing vancomycin-induced nephrotoxicity and AKI. However, more studies with higher sample size are necessary to confirm this effect.

Keywords: Vancomycin; Nephrotoxicity; Vitamin E; Clinical Trial.



Evaluation of the Effects of *Tamarindus Indica* L. Fruit on Body Weight, Serum Lipid Profile, and Blood Pressure of Obese and Overweight Adult Patients: A Randomized Controlled Clinical Trial

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Abstract

Introduction: The obesity has increased over the past 50 years. It is a chronic metabolic disorder resulting from several biologic and environmental factors including sedentary life style (1). Current pharmacologic therapies for obesity have several limitations such as serious side effects (2) and approval for short-term use. There are reports from animal studies showing anti-obesity and lipid-lowering effects of *Tamarindus indica* L. (Tamarind) fruit; however, there is no related clinical study. The aim of this study was to evaluate these effects in either obese or overweight adult patients.

Methods: In a randomized controlled clinical trial, 40 obese or overweight patients were randomly and equally assigned to two groups of Tamarind and control. The first group consumed 10 g of *Tamarindus indica* fruit twice daily for 6 weeks. The patients of both groups were instructed appropriate diet and physical activity by a trained dietician. Body mass index (BMI), waist circumference, systolic and diastolic blood pressure, and serum lipid profile were determined pre- and post-intervention in both groups and finally compared.

Results: No significant changes were observed in evaluated parameters of Tamarind group compared to control group. However, in Tamarind group, significant reductions were observed in systolic blood pressure (113.25 ± 13.40 vs 107.50 ± 11.64 ; $P < 0.01$) and BMI (29.54 ± 3.16 vs 28.91 ± 3.43 ; $P < 0.001$) compared to baseline.

Conclusion: The consumption of *Tamarindus indica* fruit with the dose of 10 g twice daily has no significant effect on BMI, waist circumference, systolic and diastolic blood pressure, and serum lipid profile of obese and overweight adult patients. However, use of higher doses for longer periods might have more effects.



Assessment of Demographic and Medical Factors on 5-Year Survival in Patients Diagnosed with Colon Cancer

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Abstract

Introduction: Colon cancer is one of the most common cancer among men and women with high rate of mortality. Knowing the medical and social factor that can affect its mortality can help health system to decrease its mortality. The aim of this study is to assess medical and demographic factors that can affect 5-year survival of this disease.

Methods: This was a descriptive retrospective study and the data were gathered from archive of Shohaday-e-tajrish cancer research center. All patients who were referred to this center between Farvardin 1384 to Aban 1385 (a year and half) were enrolled in this study. Sample size was calculated to be 580 (with alpha error equivalent to 5% and beta error equivalent to 20%). Their information was obtained from patient (if she or he was alive) or from relatives by telephone calls was made to answer them the questions that was prepared as a questionnaire. All data about demographic, social, economical and medical information were recorded and was analyzed.

Results: According to descriptive statistics and Chi-square test, from 580 patient, average age was 22-83 years old with mean of 63. Log rank test assessed the effective factors and according to this test, age, sex, complete treatment and follow-up treatment had significantly improved 5-year survival. The most effective factor among them was completion of treatment.

Conclusion: Our study showed that completing the cancer treatment is the most effective factor in 5-year survival of colon cancer. This can be a new research aim for pharmacotherapist to investigate how they can act to affect completing of treatment in colon cancer patients. It needs also consideration of other clinicians and insurance companies to help improve mortality rate of colon cancer

Keywords: Colon cancer, Demographic factors, complete treatment of cancer, 5-year survival rate.



The Effects of *Rosa Persica* Extract on Hepatotoxicity Induced By Cadmium in Male Mice

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Abstract

Introduction: Cadmium is one of the most important environmental pollutants that specifically accumulate in the liver and kidneys. *Rosa persica* is part of Rosaceae family, that due to having antioxidant properties are the important medicinal plants in the field of medicine. According to oxidative stress is a mechanism involved in the pathogenesis of liver damage caused by cadmium, in this study, the effect of the hydroalcoholic extract of *Rosa persica* was evaluated in hepatotoxicity induced by cadmium in mice.

Methods: 36 mice were randomly divided into 6 groups and treated for 14 days, intraperitoneally. In the control group, normal saline, the second group, cadmium (3 mg/kg) and the third group, hydroalcoholic extract of *Rosa persica* (50 mg/kg) were administrated. The other groups were received different doses of extract (12.5, 25 and 50 mg/kg) as well as cadmium. Finally, the serum samples and liver tissue were collected for oxidative stress and histological tests, respectively.

Results: The results showed that cadmium significantly increased ALT and AST serum levels, the level of TNF α and lipid peroxidation level in the liver tissue. Following administration of the extract, a significant decrease was observed in ALT and AST levels, and also the levels of TNF α and lipid peroxidation in liver tissue, in comparison with cadmium group.

Conclusion: Hydroalcoholic extract of *Rosa persica* is effective in protection of mice against cadmium-induced hepatotoxicity possibly via increased resistance to oxidative stress.

Keywords: *Rosa persica*, Cadmium, Heavy metal, Liver, Oxidative stress



***In Vitro* Evaluation of Drug Release and Permeability from Polymeric Micellar Formulations**

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Abstract

Introduction: Many of drugs have poor permeability and so the oral delivery of such drugs is usually associated with limitation of low bioavailability and lack of dose proportionality. Micellar systems are excellent potential formulation for increasing permeability and bioavailability of drugs. The aim of this study was to formulate polymeric micellar containing a hydrophilic drug, deferoxamine mesylate, and to explore the potential of carriers for such system.

Methods: Full factorial design with three variables; type of surfactant, surfactant concentration and type of polymer in two levels were used. The effects of variables on formulation characters; particle size, drug release and rat intestine permeability were evaluated.

Results and Discussion: All formulations with particle size between 2 to 65 nm, which made high surface area for intestine absorption. The profile of release of drug showed that drug has continuous release from the formulation which that is most in acidic condition. The change of polymer type from carbomer to Ploxamer increased drug release significantly.

Conclusion: all of the formulations increased drug permeability through intestine compared to control, which most of this is for formulation NO. 2 which contains poloxamer as a polymer and caused increment in permeability more than 2-folds.

Key words: polymeric micelle, drug release, drug permeation, deferoxamine mesylate



Clinical Applications of ^{99m}Tc-HMPAO Labeled Platelet

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Abstract

Introduction: The ^{99m}Tc-HMPAO because of having high lipophilicity and neutral property is a suitable complex for cell labeling such as platelets labeling. It is rapidly crossed from cell membrane of platelets and incorporated inner of them and converted to the less lipophilic state by reductive agents such as glutathione (GSH) or tight binding to intracellular microorganisms and trapped into the platelets. Then labeled platelets can be used for clinical applications in detection of Deep Vein Thrombosis (DVT), Venous Thromboembolism (VTE), Tumors, Dementia.

Method: The whole blood should be centrifuged two times to extract platelets and plasma before labeling with ^{99m}Tc-HMPAO. The labeled platelets must be inspected for purity, viability, release of ^{99m}Tc out of the platelets, and sterility. Microscopic examination and TLC assays were done. The biodistribution of labeled platelets were assessed in sacrificed BALB/c mice. Pharmacokinetics and accumulation of the tracer within organs of New Zealand rabbits are calculated by imaging method.

Results: The acceptable %LE was obtained about over 50%. Incubating in plasma as medium of incubation, at 37° had the lowest amount of release ^{99m}Tc-labeled out of platelets 10%/1h. The microscopic examination indicated cell viability about more 95% and any clot of platelets. HPLC, TLC results represented the radiochemical purity over 80%.

Conclusion: The ^{99m}Tc-HMPAO with having appropriate lipophilicity could be useful for blood cell labeling in clinic. The labeled platelets could be incorporated directly into the thrombotic lesions and detected sites of thrombus. Overlay, the most % LE of platelets with ^{99m}Tc-HMPAO resulted in ACD: saline and incubation at 37° for 25 min and at pH: 6-6.5 because of lowest aggregation of platelets in this pH was reported.

Keywords: Technetium 99m-HMPAO, labeled platelets, thrombus imaging



Evaluation of the Protective Effect of Sildenafil On Pulmonary Fibrosis Model Induced By Bleomycin In Rat

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Abstract

Introduction: The present study aimed to investigate effects of sildenafil on bleomycin (BLM)-induced lung fibrosis in rat.

Methods: Animals were divided into five groups and treated according to the following treatments. group 1 received daily normal saline, intraperitoneally (ip); group 2 received a single dose of BLM (7.5 IU/kg), intratracheally, and then received normal saline like the control group; groups 3, 4 and 5 were BLM groups which received sildenafil (5, 10 and 25 mg/kg/day ip, respectively) from 1 week before to 3 weeks after BLM administration. Finally, the animals were killed and the changes of hydroxyproline (HP) and histology were evaluated in lung tissue.

Results: The results showed that HP level was significantly lower in the sildenafil treated rats as compared to BLM group. In addition, the HP changes were well related with the pathological findings.

Conclusion: This study suggests that blocking of type 5 phosphodiesterase may prevent progression of BLM-induced lung fibrosis.

Keywords: Pulmonary Fibrosis, Phosphodiesterase Inhibitor, Oxidative Stress, Bleomycin, Sildenafil



The Protective Effect of Hydro-Alcoholic Extract of Green Coffee (*Coffea arabica*) on Acute Hepatotoxicity Induced by CCl₄ in Rats

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Abstract

Introduction: Carbon tetrachloride (CCl₄) as a chemical agent used to induced oxidative toxicity in hepatocytes. Green Coffee has a wide range of bioactive compounds such as flavonoids (Catechin and Anthocyanins), Chlorogenic Acid, Caffeic Acid and so on. One of the most important of them is the antioxidant compounds contained in the green hydroalcoholic extract. The aim of this study was investigated the hepatoprotective effect of Green Coffee extract (GCE) on acute hepatotoxicity induced by carbon tetrachloride (CCl₄) in rats.

Methods: 36 Wistar male rats were randomly divided into 6 groups (n=6). The animals in the control group, received orally normal saline. In the positive control group CCl₄ (1 mg/kg) was used intraperitoneally as standard hepatotoxic agent. In the three treatment groups different doses of GCE (100, 200 & 400 mg/kg) given daily to each rat for two weeks and in day 14th a single dose of CCl₄ was administered as IP injection to the test animals. The Sixth group (Sham) received the highest dose of GCE (400 mg/kg). Finally, the serum and tissue samples were collected for further biochemical and histopathologic investigations.

Results and Discussion: The results showed that CCl₄ could significantly increase the activity of liver function indicating enzymes such as ALT, AST and ALP in serum. The concentration of TNFα, measured in the liver homogenized tissue sample increased in positive control group. Following administration of the extract, a significant improvement was observed in ALT, AST, ALP and TNFα levels. The histopathological observations confirmed the results obtained through the biochemical assays.

Conclusion: Hydroalcoholic extract of Green Coffee is effective in protection of rat against CCl₄-induced hepatotoxicity possibly via increased resistance to oxidative stress.

Keywords: Green Coffee, CCl₄, Liver, Oxidative stress

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