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Combined gene therapy with chemotherapy for targeted treatment of melanoma

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Introduction:

Melanoma is one of the most life threatening forms of cancers accounts with the 75% of deaths among skin cancer. DNA fragmentation factor (DFF40) is an apoptotic protein which is down regulated in some type of cancers including melanoma. The aim of this study was to trigger cancer cell death by inducing apoptosis mediated using combined DFF40 gene therapy and chemotherapy.

Method:

Recombinant vectors expressing DFF40 under the control of CMV promoter (pcDNA3.1-CMV-DFF40) and a tumor specific promoter (pcDNA3.1-Sur-DFF40) were constructed using standard restriction digestion/ligation methods. B16F10, mouse melanoma, L929, and mouse normal fibroblast cell lines were transfected by constructed plasmids based on the Lipofectamin 2000 transfection protocol. Cytotoxic effect of expression of DFF40 in cancerous and normal cell was determined using cell viability assay (MTT method) 48h after transfection. Additionally, to evaluate synergic effect of gene therapy and chemotherapy 24h after transfection the chemotherapeutic agents, Dacarbazine, was added to each well and after 48h the viability of cells was evaluated by MTT assay.

Results:

Combination of gene therapy and chemotherapy led to a significant decrease of cell survival in B16F10 cells transfected with pcDNA3.1-Sur-DFF40 (42%) and pcDNA3.1-CMV-DFF40 (14%) when compared with empty vector. However, this synergism effect was not observed in normal cell, L929, as the decrease of cell viability in cell transfected with pcDNA3.1-Sur-DFF40 and pcDNA3.1-CMV-DFF40 was 25% and 9%, respectively.

Conclusion:

The proposed approach of combined chemotherapy and gene therapy could be promising for clinical applications in treatment of resistant and metastatic cancers. However, further in vivo and clinical studies are still needed to evaluate the safety and efficacy of this system.

Keywords: gene therapy, melanoma, gene therapy, melanoma

A computational Investigation of point mutation effect on decreasing reteplase neurotoxicity

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Introduction and background:

Reteplase is a non-glycosylated modified recombinant form of human tissue plasminogen activator (t-PA). This thrombolytic drug consists of kringle2 and serine protease domains. The interaction between lysine binding site of kringle2 with amino terminal domain of the NR1 subunit from N-methyl-d-aspartate (NMDA) glutamate receptors and then cleavage of this receptor by the proteolytic activity of reteplase, leads to calcium influx in neurons and then potentiation of excitotoxic neuronal death. This means a neurotoxicity effect from this proteolytic drug. It seems that mutation creation in lysine binding site of kringle2 domain can be interfere with kringle2 and NR1 interaction so it leads to decrease neurotoxicity.

Methods:

In this study three-dimensional structure of NR1 subunit from N-methyl-d-aspartate (NMDA) glutamate and wild reteplase were created by modeller softwere. In addition, sequence of mutated reteplase that is include of a substitution mutation(W81A) in lysine binding site of kringle2 domain was designed and three-dimensional structure of this reteplase was created with modeller software too. The interaction between wild and mutated reteplase with NR1 subunit, was assessed by protein docking in HADDOCK2 server.

Results:

The results showed that mutated reteplase has lower interaction with NR1 subunit compared with wild type. HADDOCK scores were -112±4.5 in the case of mutated reteplase and -131.8±8.1 for wild reteplase. More negative score means better interaction.

Discussion and Conclusion:

Excitotoxic neuronal death is a neurotoxicity effect that occurs by some thrombolytic drugs such as reteplase. It's happening by cleavage of NMDA receptor and then neuron calcium influx. Design of new mutated reteplase that has lower interaction propensity with this receptor, can diminish neurotoxicity of reteplase.

Modulation of Cisplatin-induced p53-mediated Drp1-dephosphorylation and Apoptosis by Cellular Gelsolin in Ovarian Cancer

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Mitochondria are highly dynamic, and the mitochondrial fission is a crucial step of apoptosis. Although Drp1 is believed to be involve in mitochondrial fragmentation, whether and how its dysregulation is involved in the modulation of cisplatin (CDDP) resistance is unknown. Moreover, the involvement of intact cellular Gelsolin (I-cGSN) in this regard is not clear.

Chemo-sensitive and -resistant ovarian cancer cells (OVCA) were treated with CDDP. Apoptosis, protein contents and phosphorylation were assessed by nuclear Hoechst staining and Western blot, respectively. The I-cGSN and p53 involvement in CDDP-induced Drp1 processing and apoptosis were examined by siRNA or cDNA. Protein interaction is also detected by Proximity Ligand assay (PLA) and Western Co-IP.

a) CDDP-induced Drp1 and p-Drp1 (ser637) down-regulation, ser616/637 ratio enhancement is not observed in chemoresistant ovarian cancer cells. b) CDDP increased p-p53 (ser15)-Drp1 and decreased GSN-Drp1 interaction in chemosensitive but not resistant cells, a response which is dependent to p53. c) I-cGSN inhibits CDDP-induced Drp1 and p-Drp1 (ser637) down-regulation and apoptosis in ovarian cancer cells

These findings demonstrate that p53 (a) mediate Drp-1 dephosphorylation (ser637), (b) mitochondrial fragmentation and involved in CDDP-induced apoptosis in OVCA cells, and (c) dysregulation of mitochondrial dynamics by I-cGSN may in part be involved in the pathophysiology of CDDP resistance.

Key words: Cisplatin, p53, Drp-1, gelsolin, mitochondrial dynamic, ovarian cancer

Preparation of chitosan Biomembranes conjugated by endolysin chimeric antibiotic protein for wound healing

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Abstract

Over the recent years, resistance to antimicrobial drugs has become a growing global concern. The rise of these multi-drug resistant bacterial strains highlights the need to develop new antimicrobial compounds. Bacteriophage-derived enzymes, so-called endolysins with the ability to disrupt cell walls represent possible alternatives to conventional antibiotics. Recombinant Cysteine/histidine-dependent amidohydrolase /peptidase (CHAP) and amidase are known as catalytic domains of the bacteriophage-derived endolysinLysK and were previously reported to show lytic activity against methicillin-resistant Staphylococcus aureus. In the current study, the antimicrobial activity of CHAP-amidase was evaluated in conjugation with chitosan bio-membrane in order to heal wounds. Briefly, the recombinant pET-22b plasmid in E. coli strain BL21 (DE3) cells were cultured in TB medium containing 100 µg/mL of ampicillin in addition 2% Glucose as well as 1% glycerol. Furthermore, protein expression was induced by 1 Mm IPTG in 37ºC for 4h at logarithmic phase. Protein purification was done by Ni-NTA column by 300 mM Imidazole for protein elution. Due to CHAP-amidase conjugated chitosan bio-membrane synthesis, 1mg of protein was mixed with 1% chitosan in 0.1M acetic acid solution, the bio-membrane completely dried in 40ºC for 24h. 0.1% TPP solution was prepared as cross linking agent. The physical characterizations of bio-membrane were estimated by FTIR and SEM. Furthermore water absorption and erosion analysis were essayed. The expression and purification of the proteins were confirmed by SDS-PAGE and western blotting. FTIR results confirmed covalent conjugation of CHAP-amidase on chitosan membrane as well as TPP attachment as a cross linking agent. SEM images showed smooth surface of membrane with tiny pores which is compatible as a wound dressing. Water absorption showed capability of bio-membrane for wound draining and the stability of bio-membrane was confirmed by erosion assessment. All of these findings favor the notion that the chimeric endolysin conjugated on chitosan biomembrane produced in our work may offer promise for the development of an efficient therapeutic agent and antimicrobial dressing for wound healing in the future. However, further investigation is required to provide more evidence on different aspects of the antibacterial activity of this biomembrane.

Key Words: CHAP-amidase, Antibiotic protein, Bio-membrane, Chitosan, Wound.

Boosted wound healing activities by Epidermal Growth Factor conjugated chitosan nanoparticles

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Abstract

Poor wound healing and scar formation remains a critical problem in daily surgical practice. Chitosan exhibits unique properties such as biocompatibility, biodegradability and bacteriocidity. Moreover, Chitosan nanoparticles can transiently open the gap junctions between cellular membranes to accelerate drug delivery through skin layers. One of the drugs used alongside chitosan andis effective in treating wounds, is epidermal growth factor (EGF). EGF signals new skin cells to be created, counteracting the thinning of skin that occurs with age. In the current study, the EGF conjugated chitosan nanoparticles (EGF-CH) were prepared, then, physical and cellular functions have been characterized.
Chitosan nanoparticles were prepared by Ion gelation method with 1% chitosan in 1% of acetic acid. The chitosan nanoparticles were prepared with drop wise addition of TPP (0.1% w/v) under ultrasonication in 7 minutes at 4˚C following shaking on magnetic stirrer for 1 hr in 800 rpm. The resulting mixture was dialyzed overnight at 4˚C in PBS buffer. The nanoparticle solution physical and cellular characterizations were estimated by DLS, TEM and FTIR. Moreover, the cytotoxicity assay, Cellular proliferation as well as migration were evaluated by MTT after 24h, 48h and 72h,and then the scratch test was assessed after 24h and 48h on HFF-1 (Normal Human Fibroblast) cell line.
Physical characterization showed the final nanoparticles adjusted to 130±10 nm by DLS analysis. Furthermore, the TEM imaging illustrated absolute diameter near 90±10 nm. FTIR results confirmed covalent cross-link made in Chitosan TPP and EGF-Chitosan samples in turn. MTT assay verified biocompatibility of nanoparticles during 24 h and proliferation assay approved the role of EGF-Chitosan in inducing cell multiplying effectively. Migration assay depicted the massive influence of final nanoparticles on cell movement in in vitro assay. All of these findings favor the notion that the EGF conjugated chitosan nanoparticles produced in our work may offer promise for the development of an efficient therapeutic drug for wound healing and anti-aging treatment in the future. However, further investigation is required to provide more evidence on different aspects of the molecular activity and stability of this nanoparticle in in-vivo.

Key Words: Chitosan nanoparticles, Wound healing, Epidermal Growth Factor, Skin

A novel electrochemical aptasensor for bisphenol A: fabrication and efficacy assessment on real samples

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Abstract

Bisphenol A (BPA) is an important organic monomer which is widely applied in food packaging industries and water containers. The release of BPA into drinks and food resulting in serious adverse effects. In this study, a novel electrochemical sensing strategy was developed based on nontarget-induced bridge assembly and aptamer (Apt) extension reaction triggered by terminal deoxynucleotidyl transferase (TdT). Apt and CS (complementary strand) were attached on the surface of SPGE. Then the analytical performance of aptasensor was evaluated. Afterwards the specificity of the aptasensor was assessed. Next, the designed aptasensor was applied to determine the concentrations of BPA in the spiked tap water samples. This electrochemical sensor is based on nontarget-induced extension of aptamer length triggered by TdT and formation of bridge on the surface of electrode. The concentration of TdT was adjusted at 10 U. The concentration of immobilized Apt on the surface of electrode was also optimized at 400 nM. DPV method was used to investigate the performance of the proposed aptasensor in quantitative analysis of BPA. To assess the selectivity of the aptasensor, BPA, BPB, BPS, estradiol and testosterone were chosen and tested using the designed sensing system. In the absence of BPA, the 3′-end of Apt was extended by TdT and formed a bridge (Apt-CS) on the surface of electrode. This procedure restricted electron transfer, leading to improving the sensitivity of the sensing platform. The designed aptasensor could selectively and sensitively detect BPA with a detection limit of 15 pM. Moreover, the aptasensor showed good accuracy for detection of BPA in tap water and grape juice samples.

Key Words: Bisphenol A, Aptamer, Electrochemical sensor.

Optimization a preparation method for cationic nanoliposome containing soluble Leishmania antigens (SLA) and characterization of their physicochemical properties

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Liposome technologies are one of the fastest growing scientific fields that have been shown to be an effective adjuvant formulation to elevate the immunity to a large variety of bacterial, protozoan, viral and tumor cell antigen (1,2).

Refers to a variety of disease, cutaneous lesions to potentially fatal visceral forms, which is caused by different species of protozoan parasites called leishmania (3). In the world, 2 million people are infected every year, and 10% are exposed to the infection. The disease has been endemic in Tehran, Shiraz, Mashhad, Sabzevar, Neyshabor and Bam (4). Despite numerous efforts and studies to produce an effective vaccine against Leishmaniasis, None have been reported satisfactory results in human for this disease yet (5). According to studies, we have selected a formulation required to be optimized and different buffers were studied as effective factors. The SLA and bovine serum albumin (BSA) proteins were used to prepare the formulation. Liposomes were prepared with 4 millimolar concentration of 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) as a cationic lipid either individually or in combination with cholesterol containing SLA. Then, some tests including average particle size, zeta potential, poly dispersity index (PDI), and entrapment percentage of SLA has been PERFORMED on the final products as well as quality study tests for presence of protein through SDS-PAGE method. Finally, based on the obtained results, the optimal formulation for SLA-containing products was selected as formulation containing DOTAP and cholesterol (4 millimolar concentration each) prepared via the film method accompanied by sonication in the HEPES buffer, and the formulation containing DOTAP and cholesterol (4 millimolar concentration each) prepared via the film method accompanied by sonication in 5% dextrose solution was selected as the optimal formulation for the product containing BSA.

Hybrid Silica-coated Gd-Cu-In-S/ZnS Bimodal Quantum Dots as a Epithelial Cell Adhesion Molecule Targeted Drug Delivery and Imaging system

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Dual-modal imaging probes based on fluorescence (FL) and magnetic resonance (MR) modalities have attracted great attention due to their ability to combine the target specificity and high penetration into body tissues. In this study, we developed a potent nanocarrier with an effective photo luminescent emission and MR imaging capacity to deliver the doxorubicin to breast cancer 4T1 cells. The nanocarrier was fabricated by coating of quantum dots (QDs) with mesoporous silica followed by amine functionalization of the silica surface. Then, the doxorubicin (DOX) was loaded into the silica pores and heterofunctional PEG was covalently bound to the surface of core-shell quantum dot mesoporous silica nanoparticles. In order to target the DOX-loaded nanoparticles, the EpCAM DNA aptamer was attached on the surface of the DOX-loaded PEGylated nanoparticles. The synthesized NPs were analyzed for their size distribution, morphology, zeta potential and magnetic susceptibility using TEM, SEM and VSM analysis. The QD-encapsulated mesoporous silica revealed spherical shapes with an average particle size of 100 nm. The maximum encapsulation efficacy of doxorubicin in the silica pores was 25%. The in vitro release assessment demonstrated the pH-sensitive release of doxorubicin from the designed formulations. Moreover, the cellular uptake studies revealed that the EpCAM aptamer enhanced the cellular uptake of doxorubicin in the 4T1 cell line. The in vitro cytotoxicity assays indicated that the aptamer targeted nanoparticles showed greater cytotoxicity than both non-targeted NPs and free DOX toward 4T1 and MCF-7 cell lines. The in vivo studies in 4T1 tumor-bearing Balb/c mice demonstrated that EpCAM DNA aptamer could specifically deliver the DOX-loaded nanoparticles into the tumor tissue and cause remarkable inhibition of tumor growth as compared to non-targeted formulation and free DOX. Moreover, the in vivo MR and fluorescent imaging in 4T1 tumor bearing mice confirmed the accumulation and residence of targeted system in tumor tissue even 24 h post-injection.

This paper presents a novel system for preparing bimodal imaging theranostic NPs through hybridization of silica and magnetic-fluorescent quantum dots.

Keywords: Bimodal imaging; Quantum dots; EpCAM; DNA aptamer; Targeted drug delivery

Investigation inhibitor compounds of α-synuclein fibrillation associated with Parkinson's disease by in silico molecular docking studies

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Abstract:
Parkinson's disease (PD) after Alzheimer's are among the most frequent neurodegenerative diseases in the elder people. The main charactristic of PD is the accumulation of proteins Lewy Bodies (LB) and Lewy Neurites (LN) in dopaminergic neurons. Proteinous fibrils of alpha-synuclein (ASN) are the main component of LB and the process of ASN fibrillation plays main role in the pathology of other synucleopathies. In this regards the strategies for blocking fibrillation ASN is a brilliant solution for these kinds of cureless diseases. One of the approaches in inhibiting ASN fibrillation is using the small molecules such as Baicalein, Myricetin, Quercetin, Tricetin, Luteolin and EGCG and other flavonoids (D-258, T-601, D-406, G-500, 6-HP compounds) with meaningful fibrillation inhibitory activity. According to the different behaviors of the small molecules against ASN , its neurotoxicity and the mechanism of interaction between them and ASN , we analyzed, molecular interactions by an in silico method. In this regard, a few small molecules containing mentioned compounds were selected for comparative studies and binding affinity by in silico approaches in order to inhibit the alpha-syncoline protein fibrillation process. Using the ZINC15 and drug bank databases, also Hyperchem, Chimera 11 and molegro virtual the docker 6.0 software structure in (SDF) format of these compounds was determined and then docking and screening studies were conducted in alpha-syncloin interaction positions. The results showed EGCG in terms of bond strength, binding energy (kcal / Mol-125) and seven hydrogen bonds was the best for ASN relative to other compounds?.also, Experimental studies have shown that this small molecule has high inhibitory activity against fibrillation and also ASN toxicity. According to these results, we can have deeper knowledge about the mechanism of inhibition of ASN and the way of interaction and the place of it with molecular interaction between small molecules and ASN and the way for designing the new analogues and finding effective drugs against synucleinopathies.

Key Words: Parkinson's disease, Alpha-synuclein, Small molecule, fibrillation, Docking

Systematic mining of gene co-expression network suggests new drug repositioning in Duchenne Muscular Dystrophy through regulation of COL1A1

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Abstract:
Duchenne muscular dystrophy (DMD) is identified as a severe X-linked recessive neuromuscular disease. In this study we aimed to use a weighted gene co-expression network analysis (WGCNA) to identify the main attributing modules, hub genes, and mRNA-miRNA regulatory network in DMD disease as novel biomarkers. Module preservation analysis was performed to compare our results with other DMD datasets. Moreover, enrichment analysis was done to reach significant biological pathways. Our result showed a module, which has significant correlation with DMD state. Also, genes set enrichment analysis indicated that genes of this module mostly involved in some biological activities, including positive regulation of collagen fibril organization, cellular response to amino acid stimulus, and response to amino acid, and etc. Co-expression network was constructed using hub genes of correlated module, which are named as TYRP1, CFAP46, COL3A1, SBF1, and SPARC. Finally, DGIDB database reveal rizatriptan, paclitaxel, ocriplasmin, flanvotumab as top drugs correlated with hubgenes. Our findings specified one important module and explained its genes and biological activities and potential drugs which may use as potential targets for therapeutic goals.

Key Words: Co-expression network, Drug-target network, Duchenne muscular dystrophy, WGCNA

A novel p28-Apoptin chimeric with enhanced cytotoxic effects on breast cancer cell lines

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Abstract:
Backgrounds: To address chemotherapeutic drugs limitation and improve patient survival, several therapeutic strategies are in development, including targeted therapies (1, 2). Peptide-based drugs have shown promising results in overcoming these limitations while also addressing the issue of heterogeneous tumors (3). In this study, we designed and produced a chimeric protein containing p28 as a homing and killer moiety, and apoptin as a killer moiety. The goal was to find effective peptide combinations for the targeted treatment of breast cancer arising from different mechanisms.
Methods: Different linkers were evaluated when designing the chimeric protein. Three-dimensional structure predictions of chimeric proteins with different linkers were carried out by Modeller 9.19, and their validation and analysis were performed by RAMPAGE. After linker selection, cloning, expression and purification of the chimeric protein, we evaluated its cytotoxicity against MCF7 and MDA-MB-231 breast cancer cells and HEK-293 normal cells by the MTT assay
Results: Results showed that a cleavable linker, including furin cleavage sites, is preferred over other linkers. The chimeric protein was then successfully expressed in E. coli and purified by affinity chromatography under native conditions, then confirmed by SDS-PAGE and Western blot analysis. Compared with apoptin alone, the chimeric protein showed significantly higher toxicity against breast cancer cell lines in a dose-dependent manner. The IC50 values of the chimeric protein for MCF7 and MDA-MB-231 cells were 38.55 µg/mL and 43.11 µg/mL, respectively. There was no significant cytotoxic effects on the normal HEK293 cell line.
Conclusion: This study demonstrates that fusion of p28 peptide to a potent protein could provide an effective method for tumor targeting. Further, in vitro and in vivo studies of this novel chimeric protein are underway.

Cold atmospheric pressure plasma induced chemosensitivity effect in breast cancer cells

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Abstract

Chemo resistance is the major problem in cancer therapy. Cold atmospheric plasma (CAP) is a novel method to inhibition of tumor growth. CAP is a partly ionized gas, which is generated in a high-voltage electric field in a low pressure.The purpose of this study is breast cancer cell death induction by cold atmospheric plasma in combination with paclitaxel chemotherapy drug. The combination therapy effect on MCF-7 and MDA-MB-231cells viability was evaluated by MTT assay. Real time-PCR was used for the expression level analyzing of mRNA (P53 and CASPASE3). In addition, cell cycle changes under the influence of paclitaxel and CAP were estimated by flow cytometry. A significant expression of P53 and CASPASE 3 has been shown in cells at 24, 48 and 72 hours after treatment (p=0.002). An increased chemo-sensitivity has been detected to paclitaxel in both of cell lines. Also, it showed that cell cycle arrest has increased in G2phase with the combined effect of CAP and paclitaxel in MDA-MB-231 cells. The CAP treatment induced breast cancer cell sensitivity to paclitaxel.

Preparation and evaluation of cellular uptake of liposomes modified with cell penetrating lipo peptides

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O15

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Abstract:
Raloxifene HCl (RH) is a highly insoluble and metabolized serum estrogen receptor modulator approved for using in the treatment of osteoporosis (1). RH belongs to the class II of BCS (Biopharmaceutics Classification System) and due to its extensive first pass metabolism, the bioavailability of RH is only 2% (2,3). Therefore, the objective of the present work was to enhance the solubility and dissolution rate of RH by developing novel electrosprayed nanoparticles. Various nanoparticles containing RH and different ratio of poly (methyl vinyl ether-co-maleic acid) (PMVEMA) were electrosprayed. The voltage, distance of needle to the collector, flow rate of the solution, and polymeric percentage were optimized according to the size of the nanoparticles and drug solubility. Finally, the optimized formulation was characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD), differential scanning calorimetry (DSC), and Fourier transform infrared spectroscopic (FTIR) analyses. The pharmacokinetics of RH was evaluated in Wistar rats by oral administration of the optimum formulation. The anti-osteoporotic effects were studied in female ovariectomized rats. Animals were treated with 6 mg/kg/day for 2 months then serum calcium, phosphorous, and alkaline phosphatase levels were measured. All developed formulations of the RH loaded electrosprayed nanoparticles showed remarkably enhanced solubility compared to the free drug. Mean particle size of the optimized nanoparticles was 201.73.9 (?)± 62.60 nm and the saturation solubility increased up to 219.91 ± 14.68 µg/mL which is about 10-fold better than the pure drug. Moreover, the XRD and SEM tests displayed that the drug presented in the amorphous state in the nanoparticles. FTIR and DSC tests revealed no interaction between the polymer and the drug. Serum calcium, phosphorous, and alkaline phosphatase levels were significantly decreased in ovariectomized rats receiving oral RH NPs (P0.05). Oral bioavailability of NPs showed 7.5-fold increase compared to the pure drug. In conclusion, the electrospraying method was showed to be a novel appropriate technique for enhancement of the solubility of raloxifene HCl using PMVEMA.

Key Words: Electrospray, Raloxifene, solubility enhancement, poly methyl vinyl ether maleic acid, pharmacokinetic

Green-synthesized mesoporous silica nanoparticles (MSNs) for effective iron adsorption in acute poisoning in rat model

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O16

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Abstract:
Iron poisoning can induce different toxicities, besides there is no effective sorbent for acute iron poisoning detoxification. So we synthesized and characterized different nanoparticles and evaluate for iron adsorption.
In the present study non-functionalized and aminopropyl-functionalized MSNs were synthesized by using a non-surfactant template (tannic acid) and surfactant template (CTAB) methods for iron adsorption in ferrous sulfate acute poisoning in rat. The nanoparticles were characterized by particle size analyzer, zeta potential, transmission electron microscopy (TEM), elemental analysis (CHN), Fourier transformed infrared spectroscopy (FTIR), Thermogravimetric Analysis (TGA) and N2 adsorption–desorption (BET). Then the effects of different parameters such as pH, exposure time, iron concentration and amount of nanoparticles on the adsorption capacity were studied.
The hydrodynamic size of aminopropyl-functionalized MSNs with tannic acid template (TA-MSN-NH2) was 189.4 nm with polydispersity index (PDI) below 0.1 and positive surface charge. The surface area of TA-MSN-NH2 was 370.28 m2/g based on BET theory. It was indicated that TA-MSN-NH2 exhibited maximum adsorption of Fe2+ in in vitro study so it was selected for in vivo studies. In vivo experiments on rats showed Fe2+ concentration was significantly dropped down after nanoparticle administration with doses of 1 g/kg. The results of this study indicated that TA-MSN-NH2 could be used as an antidote agent against iron poisoning.
Key Words: tannic acid, iron poisoning, mesoporous silica nanoparticles (MSNs)

Cyproterone Acetate-Loaded Lipid Nanoparticles: Formulation Optimization and Evaluation of the Effect of Nanoparticles Size on Skin Penetration and Follicular Targeting

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Abstract:
Introduction: Cyproterone acetate (CPA) is used to treat various skin disorders such as acne, hirsutism and alopecia. Due to the limited skin penetration of CPA, nanostructured lipid carriers (NLCs) with different size ranges were considered in this study in order to enhance skin penetration and to target hair follicles.
Materials and Methods: Different variables including; surfactant/lipid ratio, mixing rate and addition time of organic phase to aqueous phase were utilized in optimization process in order to fabricate nanoparticle at specified particle size ranges to target the particle to hair follicles. Drug loading, drug release and morphological assessment were assessed for each targeted size (100, 300 and 600 nm). Ex vivo skin penetration was also investigated using Franz diffusion cells. In vivo follicular targeting was also assessed using rhodamine B-loaded micro and nanoparticles.
Results and Discussion: Statistical data showed that the model is significant (p-value of 0.0001) to prepare lipid based nanoparticle having specified size ranges. The results showed that there is interaction between different parameters and 3-D graphs indicated the optimum point of interactions between various parameters. Drug entrapment efficiency was 99.03%. Results revealed that 60-85% of drug was slowly released from lipid nanoparticles during 72 hours. Drug release pattern from nanoparticles was best fitted to Higuchi model which is a suitable model for matrix based delivery systems. CPA-NLC with average diameter of 600 nm had better penetration and deposition in dermis-epidermis layer, also CPA-NLC 100 and 300 nm were significantly increase drug penetration in dermis-epidermis in comparison to free CPA. Follicular targeting results revealed that NLC 300 nm had the best accumulation capacity in hair follicles.
Conclusion: CPA-NLC with average diameter of 300 nm would be a promising topical novel drug delivery system for specific targeting of hair follicles and sebaceous glands to treat androgenic skin disorders.

Key Words: Cyproterone acetate, Solid lipid nanoparticles (SLNs), Nanostructured lipid carriers (NLCs), Particle size, Skin penetration and follicular targeting

Synthesis of PEG-PCL polymersomes containing Doxorubicin and indium-copper-gadolinium-zinc sulfide Quantum dots: in vitro evaluation

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Introduction:

Polymersomes are self-assemble core/shell nanostructures which can be used as a theranostic platform with many advantages in comparison with other kinds of nanostructures. QDs are nano-crystals with high photo-stability, special optical, and electrical properties, applying for construction of biological diagnostic probes. Synthesis of indium-copper- zinc -gadolinium sulfide QDs can provide dual MR and florescent imaging with the benefit of not being toxic unlike the other metal-based QDs.

Methods:

Indium-copper-gadolinium-zinc sulfide QDs were synthesized and characterized. Hydrophobic QDs were encapsulated in the bilayer of polymersomes with single emulsion method. Hydrophilic Doxorubicin (loaded in the core) and QDs encapsulated in polymersomes via double emulsion method. The florescence and magnetic properties of bare QDs and the prepared theranostic polymersomal formulation were studied precisely. Probable toxicity of PEG-PCL polymersomes accompanied by QDs examined in two different cell lines. The in vitro drug release from the polymeric vesicles was investigated in pH 5.5 and 7.4 at 37ºC during 9 days. The chemotherapeutic potential of the Doxorubicin loaded nanopolymersomes formulation was evaluated in 4T1 and MCF7 cell line in vitro (from 0.78 to 50 µg/ml concentration).

Results:

Inductively coupled plasma (ICP) results demonstrated that the synthesized QD composed of %17.66 Gd %16.33 In %6.79 Cu %9.33 Zn. Vibrating sample magnetometery (VSM) test showed the magnetic property of the QDs and its related polymersomal formulation. On the other hand, spectrofluorometer confirmed the fluorescence properties of the prepared formulation. The obtained data illustrated that the polymersomes were capable of controlled and sustained release of doxorubicin for a period of 9 days. MTT results showed %85 to %95 cell survival in both 4T1 and MCF7 cell lines after 24 h of exposure to the polymersomes-encapsulated-QDs in comparison with control cells. In addition, it was demonstrated that free DOX have higher cytotoxicity (IC50= 1.4µg/mL) than DOX loaded nanopolymersomes (19.6 µg/mL) in MCF7 cell line which could be attributed to the structural stability and controlled release property of the polymersomes.

Novel Electrosprayed Nanoparticles for Enhanced Aqueous Solubility, Oral Bioavailability and Anti-Osteoporotic Effects of Poorly Water-Soluble Raloxifene Hydrochloride

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Abstract:
Raloxifene HCl (RH) is a highly insoluble and metabolized serum estrogen receptor modulator approved for using in the treatment of osteoporosis (1). RH belongs to the class II of BCS (Biopharmaceutics Classification System) and due to its extensive first pass metabolism, the bioavailability of RH is only 2% (2,3). Therefore, the objective of the present work was to enhance the solubility and dissolution rate of RH by developing novel electrosprayed nanoparticles. Various nanoparticles containing RH and different ratio of poly (methyl vinyl ether-co-maleic acid) (PMVEMA) were electrosprayed. The voltage, distance of needle to the collector, flow rate of the solution, and polymeric percentage were optimized according to the size of the nanoparticles and drug solubility. Finally, the optimized formulation was characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD), differential scanning calorimetry (DSC), and Fourier transform infrared spectroscopic (FTIR) analyses. The pharmacokinetics of RH was evaluated in Wistar rats by oral administration of the optimum formulation. The anti-osteoporotic effects were studied in female ovariectomized rats. Animals were treated with 6 mg/kg/day for 2 months then serum calcium, phosphorous, and alkaline phosphatase levels were measured. All developed formulations of the RH loaded electrosprayed nanoparticles showed remarkably enhanced solubility compared to the free drug. Mean particle size of the optimized nanoparticles was 201.73.9 (?)± 62.60 nm and the saturation solubility increased up to 219.91 ± 14.68 µg/mL which is about 10-fold better than the pure drug. Moreover, the XRD and SEM tests displayed that the drug presented in the amorphous state in the nanoparticles. FTIR and DSC tests revealed no interaction between the polymer and the drug. Serum calcium, phosphorous, and alkaline phosphatase levels were significantly decreased in ovariectomized rats receiving oral RH NPs (P0.05). Oral bioavailability of NPs showed 7.5-fold increase compared to the pure drug. In conclusion, the electrospraying method was showed to be a novel appropriate technique for enhancement of the solubility of raloxifene HCl using PMVEMA.

Key Words: Electrospray, Raloxifene, solubility enhancement, poly methyl vinyl ether maleic acid, pharmacokinetic

Effect of high pressure homogenization on physicochemical properties of Curcumin nanoparticles prepared by antisolvent crystallization using different stabilizers

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Absract

Dissolution enhancement of poorly water soluble drugs is a major challenge in pharmaceutical industry. The aim of this study is to fabricate curcumin nanoparticles by antisolvent crystallization in the presence of PVP-K30, HPMC E3, Poloxamer 188, and Soluplus with various concentrations as a stabilizer. The effect of high pressure homogenization on properties of curcumin particles is also investigated in this study. The antisolvent crystallization method followed by freeze drying (CRS-FD) and also antisolvent crystallization and high pressure homogenization followed by freeze drying (HPH-FD) were employed to modify curcumin particles. Physical mixtures of the drug and additives were also prepared for comparison purposes. The solid state analysis (DSC, XRPD, and FT-IR studies), particle size measurement, morphological analysis, saturation solubility, and dissolution behavior of the samples were investigated. The curcumin was crystallized without using stabilizer produced polymorph curcumin with lower crystallinity and higher solubility. The samples obtained in the presence of stabilizers showed higher solubility compared with its physical mixtures counterpart. It was found that the stabilizers used in the current study were capable of inhibiting the crystal growth of particles during crystallization. High pressure homogenizer method generated smaller particles compared with those samples that were not subjected to high pressure homogenizer. Particles obtained via HPH showed better solubility and dissolution rate compared with those samples that HPH was not employed. The effect of high pressure homogenization on dissolution rate is more pronounced for samples with lower stabilizer ratio. The samples prepared with high pressure homogenizer using 50% PVP showed 25-fold higher solubility compared with untreated curcumin. Generally, it can be concluded that the method of preparation, selection of suitable stabilizer, and concentration of stabilizer play a critical role on particle size and dissolution rate of curcumin.

Providing walnut toothpaste for suitable appearance, pharmaceutical properties and acceptable stability.

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Introduction: Toothpastes are preparations which have been used for oral health and brush on the teeth. Hard shell of the walnut (Juglans regia) has antibacterial and abrasive properties, adsorbs dyes which may induce stain or decay teeth. Because of vast acceptability of the herbal medicine, the main aim of this study was formulation of dentifrice from walnut hardshell and to evaluate the physical appearance, organoleptic, abrasion of the formulations were studied.

Methods: Hardshell of the walnut was completely separated from the other parts of the plant, washed, dried and milled to a fine powder and was passed through a sieve number of 200.Finally 4 formulations were prepared and evaluated for their physical, organoleptic, abrasion properties and microbial contamination.

Results: About 4 formulations were prepared from walnut hardshell. Stability tests during 3-month showed an acceptable physical stability. The pH of formulations were determined 5.5 - 7.2 and their fluoride content was determined to be between 4.32 to 11.76. The abrasion, lead and arsenic content of the formulations were within the eligible range and the all formulation were free of microbial contamination. In all, most of the characteristics of formulations were in accordance to the national Iranian standard Institute and were in the acceptable range especially.

Conclusion: This research project indicated capacity of providing walnut toothpaste for suitable appearance, pharmaceutical properties and acceptable stability.

Keywords: toothpaste, walnut shell, formulation

The evaluation of cytotoxic activity of soft corals: Junceella juncea, Cavernularia sp., Menella sp., and Virgularia sp. of Persian Gulf

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Introduction and background: Methanol : Ethyl acetate (1:1) extracts of five species of soft corals in Persian Gulf were screened for cytotoxic activity against the growth of two cancer cell lines(1-3).

Material and method: Cytotoxic activity was measured by using MTT tetrazolium salt colorimetric assay to measure cytotoxicity, cell proliferation and cell activation.

Result and discussion: All the extracts showed moderate to low activity comparable to positives and negatives controls. It was observed Methanol : Ethyl acetate (1:1) acetate extracts suppressed growth and proliferation of MCF-7 cells and OVCAR-3 cells that were derived from a breast cancer cell line and ovarian cancer cell lines, respectively. Morphological features of treated cells and characteristic DNA fragmentation revealed that the cytotoxicity was due to induction of apoptosis. This study confirms that due to their cytotoxic effects upon cells during culture Menella sp. had the best activity against OVCAR-3 cells (with IC50= 281.843µg/ml).

Conclusion: These species are worthy candidates for further bioassay-guided fractionation to identify active constituents.

Keyword: cytotoxicity, soft corals species, MTT assay

Dose-dependent Effect of Root Extracts of Eurycoma longifolia Jack on Testosterone Regeneration in Adult Male Rats

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O25

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Abstract

Introduction

Physiologic testosterone levels are essential in the development and maintenance of sexual organs and their functions. For centuries, men in south East Asia have used home remedies prepared from the long twisted roots of Eurycoma longifolia Jack (better knowns as Tongkat Ali) to improve male prowess and fertility. The objective of this study was to investigate the effect of root extracts of Eurycoma longifolia Jack on testosterone regeneration in adult male rats.

Materials and Methods

Three different extracts viz. ethanol (ETHEL), methanol (METEL), and aqueous (AQUEL) were prepared from long twisted roots of E. longifolia by hot maceration technique. Healthy adult male Sprague Dawley rats (250 – 300 g) were randomly divided into (i) Control, (ii) ETHEL, (iii) METEL, and (iv) AQUEL groups. Each treatment group was further subdivided into four dosing groups viz. 25, 50, 100, and 200 mg/kg (n=6). All drugs were given via oral gavage daily for up to 6 weeks. At the end of the treatment, rats were sacrificed via CO2 asphyxiation and adequate blood samples were collected by cardiac puncture for the determination of serum testosterone levels.

ResultsA dose-related increment in total serum testosterone concentrations was evident at higher doses in METEL-treated animals where its daily oral administration at 100 and 200 mg/kg substantially elevated serum testosterone levels as compared to control after 6 weeks of treatment. Meanwhile, alterations in testosterone concentrations of serum samples from animals treated with similar doses of ETHEL and AQUEL extracts were not statistical importance. All treated animals in all dosing groups including control group displayed major body weight gain by the end of the treatment course. Even though, vital organs showed no major changes in weight some reproductive organs like ventral prostate and seminal vesicles experienced significant increase in gross weight in METEL (200 mg/kg) group as compared to normal control.

Conclusion

Long-term treatment with METEL at relatively higher doses for six consecutive weeks elevated total serum testosterone concentrations indicating the effectiveness of E. longifolia root extract as a potential aphrodisiac in rodents.

Keywords: Eurycoma longifolia, Tongkat Ali, Serum Testosterone, Aphrodisiac.

Clarithromycin synergistically enhances doxorubicin-induced apoptosis through inhibition of autophagy in MCF7 cells

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A growing number of studies have reported the correlation between autophagy and apoptosis, mostly, in an inhibitory manner, meaning autophagy blocks the induction of apoptosis. Due to this fact, using autophagy inhibitors in combination with chemotherapy has become a novel chemotherapeutic strategy. In the present study, we investigated if the effectiveness of doxorubicin (DOX) was augmented by using clarithromycin (CAM) as an autophagy inhibitor. The cytotoxic effects of DOX and CAM alone and in combination, on MCF7 cells were designed according to Chou-Talalay method and assessed by MTT assay. Also, the involvement of autophagy in the DOX-induced apoptotic death of MCF7 cells was investigated using flow cytometry. Simultaneous treatment with DOX (0.05, 0.1, 0.2, 0.5, 1, 2 µM) plus CAM (100, 500 µM) caused a significant reduction of DOX IC50 value. The median effect analysis generated by Compusyn software revealed that DOX and CAM combination in vitro exerted synergistic effect. Flowcytometry analysis indicated that CAM at 100 µM caused an accumulation of LC3II, and increased LysoTrackerGreen (LTG) signal, suggesting that CAM inhibits autophagic flux at late stage. On the other hand, DOX caused induction of autophagy flux that was confirmed with significant increasing in LC3II level but not LTG signal. Combination with CAM blocked autophagy flux induced by DOX that led to enhanced apoptosis. In summary, this study is in accordance with this theory that inhibition of autophagy would enhance apoptotic cell death of anti-cancer drugs.

Keywords: autophagy, apoptosis, breast cancer, clarithromycin

Evaluation of anticonvulsant activity of new isatin-hydrazone derivatives in mice

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Introduction:

Epilepsy is a major neurological disorder and up to 5% of the world populations experience epilepsy in their lifetime. Treatment of epilepsy is based on the pharmacotherapy and many drugs with different chemical structures are used. However, only 70% of patients respond to pharmacotherapy and drug resistance in 10-30 % of patients is an important factor that shows requirement for new antiepileptic drug development with more efficacy and less side effects. In this research, anticonvulsant activity of a new synthesized group of isatin-hydrazone compounds was evaluated by PTZ and MES methods.

Methods: Male swiss mice (20-25 g) were used and different doses of the 10 compounds were administered (30,100,300 mg/kg i.p, dependent on the response, n=4-6). Thirty minutes later PTZ was injected (100 mg/kg) and the number of death following tonic and clonic seizure was noted. In MES method, 30 min after injection of the compounds, maximal electroshock seizure was elicited via a 60 Hz alternating current of 50 mA intensity for 0.2 s via ear electrodes. Abolition of the hindlimb tonic-extensor component of the seizure indicated as protection. Diazepam was used as a standard drug in both tests and a group of animals received the solvent.

Results: In PTZ method, two compounds showed maximum 33% protection. Moreover, all compounds showed 33–100% protection against MES-induced seizures.

Conclusion: Our results indicate favorable anticonvulsant profile of the new isatin-hydrazone compounds. More studies are needed to explore their exact mechanism of action.

Green synthesis of highly luminescent carbon quantum dot using Asafoetida as carbon precursor and its antimicrobial activity

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Introduction and background:

Carbon quantum dots (CQDs) are a new class of metal-free fluorescent nanoparticles that have attracted interests of scientists because of their simple synthesis, low toxicity, good biocompatibility, and easiness of surface modifications (1). They consist of a fraction of nanometer-sized carbon core surrounded by amorphous carbon frames. Recently, several studies have been carried out on CQDs bactericidal properties (2). The antibacterial properties of CQDs depend on their surface functional groups. Therefore, selection of carbon precursor in CQDs synthesis is almost importance. Ferule asafoetida Linn. Contains sulfur-containing compounds. Recent studies have also showed its antimicrobial and antitumor activities (3, 4). Thus, sulfur doped CQDs can be prepared using this resin as carbon source and may infer antibacterial activity effectively as its essential oil.

Methods:

Carbon quantum dots were prepared by hydrothermal methods at 200□C and were characterized by different spectroscopic and microscopic methods. Antimicrobial activity was evaluated by the well agar diffusion against Gram positive/Gram negative bacteria and yeast.

Results:

Highly luminescent sulfur doped CQDs that showed emission at 450 nm while excited at 340 nm were prepared. The mean particle size was 7.51 nm. The resultant particles exhibited effective antimicrobial and antifungal activity against test microorganism.

Discussion and Conclusion:

The CQDs were stable and highly luminescent. They inhibited bacterial growth in vitro. This growth inhibition may attributed to the electrostatic interactions between their protonated forms and the lipids of the bacterial cell membrane. The bacteriostatic activity may also be due to their ability to activate oxygen species by the CQDs surface. Comparison of the effect of different carbon sources on CQDs bacteriostatic properties is under investigation.

Study on the Effect of Estradiol Against Tributyltin Toxicity in Rat Pancreatic Islet

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Introduction: Discovery of estrogen receptors in the pancreatic beta cells supported the hypothesis of protective effects of female sex steroids on pancreatic beta cells due to lower prevalence of diabetes in females. Studies show that estradiol can increase viability of beta cells, enhance insulin secretion and prevent apoptosis in vivo and in vitro. Some metals particularly tin and cadmium have been reported to interfere with estrogen receptors and exert toxic effects through disrupting related endocrine pathways. Tributyltin is known as an endocrine disruptor which is used as a biocide against a broad range of microorganisms. Some sporadic studies indicated that tributyltin induces beta cell apoptosis and disturbs glucose homeostasis. This study was designed to assess the effects of tributyltin and estradiol on rat pancreatic islets.

Methods and Results: Pancreatic islets of male rat were isolated, grouped (10 islets in each group) and cultured in RPMI for 24 hours at 37° C. After calculating EC50 of tributyltin and estradiol by using MTT assay, islets were treated with estradiol and tributyltin for 24 hours. Then viability and level of reactive oxygen species ROS were measured.
Tributyltin decreased cellular viability of islets along with an increase in the ROS formation, while estradiol increased viability and decreased ROS when added to both control group and tributyltin treated group.

Conclusions: Our results indicate that estradiol can protect beta cells of the pancreas by increasing viability and decreasing ROS formation against tributyltin toxicity. It can be concluded that function of estrogen receptors in the pancreas particularly beta-cells might be an important target of pharmacological and toxicological modifications in order to discover new aspects of pathophysiology and therapeutic strategies for diabetes.

Key Words: Islets of Langerhans, Estrogen receptors, Estradiol, Tributyltin

Long-term Administration of Eurycoma longifolia Root Extract Restores Depleted Tetosterone Levels in Diabetic Rats

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O32

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Introduction: Men in south East Asia have traditionally used remedies prepared from the roots of Eurycoma longifolia Jack (Tongkat Ali) as potent aphrodisiac to improve male virility. Under diabetic condition, testosterone levels tend to deplete affecting by various metabolic functions as well as causing erectile dysfunction in male. The aim of this investigation was to evaluate the effect of methanol extract of Eurycoma longifolia Jack roots (METEL) on total serum testosterone levels in normal and diabetic adult male rats.

Methods and Results: Healthy adult male Sprague Dawley rats weighing 250 – 300 g were randomly divided into (i) control, (ii) testosterone, (iii) METEL, (iv) diabetic control, (v) diabetic testosterone, and (vi) diabetic METEL groups (n=6). Streptozotocin (STZ) at 50 mg/kg (i.p.) was used to induce diabetes mellitus. Rats in METEL group were treated orally with 200 mg/kg of the extract (in 5% tween-80) whereas control group received 10 mL/kg of the vehicle daily for six consecutive weeks. Testosterone enanthate was injected weekly at 30 mg/kg (s.c.) for similar period. Body weights and fasting blood glucose (FBG) levels of individual animals were measured on day 0, day 3, and weekly thereafter for up to six weeks. At the end of the treatment period, rats were sacrificed and adequate blood samples were collected by cardiac puncture for the determination of serum testosterone concentrations.

Serum samples from normal animals showed substantial elevation in serum testosterone concentrations in both testosterone and METEL treated animals. In addition, depletion of serum testosterone levels due to diabetes was successfully restored by both METEL and testosterone administration. Meanwhile, FBG levels in METEL treated diabetic animals reduced significantly on week 5 and 6 of the treatment. A similar trend was observed in testosterone-treated diabetic rats on week 6.

Conclusions: Daily administration of METEL for six weeks was able to restore depleted serum testosterone concentrations in diabetic rats demonstrating the effectiveness of E. longifolia in upregulating testosterone production under diabetic condition. However, further studies are warranted to elucidate the possible mechanism of action.

Key Words: Eurycoma longifolia, Tongkat Ali, Testosterone Enanthate, Diabetes Mellitus

Toxicity of SWCNTs and MWCNTs in isolated rat liver mitochondria: an in vitro study

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O35

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Introduction: Due to the unique physicochemical properties of single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs), many applications in medicine have been found. It is important to investigate the fate and toxicological potentials of CNTs after administration. There is not any study on the toxicity of CNTs in isolated liver mitochondria in humans and animals. The aim of this study was to investigate the toxicity effects of SWCNTs and MWCNTs in isolated rat liver mitochondria.

Methods and Results: We isolated rat liver mitochondrial by different centrifugation methods. Isolated liver mitochondrial treated by different concentrations of SWCNTs (2.5, 5, 10, 20 and 40 µg/ml) and MWCNTs (40, 80, 120 and 160 µg/ml) for 30 and 60 min separately. By MTT assay, the LD50 (lethal dose 50) of SWCNTs were obtained 20 µg/ml for 30 min and 5 µg/ml for 60 min and also the LD50 of MWCNTS were obtained 120 µg/ml for 30 min and 80 µg/ml for 60 min in isolated rat liver mitochondria.
Results:
Isolated mitochondrial exposure to LD50 of SWCNTs and MWCNTs in 30 and 60 min caused impaired mitochondrial dehydrogenase activity (mitochondrial complex II), induced ROS generation, increased $\Delta\Psi m$ levels, and decreased GSH levels compared with the control group.

Conclusions: However, there was not any statistically significant between the LD50 of SWCNTs and MWCNTs to induce mitochondrial toxicity. These findings suggest that SWCNTs and MWCNTs have the potential to induce liver mitochondrial toxicity in rat via activation of the mechanisms of oxidative stress.

Key Words: carbon nanotubes, rat, isolated liver mitochondrial, toxicity, oxidative stress

Study expression of apoptotic and autophagic markers in amyloid beta-injected rats following inhibition of nitric oxide/protein kinase G signaling pathway

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O37

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Introduction: Alzheimer's disease (AD) is the most common cause of dementia. It is one of the age-related disorders that considers as a public health problem. The role of nitric oxide/protein kinase G (NO/PKG) in neurodegenerative disorders is controversial in different circumstances. This study is aimed to evaluate apoptotic and autophagic markers in amyloid beta-injected rats by inhibiting nitric oxide/protein kinase G signaling pathway.

Methods and Results: We assessed the apoptosis and autophagy markers by western blot analysis as two possible interfering pathways with the NO/PKG signaling. For this purpose, we assessed the effect of co administration of L-NG-Nitroarginine Methyl Ester (L-NAME) as a nitric oxide synthase (NOS) inhibitor and KT5823 as a PKG inhibitor in AD rats. The molecular evaluations were examined on 7th day after drug injections. Results: The role of NO and PKG inhibition in apoptosis and autophagy pathways were determined by Western blot method. The molecular findings showed that in Aβ pretreated rats, intra-hippocampal injection of 1 µg/side of L-NAME or KT5823 (5 µM /side) caused a significant reduction in apoptosis markers and an increase in autophagy markers comparing to AD rat group. Besides, intra-hippocampal injection of L-NAME (1 µg/side) + KT5823 (5 µM /side) could induce autophagy and attenuate apoptosis significantly in AD rat too, but there was not a significant difference between the combination group and each of L-NAME or KT5823 (5 µM /side) alone.

Conclusions: The data revealed that KT5823 or L-NAME could debilitate the Aβ-induced apoptosis and also intensify autophagy at individual doses, but in combination they indicated no additive effects.

Key Words: L-NAME, KT5823, Autophagy, Amyloid beta, Apoptosis

The pattern of Imipenem/Cilastatin administration in Imam Khomeini hospital (Ardabil) in the year 1397

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Introduction: Nowadays antimicrobial resistance is one of the most important concerns of medical care system in the world. Broad-spectrum antimicrobial drugs are the last gun?? against the complicated microbial infections in the hospitals. Therefore, the indiscriminated use of these drugs in addition toincreasing costs of hospitalization, increases the antibiotic resistance and this opportunity makes ecologic change in bacterial spices to develop new resistant infections against our current drugs? Imipenem is of carbapenem class of beta-lactam antibiotics that prescribed mostly in our hospitals because of its broad activity against bacterial infections. Drug Utilization Evaluation (DUE) process is an official, ongoing and systemic program that collects information in order to identify and improve probable adverse effects of drugs, and shows us complains?? that reduces cost effectivness of medicalization in hospitals.
Objective: To evaluate appropriate use of Imipenem/Cilastatin (IC) antibiotic in educational Imam Khomeini hospital in Ardabil.
Methods and Results: 100 hospitalized patients who received IC from September to December of 2018 were included in this study. Patients' demographic data, dose, dosage adjustment in renal insufficiency and co-prescribed antimicrobial drugs were extracted from current medical file of hospitalized patients and evaluated with Up-to-date and Lexi-comp references.
Results: 75% were empirically received IC and antibiogram tests were ordered for only 25% of patients. 64% of patients received Imipenem in first day of hospitalization. Serum creatinine tests was ordered for most of the patients but correct dose regimens for patients who get non-empiric antibiotic therapy were only 24%.
Conclusions: High rate of empiric prescription of IC without considering culture and antimicrobial susceptibility results and initiation of antimicrobial therapy at the time of admission were the most important aspects of irrational use of this antibiotics are observed in this study. Paying more attention to sampling, culturing and sensitivity tests and prescription of IC based on specific guidelines are recommended.

Key Words: Imipenem/Cilastatin, Drug Utilization Evaluation, Microbial Drug Resistant

The Efficacy of New Treatments (Sofosbuvir base) In Hepatitis C Patients_Southern Khorasan province (East Iran)

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Background and Aims:
To deliver mass scale hepatitis C treatment an inexpensive, potent, pan-genotypic regimen is required. This treatment has been undertaken using sofosbuvir and daclatasvir(Sovodak) in a largely genotype 4 population. Sofosbuvir and daclatasvir was co-formulated into a single tablet and mass scale treatment was initiated. This Combination of both drugs has been first available in Iran.
The aim of this study was evaluation of effectiveness of the novel interferon-free(Sofosbuvir base) regimens in patients with hepatitis C in Southern Khorasan province.

Methods:
The study was to include at least 24 patients with hepatitis C including patients infected with all genotypes of hepatitis C and patients with previous Interferon-based treatment experience. Patients were treatment with a single tablet dose form containing 400 mg of sofosbuvir and 60 mg of daclatasvir (Sovodak 60/400). Haemodialysis patients were dosed according to a simple and effective locally developed protocol. Response to treatment was evaluated 12 weeks after the end of treatment with a sensitive PCR assay(SVR 12).

Results: A total of 24 patients were entrolled. Overall the patients were 83.3% male with a mean age of 48 years. 29.2% were genotype 1 and 70.8% were genotype 3. 12 weeks after treatment 100% of patients achieved SVR12(sustained virological response). Treatment was well tolerated, and compliance with the single tablet regimen was excellent.

Conclusions: In this analysis treatment with co-formulated sofosbuvir/ daclatasvir tablets achieved high SVR12 rates (100%). The high efficacy of this combination and rhe ease of use makes Sovodak an excellent choice for treating all cases of hepatitis C, especially in elimination protocols.With cost efficient treatment now available treatment mass scale HCV eradication using a single pill a day dose form appears entirely possible.
Keywords: East iran, New treatment, sofosbuvir, hepatits C

The evaluation of the effect of melatonin on the reduction of the dose of fentanyl in the patients admitted to the intensive care unit; a double-blind clinical trial

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Introduction: Melatonin is a hormone that is produced in the pineal gland and affects sleep induction and changes in the circadian rhythm phase.
By reducing the dosage of fentanyl in patients admitted to the intensive care unit (ICU), can reduce the side effects of the opioids in patients and get more appropriate treatment response. The aim of this study was to evaluate the effect of the consumption of melatonin in reducing the dose of fentanyl prescribed in the intensive care unit.

Methods and Results: This study was performed on 40 patients admitted to the intensive care unit. Patients were randomly divided into the two intervention and control groups. After obtaining written consent, every night at 9 o'clock, 3 mg melatonin was given to the intervention group and one placebo to the control group. This prescription continued until the mechanical ventilation of the patient. The patients' demographic information and the need for consumption of fentanyl were recorded.
According to the analysis of the obtained data and their comparison between the two groups, we concluded that there was a significant difference in the stat dose of fentanyl between the two groups.

Conclusions: According to these findings, melatonin can probably reduce the dose of opioids and the side effects related to them.

Key Words: melatonin, fentanyl, ICU

Efficacy of Ivabradine and beta-blocker in patients with stable pectoris angina: a systematic review and meta-analysis

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O45

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Introduction: Managing angina pectoris is crucial due to its considerable prevalence and occurrence in different age groups. The new drug used in Angina, Ivabradine has been evaluated for its effectiveness in several clinical trials compared to beta-blockers. The main goal of this study was to evaluate the efficacy of Ivabradine in comparison to beta-blockers in patients with angina pectoris in a systematic review and meta-analysis.

Methods and Results: A systematic search was conducted in the relevant electronic search engines including Cochrane library, PubMed, Web of Science, CRD, Scopus, and Google Scholar by the end of 31 December 2017. Two investigators independently reviewed each article. We evaluated the quality of articles with the Cochrane checklist and RevMan software version 5.3. For the two studies according to the extraction table, the required data were extracted. The Meta-analysis was performed using CMA v.2.0 software and fixed effect model.
From the 693 related articles, two articles were entered into meta-analysis. Data related to the outcomes of "maximum heart rate" and "Exercise duration" were extracted. The results of meta-analysis showed that in comparison of Ivabradine to beta-blockers, Ivabradine reduced the maximum heart rate to 4.30 (Pooled Estimate(SD)=4.30(0.75), 95% CI= (2.83-5.77), Z= 5.72, P-Value0.001) and by increasing the duration of the exercise test to 9.65 (Pooled Estimate(SD)=9.65(6.48), 95% CI= (-3.04-22.35), Z= 1.49, P-Value=0.136) had more efficacy. Heterogeneity between studies assessed by Cochrane test and I2 statistic.

Conclusions: This meta-analysis showed that treatment of angina pectoris with ivabradine can be more effective than when it treated with beta-blockers.

Key Words: Efficacy, Ivabradine, beta-blocker, angina pectoris, Meta-analysis

The wall of distrust is tall yet between the patients and pharmacists; a study to unwrapped this sophisticated skein

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Abstract:
Despite the vast efforts to stabilize the key position of the pharmacist in the health system, many people summarize the role of pharmacists in selling and distributing of medicines and in this way the pharmacists are less likely to be imagine as the drug advisers by the patients. One of the major reasons of non-efficient interaction between the pharmacist and the patient is the inappropriate design of the physical space of the pharmacies. The main examples of this mis-design categorized as four cases: inappropriate design of the counter, existence the glass barriers between the patient and pharmacist, absence of counseling room and waiting space of the pharmacy to preserve the patient's distance with other patients, and his privacy right in counselling procedure. The aim of this study was to investigate the effect of these parameters on the viewpoint of pharmacists and patients about the quality of drug counselling services.
This descriptive-analytic study was conducted in two phases. The first step was the evaluation of pharmacies corresponding to the four above mentioned physical parameters. The second step was to evaluate the views of pharmacists and patients related to the impact of the mentioned parameters on the quality of drug counselling and their satisfaction with these services. This phase was performed through filling the two separate questionnaires for two target population groups (30 pharmacists and 90 patients). Data were analyzed using SPSS software and statistical tests.
The results showed that the design of the physical space of the pharmacies is often non-standard, suffered from lacking of the consulting rooms and suitable waiting space, inappropriate glass barriers and non-standard height of counters. The results of the questionaries' indicated that the mentioned defects caused an insecure space to the patients and, as a result, their reluctance to receive pharmaceutical counseling from pharmacists. On the other hand, despite the emphasis of pharmacists to change the physical space of pharmacies to deliver the pharmaceutical services beter, they identified the economic factor as one of the most important obstacles to reach this goal.
With regard to these findings, it is necessary to change the pharmacy space in order to provide better services. These changes should be such that provide a safe, private, comfortable, and direct access between the patient and pharmacist. Based on the findings of the present and other studies, a schematic design of an ideal pharmacy is proposed in this presentation.

Key Words: Pharmaceutical services, counter design, consulting room, drug counselling, patient privacy

Hypersensitivity reaction to cyclosporine

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Introduction:

Cyclosporine is a potent immunosuppressant used for prophylaxis of Graft Versus Host Disease in allogenic Hematopoietic Stem Cell Transplantation (HSCT). Hypersensitivity reactions are rare with cyclosporine; however, few cases of anaphylaxis have been reported. We present a case of anaphylactic hypersensitivity reaction to cyclosporine IV; a sixteen-year old male with thalassemia major and candidate for HSCT who experienced anaphylaxis following injection of cyclosporine. We also explain therapeutic alternatives in patients with hypersensitivity reaction to cyclosporine iv.

Materials and methods:

We searched pubmed using keywords "Cyclosporine" and "Hypersensitivity" in title/abstract from 1990 to 2018 including clinical studies, clinical trials and case reports in humans. Sixty-three results were found, of these six case reports were attributed to anaphylactic reactions to cyclosporine IV.

Results:

The hypersensitivity reactions were attributed to the Cremophor EL (Polyoxyl 35 hydrogenated castor oil) which is used in formulation of Sandimmun. Ig E mediated reactions and histamine release could explain the mechanism of hypersensitivity to Cremophor EL. Oral cyclosporine which does not contain Cremophor EL was well tolerated in all studies. Hypersensitivity to Cremophor has been reported with the use of vitamin K IV, Tacrolimus IV, Paclitaxel IV, Teniposide IV and Ritonavir capsules and Tegretol. Possible cross reactivity has been reported between Cremophor and Polysorbate 80 (a non-ionic surfactant). Some brands of oral cyclosporine contain polysorbate 80, therefore their use should be with caution in patients who have experienced anaphylactic reactions with medications containing Cremophor EL.

Conclusion:

Clinical trials have demonstrated that methotrexate plus tacrolimus is as effective as cyclosporine for prophylaxis of GVHD. Oral tacrolimus does not contain polysorbate 80 or cremophor and therefore can be safely used in patients with prior history of anaphylactic reactions to cyclosporine IV.

Keywords: Cyclosporine, Cremophor EL, Hypersensitivity

Evaluation of rational prescription of proton pump inhibitors in a teaching hospital in Birjand

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O48

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Background and Aim: Recurrent aphthous stomatitis (RAS) is the most common pathological lesions in the oral mucosa, with an incidence rate of 5-50%. This study aimed to compare the efficacy of diphenhydramine solution (DS) and diphenhydramine containing 5% of glycyrrhiza glabra extract (DSG) in the management of RAS.

Materials and Methods: This was a double-blind, randomized, clinical trial recruiting 70 RAS patients who had no systemic disease. Participants were randomly assigned into DS and DSG groups (n = 35 per group).The severity of pain were assessed at the baseline and after 2, 3, and 5 days of intervention using visual analog scale (VAS), as well as the duration of wound healing was measured by photography. The data were analyzed in SPSS software version 18 using descriptive and inferential statistical tests.

Results: Both solution has significant effect on pain score but pain score on DSG (7.96 on the first day versus 0.28 5th day) was significantly lower than DS group (8.56 on the first day versus 2.53 5th day). The mean wound healing duration in the DSG group was 1.6 days less than in the DS group, and there was a significant difference between the two groups concerning the mean wound healing duration (p = 0.000).

Conclusion: DSG appears to be more effective than DS alone in RAS treatment.

Keyword: prescription pattern, hospital, proton pump inhibitors,

Knowledge, attitude and performance in patients with Hypertension referred to the 13 aban pharmacy Ramsar, in the 2017 year

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Introduction: Nowadays, the elderly population is increasing all over the world. So, diseases and complications result of it especially hypertension impose high costs on societies and cause a lot of inabilities. This study was aimed to determine knowledge, attitude and the nutrition-related performance of patients suffering from hypertension in the 2017 year.

Materials and Method: This descriptive-observational study was designed at Ramsar's 13th Aban school of pharmacy. The sample size was 200 patients. The sampling method was convenient sampling. Each patient who entered the pharmacy on different days with hypertension and accepted the conditions of the study was included in the study after explaining the method of investigation. Patients were asked oral questions in three levels of knowledge, attitude and practice of the patient regarding hypertension, and a significant level of 0.05 was considered.

Results: The mean SD mean age of patients was 56.22 ± 12.12. In this study, 83% of the subjects had good knowledge and awareness of hypertension, while 15% Individuals with moderate knowledge and awareness of high blood pressure and only 2% of subjects had poor knowledge and awareness of hypertension. 56.5% of the subjects had a moderate attitude about hypertension. Also, 79% of the subjects had a good performance of hypertension, while 20% of the subjects had a moderate performance of hypertension and only 1% Researchers had poor performance from over-pressurized blood. Using Pearson Correlation coefficient, it was also found that positive correlation between the scores obtained from the field of knowledge and the attitude with the points obtained from patients' performance was seen relative to hypertension (P = 0.0001 and P = 0.001).

Conclusion: Overall, this study showed that the knowledge, attitude and practice of patients participating in the present study are at an acceptable and high level. Increasing knowledge and awareness about patients' behavior is considered as a prerequisite and necessary in order to develop an appropriate attitude towards that particular topic and to adopt appropriate behavior.

Keywords: Knowledge, attitude, performance, Hypertension

Electrochemical determination of risperidone using modified carbon paste electrodes with ionic liquid and magnetic nanoparticles

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O52

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Risperidone (RPN) belongs to a class of antipsychotic drugs known as atypical neuroleptics. It is used to treat schizophrenia, schizoaffective disorder, the mixed and manic states associated with bipolar disorder, and irritability in people with autism. It is associated with significant weight gain and metabolic problems, as well as tardive dyskinesia and neuroleptic malignant syndrome. Risperidone and other antipsychotics also increase the risk of death in patients with dementia. Incurrent paper, a ZnFe2O4 nanoparticle-ionic liquid modified carbon paste electrode (ZnFe2O4/NPs/1B3MI/CPE) was introduced as a renewable, fast and sensitive tool for quantitative determination of RPN liposomal loading efficiency using voltametric methods.

Methods and Results: All the voltammetric measurements were performed using Autolab PGSTAT204-Metrohm potentiostat/galvanostat connected to a three-electrode cell including Metrohm platinum wire electrode, Metrohm Ag/AgCl/KClsat electrode, and ZnFe2O4/NPs/1B3MI/CPE was used as a counter, reference and working electrodes, respectively. Extra pure paraffin and 1-butyl-3-methylimidazolium tetra-fluoro-borate (1B3MI) from Merck were used as the substrate for the preparation of the carbon paste electrode. The ZnFe2O4/NPs/1B3MI/CPE revealed great improvement to the electrode process of RPN in comparison with the CPE. Under the biological conditions, the peak current was proportional to the RPN concentration.

Conclusions: The presence of 1B3MI and ZnFe2O4 nanoparticles helped RPN to have a favored orientation and reduce the effective electron transfer distance. The oxidation peak potential of the RPN at a surface of ZnFe2O4/NPs/1B3MI/CPE revealed that the designed biosensor can be useful in the electrochemical and medical studies.

Synthesis and biological evaluation of some quinazoline derivatives

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Abstract

Cancer is a serious health problem in developing and undeveloped countries. Although much progress has been made in treating the disease, due to problems with drug resistance, further research is needed to explore new anticancer agents. Combining two or more pharmacophores into a molecule is an approach to explore new agents. Therefore, when there is more than one pharmacophore in a molecule, it can be more effective in treating cancer by different mechanisms. Hybrid pharmacophores may be attached to different sites in the receptors, which results in the loss of drug resistance. It can also reduce the side effects of anticancer drugs(1,2).
There are many reports on biological activities of synthetic and natural quinazolines including, antitumor, antifungal, anticonvulsant, antibacterial, anti-inflammatory, sedative, antitubercular, antimalarial, antiviral, anti-HIV, and antihyperlipidimic activities. Some drugs have been synthesized with quinazoline structure such as diproqualone, cloroqualone, gefitinib, lapatinib, trimetrexate, piriqualone, doxazocin, prazosin, thymitaq and raltitrexed(3-8).
Thiazole-containing compounds also have valuable biological properties, such as anti-tumor, analgesic, anti-inflammatory, antibacterial and antifungal effects. Thiazole, an important heterocycle ring, is widely used in the development of anticancer drugs. A number of anticancer drugs containing thiazole have been discovered, such as tiazofurin and bleomycin. Ritonavir (anti-HIV), meloxicam (anti-inflammatory), niacinidine (peptic ulcer) and penicillin (antibiotic) are some other examples of thiazole containing drugs(9-13).
Due to the valuable cytotoxic effects of both thiazole and quinazoline compounds, in this work a series of quinazolinone-thiazole hybrids were synthesized and their cytotoxic effects on three cell lines were evaluated using MTT assay. Compounds A3, A2, B4, and A1 showed highest cytotoxic activities against PC3 cell line. Compounds A3, A5, and A2 were most active against MCF-7 and A3, A5, and A6 showed good cytotoxic effect on HT-29 cell line. According to the results, A3 efficiently inhibited all cell growth tested in a dose dependent manner. The IC50 of A3 was 10 M, 10 µM, and 12 µM on PC3, MCF-7, and HT-29 cells, respectively.

Key Words: Quinazoline, Synthesis.

Strategies in the Design of novel antimicrobial peptides: tools and effective properties in biological activity

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Antimicrobial peptides (AMPs) are host defense molecules had discovered from both invertebrates and vertebrates as the innate immune systems. They are ancient molecules remaining potent after millions of years, therefore, can be regarded as important templates for developing a new generation of antimicrobials to combat antibiotic resistant bacterial pathogens, viruses and cancers. Other biological activities like immunomodulatory function have been illustrated in specific cases, as well. Physicochemical features of AMPs including length, charge, hydrophobicity and hydrophilicity, amphipaticity, hydrophobic moment, presence of some conserved domains and modifications such as cyclization and branching are among the most influential features on AMPs' activity. Novel artificial synthetic AMPs might be designed and developed by rational de novo design using bioinformatics modeling or random evolution from a basic template or library. Having selective potent antimicrobial bioactivity and no or least hemolytic and cytotoxic effects are the important criteria in the development of novel AMPs. The computer-based techniques can be applied for in silico design and development of novel effective therapeutic peptides. Computer-assisted molecular design cycle, applied in novel AMP design, starts from scratch (de novo) or from known peptides that have a desired activity (also termed 'seed peptides'). Several approaches had proposed, including modification of known AMP sequences (as templates) with limited computational input; rigorous biophysical modelling to understand peptide activity; and virtual screening. In an iterative process new peptides are generated in silico using alternating variation-selection operators. A 'fitness function', often a machine-learning model, guides the design towards regions in sequence space that contain residue sequences with a higher predicted biological activity. Some of these artificial synthetic AMPs have reached to clinical trials. The reasons for less success of synthetic AMPs in clinical applications include the cost, their lability to proteolytic degradation, and their unknown toxicology profile, when administered systemically. These limitations can be addressed by the peptide design approaches mentioned above.

Keyword: antimicrobial peptide- Computational design- physicochemical properties- de novo design- rational modification

In silico discovery of novel multi-target anti-virulence agents to counter Pseudomonas aeruginosa

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The rapid, incessant and global increase in antibiotic-resistant bacterial infections has motivated researchers in new strategies with the aim of keeping the pathogen in a viable state but with ineffectual virulent factors, causing in reduced resistance selection. Inhibition of quorum sensing (QS) system has been purposed as one of the novel anti-virulence strategies. The human opportunistic pathogen Pseudomonas aeroginosa has a relatively complex QS circuit that regulates the expression of hundreds of genes involved in controlling its virulence. The present study aimed to identify potential multi-target inhibitors of QS in P.aeroginosa through simultaneously targeting three pivotal key transcriptional regulatory proteins: QscR, PqsR, and LasR. We have employed a computer-assisted approach to generate and validate three receptor-based pharmacophoric models of QscR agonist, LasR antagonist, and PqsR antagonist. Prior to multiple pharmacophore-based virtual screening experiments, a library containing 555,802 synthetic and natural compounds from InterBioScreen database were subjected to Lipinski′s rule of five as a drug-like filter. Then, three pharmacophoric models were utilised in database screening in subsequent three steps, followed by molecular docking of retrieved hits in three receptors. Finally, seven natural compounds (STOCK1N-74561, STOCK1N-41688, STOCK1N-44693, STOCK1N-44910, STOCK1N-52574, STOCK1N-39865, and STOCK1N-72392) and two synthetic compounds (STOCK6S-78803 and STOCK1S-89450) exhibited key interactions at all three active sites. Best docking scores were selected as final hits and regarded as possible multi-target inhibitors of QS in P.aeroginosa. This work has uncovered a new class of anti-virulence agents as multi-target P.aeroginosa QS inhibitors which could be potentially applicable as lead scaffolds for future anti-P.aeroginosa virulence drug development.

Pharmacophore Modeling, Synthesis, Scaffold hopping And Biological β-Hematin Inhibition Interaction Studies as Antimalaria Compounds: An Approach For Multitarget Anticancer Drug Design

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Abstract

Exploring potent compounds is a critical first step in multi-target drug discovery. The primary mechanism of heme detoxification in malaria parasites is hematin crystallization, which is target of the antimalaria compounds. A series of chloroquine analogues were designed using repositioning approach to develop new anticancer compounds. Fingerprints of the protein-ligand interaction and ADMET descriptors were used to build and assess a model for structure-based discovery of new scaffold based on chloroquine hybrid β-hematin inhibitors. In the present study, 50 novel potent chloroquine hybrid β-hematin inhibitors with their IC50 values were collected andapplied. The model, built by partial least square algorithm, showed excellent predictive power with the correlation coefficients for calibration and cross validation of r2 = 0.93 and q2 = 0.72. We developed and validated QSAR model in prediction of a newly synthesized series of 4-aminoquinolin hybrids and evaluated them for their biological activity as an external test series .These compounds were evaluated by cytotoxic cell lines and β-hematin inhibition. The target compounds exhibited high β-hematin inhibition activity and were 3-9 times more active than the positive control. Furthermore, all compounds exhibited moderate to high cytotoxic activity. Pharmacophore features of 10 derivatives in model were generated with HIP-HOP algorithm, and then used for structure-based virtual screening in commercial databases, leading to the identification of the compound with the best score from ChEMBL, which was 2016904, previously reported as VEGFR-2 inhibitor. A multi-parameter analysis was performed for the comparison of the 11 selectedcompounds regarding their correlation between dual potency, target evaluation, and predicted ADMET properties for drug development.

Key words: Multi-target, β-hematin, Fingerprint, Hybrid synthesis, 3D Scaffold hopping

Design and Synthesis of a group of Chalcone derivatives as antiplatelet agents

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O57

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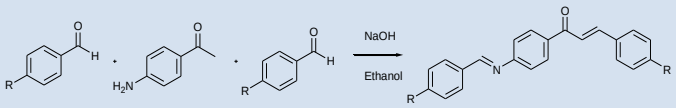
Introduction and background

Platelet activation has an essential role in thrombus formation and cardiovascular diseases. Antiplatelet agents such as acetylsalicylic acid and clopidogrel are used in the treatment of these diseases, exhibit some side effects and tolerance has been reported to them in some cases. Therefore finding new drug candidates for this therapeutic area is needed. Chalcones have a range of different biological activities, such as antihypertensive cardiovascular activity and anti-inflammatory activitie. Therefore the synthesis of a group of chalcone derivatives was selected as the main objective of the present study.

Methods

The desired chalcone derivatives were synthesized by the reaction of 4-aminoacetophenone and various substituted benzaldehydes in the presence of NaOH in ethanol.



Antiplatelet aggregation activity of the compounds was evaluated using Born turbidimetric method.

Results

All the synthesized compounds were obtained in good yields and structure of the compounds was characterized by IR, ^{1}HNMR and ESI-MS. Those compounds which showed >90% inhibition at 0.5 mmol concentration were selected for IC50 determination.

Discussion and conclusion

In general, most of the compounds showed better activities against the platelet aggregation induced by arachidonic acid. Some of the structural features of the compound showed acceptable relation with their activities.

Keywords: antiplatelet, chalcone, synthesis

Binding of Donepezil to Acetylcholinesterase: A Computational Study via Response Surface Methodology

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O58

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Abstract:
Donepezil is an oral medication used to improve cognition and behavior in people involved with Alzheimer's disease (AD). Response surface method (RSM) is an efficient computational technique for simultaneous estimation of factor effects on response, the subject not considered in traditional one-factor-at-each-time approaches. Within the present project, donepezil, an AChE inhibitor, was subjected to analysis of variance (ANOVA) incorporated into RSM statistical package. The aim was to mathematically model and estimate the effectiveness of determinant factors on in silico target binding accuracies with regard to validated experimental binding affinities of donepezil within AChE binding site.
RSM was applied to model the influence of six independent factors on AutoDock driven binding accuracies of donepezil vs validated experimental AChE inhibitory affinities. Three distinctive levels (-1, 0 and +1) were assigned for each factor under study (A: torsion degrees for drug, B: grid spacing, C: quaternion degrees for drug, D: No. rotatable bonds, E: initial drug conformation and F: target conformation) and ANOVA was performed for each endpoint (response: ΔpKi) on the basis of Box-Behnken matrix comprising 54 independent runs. ΔpKi was defined as the numerical difference between docking and experimental binding affinities. All statistical analysis and modeling procedure were performed via Box-Behnken method incorporated into Design-Expert (DOE) software-v.7. Docking simulations were done by AutoDock4.2. ANOVA results exhibited that quadratic model could best describe the relationship among dependent variable (ΔpKi) and independent ones (factors A to F) with R2 values of 0.9943. Model p-value of 0.0001 indicated that the developed model was significant. Mathematical model in terms of significant factors (p-value of 0.05) and their coded levels was as follows:
5.25+0.22B-0.19f-0.22BF=ΔnH
The most significant model terms with regard to response were found to be grid spacing (distance between autogrid adjacent points) and target conformation. Moreover BF (grid spacing×target conformation) was the significant interactive term of model. Target conformation may be translated into the induced fit models of the enzyme. Moreover; desirable solutions to achieve minimized responses (minimum differences between in silico and in vitro results) were offered. Identification of determinant methodological and structural variables might provide the comparative qualitative/quantitative exploration of donepezil in binding to its target. The outputs of this study may assist in development of optimized docking technique toward rational design of more selective and potent donepezil analogues as AChE inhibitors.

Key Words: Alzheimer, Donepezil, Response Surface Method, Docking

Development and validation of measurement methods for methadone isomers using high performance liquid chromatography in pharmaceutical forms of tablet and syrup available on the market

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Abstract:
Methadone is a synthetic opioid substance that has a chiral carbon and two isomeric forms of R and S which show significant differences in their pharmacodynamics and pharmacokinetic properties. It has been proposed that the quality of methadone pharmaceutical products is important key parameter in methadone maintenance treatment program (MMT). A sensitive, simple, fast, applicable, and validated HPLC analytical method was developed and applied for determination of R and S isomers of methadone in tablet and syrup dosage forms.

A HPLC system consist of Shimadzo Controller unit, Pumps and UV detector (ƛ=210 nm) was used. AGP, chiral column were used for separation and quantification of methadone and its enantiomers in dosage forms.

The retention time, LOD and LOQ for methadone enantiomers in final developed chromatographic methods were 9.8 min for R, and 11.8 min for S, and 2 and 5 ng/ml for enantiomers.

Standard curves were obtained for R and S methadone (5-50 ng/ml, r2= 0.999). The average of inter and intra-day variation were 3.1 and 2.6 for methadone isomers.

solvent- solvent extraction method used for methadone enantiomers. The extraction ratio for methadone in tablets was 86%.

The applicability study of developed HPLC method showed that this method can be used for QC of methadone dosage forms. Our results revealed that the amount of racemic methadone and R and S methadone were 96%, 49.6% and 50.4% in the syrups and 93%, 49.4%, 50.6% in the tablets and were within the acceptable range of USP criteria.

Our result showed that the developed method for quantification of methadone and its enantiomers in pharmaceutical samples is capable for using in pharmaceutical industries.

Key Words: enantioselective HPLC, chiral AGP column, methadone enantiomer, methadone dosage forms

Investigation and comparison of physicochemical properties of PCL/PVA and PCL/Collagen Co-axially elctrospinning nanofibers

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Abstract

Introduction and background: It has been frequently proposed that nanofibers formed by electrospinning could mimic the structure and biological function of the extracellular matrix (ECM) in terms of chemical and physical structure (1). In recent years, the coaxial electrospinning as an improved method has been extensively used for delivering protein based drug. Thus, it can be mentioned that this method is a novel approach using a special spinneret composed of two coaxial capillaries that can electrospin two different polymer solutions concurrently to fabricate ultrafine fibers with special core/shell structure (2,3). In this study we compare physicochemical properties of two kind of nanofibers contain Poly-caprolactone (PCL)/ Polyvinylalcohol (PVA) and PCL/Collagen.

Methods: Three solutions of PCL 9%w/w in mixture Dichloromethane/ Ethanol (60:40), PVA 7% w/w in distilled water and collagen 70% w/w in distilled water were prepared. The PCL solution was used as core and each of PVA and Collagen as shell. Core-shell fibers were generated with core-shell nozzle with size 14 and 18 gauge. In this study we changed voltage 8 to 20 Kvolts and changed flow rate between core and shell solution (1:1, 1:3, 1:5). The microscopic picture, TEM, FTIR, viscosity and surface tension of solutions was prepared.

Results: In low voltage 8-12 Kvolts and flow rate 1:1 no fibers were made. The optimum voltage was 16 Kvolts and the optimum flow rate was 1:3 Inspit of the PCL/PVA fibers , the PCL/collagen fibers had good stability in aqueous solution and they didn't disintegrate .FTIR didn't show any incompatible with polymers. The collagen solution was good viscosity and surface tension than PVA solution. TEM image showed core-shell structure of PCL/Col nanofibers.

Discussion and Conclusion: The PCL/Collagen fibers werebetter physicochemical properties than PCL/PVA fibers, and this is more suitable for bioengineering scaffold.

Key Words: Nanofiber, Collagen, Co-axially electrospinning.