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Pharmacy Education Science and Practice Conference 2025 Supplement Part B

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Lung cancer-targeting drug delivery systems

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Abstract

Background: Methotrexate (MTX) is an antimetabolite that is widely utilized in the treatment of pulmonary disorders. Designing an effective MTX-ABL co-delivery system is a complicated but intriguing technique for improving targeted pulmonary treatment. **Aim:** The goal of this research is to improve the pulmonary delivery and therapeutic effectiveness of Methotrexate (MTX) by focusing on three key objectives: (1) modulating MTX resistance, (2) improving MTX's physicochemical properties for better pulmonary distribution, and (3) developing a long-acting drug delivery system with an intermediate Ambroxol (ABL) coating and an outer Hydroxypropyl Methylcellulose (HPMC) coating. **Methods:** The best MTX-ABL solid dispersion was chosen using Fourier Transform Infrared (FT-IR) spectroscopy. To establish the best concentration of Hydroxypropyl Methylcellulose (HPMC) for coating, in vitro drug release tests were performed in simulated gastrointestinal conditions for both the optimized MTX-ABL dispersion and the HPMC-coated MTX-ABL gel formulation. FT-IR, X-ray diffraction (XRD), and scanning electron microscopy (SEM) were used to characterize MTX, ABL, the MTX-ABL dispersion, and the HPMC-coated gel's structural and morphological features. For biological testing, A549 human lung cancer cells were treated with MTX, ABL, and the optimized MTX-ABL dispersion for 24 hours. Cell viability tests were utilized to determine cytotoxicity, while enzyme-linked immunosorbent assay (ELISA) was employed to quantify expression levels of apoptosis- and inflammation-related biomarkers such as BAX, BCL-2, TGF-β, and folate receptor alpha (FR-α). **Results:** MTX's HPMC-ABL encapsulation and sustained release properties were confirmed, with the MTX-ABL-HPMC (1:4:4) gel demonstrating perfect release control and a similarity factor of 87.72 in simulated stomach fluid. Compared to MTX alone, the MTX-ABL solid dispersion displayed decreased MTX resistance without requiring high MTX concentrations. The MTX-ABL (1:4) dispersion improved cytotoxicity with an IC50 of 30.41 ± 2.31 µg/mL (vs. 25.21 ± 2.05 µg/mL for MTX alone), while boosting ABL effectiveness (ABL IC50: 121.64 ± 4.11 µg/mL vs. 161.32 ± 3.44 µg/mL). The ELISA study indicated improved therapeutic efficacy, with BAX (pro-apoptotic) expression up by 10.03 ng/mL and BCL-2 (anti-apoptotic) down by 5.11 ng/mL compared to the control. In MTX-ABL-treated lung cancer cells, resistance and uptake profiles improved, with lower TGF-β levels (-1.05 ng/mL) and enhanced FR-α expression (+1.07 ng/mL). **Conclusions:** When the MTX-

ABL solid dispersion was utilized instead of MTX or ABL, the apoptotic, anti-metastatic, and MTX-favored lung cancer uptake properties improved. With its increased efficacy and safety profile, the MTX-ABL-HPMC gel might be a viable alternative to the MTX oral tablets now on the market. However, more in vivo pharmacokinetic and long-term safety studies are needed to corroborate these findings and fully investigate the therapeutic potential of this unique co-delivery technology.

Keywords: Methotrexate; Ambroxol; Solid dispersion; Oral gel; Preferential lung cancer distribution;

Application of solid dispersion in conjunction with 3D printing for personalized medicine

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Abstract

Background: About 40% of the newly discovered active pharmaceutical ingredients (APIs) are poorly soluble, necessitating administration of higher doses in order to elicit desirable therapeutic responses. However, this strategy is prone to manifesting side effects or toxicity to patients. Furthermore, pharmacological responses to administered drug is dependent on genetic predispositions in patients. By improving the solubility of APIs and tuning doses to patients in a personalized framework, it is possible to derive a more effective treatment outcome in a cost-effective manner.

Aim: This study aims to improve the solubility of a typical Biopharmaceutical Class II (ibuprofen), through application of amorphous solid dispersion (ASD) and manufacture of tuneable doses of the same through 3D printing of tablets.

Methods: ASD was prepared by physical mixture of API with polyvinyl pyrrolidone and hydroxypropyl methyl cellulose and lyophilized. The ASD was then incorporated in polylactic acid by hotmelt extrusion to produce filaments, which were used to print the tablets. 3D printing of tablets permitted the production of 'adjustable' doses of ibuprofen in a personalized dose setting. The ASD, filaments and printed tablets were characterized using FTIR, DSC, XRD, SEM and drug release was assessed by dissolution study. Then the results were statistically assessed using one-way ANOVA and student T-test as required.

Results: There was a 35% increase in solubility of ibuprofen in ASD, which translated in improved release of above 90% from the 3D printed tablets, compared to 3D printed tablets containing pure ibuprofen. Crucially, it was possible to tune the release of ibuprofen from the tablets by simple adjustments in the dimension of the 2.5mm and 5mm size 3D printed tablets, with a two-fold increase in release rate from the 5 mm tablet compared to the 2.5mm tablet (t_{300min}). In all cases release remained sustained after 300min.

Conclusions: Combined ASD and 3D printing can be considered as a possible approach to manufacturing of continuous doses for poorly soluble as may be required in personalized medicines

Key words: additive manufacturing, dispensing, 3D printing, personalized medicine, solid dispersions

Computational Design of Novel MRTX1133 analogues targeting KRASG12D for cancer treatment: Molecular Docking, ADME prediction and Molecular Dynamics studies

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Abstract

Background: Kirsten rat sarcoma virus G12D (KRASG12D) is one of the most common oncogenic drivers in human cancers and is usually associated with poor response to therapy. Therefore, KRASG12Drecognised as an attractive drug target. However, the high affinity of KRAS for guanosine diphosphate guanosine triphosphate (GDP/GTP) and the lack of binding pocket made this protein a challenging target. The identification of MRTX1133 as a potent, selective KRASG12D inhibitor was a significant breakthrough in targeting KRASG12D.

Aim: This study aims to utilize computer-based drug design to develop a series of novel MRTX1133 analogues.

Methods: The 3D structure of KRASG12D bound to MRTX1133 (PDB ID: 7RPZ) was utilized as input for the ligand designer tool within Maestro v 12.8 of the Schrodinger suite to design the new analogues. The binding affinity of the designed compounds was assessed using the extra-precision (XP) glide and Molecular mechanics with generalised Born and surface area solvation (MM-GBSA). Moreover, the pharmacokinetic of the shortlisted compounds were evaluated using QikProp tool. The stability of the top three ligand-protein complexes was subsequently analysed through molecular dynamics simulations.

Results: The Glide docking results revealed that 19 new analogues showed docking scores of ≤−13 kcal/mol, compared to the docking score of −4.38 kcal/mol of MRTX1133. While the MM-GBSA results revealed that these compounds displayed superior bind free energy (-110.96 to –84.92 kcal/mol) compared to MRTX1133 (-52.7 kcal/mol). These findings highlight the potential of the designed analogues to exhibit stronger binding affinities compared to the original molecule. Moreover, the pharmacokinetic profiles of the 19 shortlisted analogues revealed that they exhibit favourable pharmacokinetic properties. Lastly, the molecular dynamics results confirmed the stability of the top three ligand-protein complexes.

Conclusion: Based on the results obtained in this study, three analogues show promise to inhibit KRASG12D and may become potential drug candidates or, at the very least, they may

stimulate new strategies for developing novel inhibitors. However, the synthesis and in vitro analysis remain necessary to confirm the potency of these agents.

Keywords: KRASG12D; MRTX1133; computer-aided drug design

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Silver Nanoparticle Pharmaceutical Hydrogels: Large-Scale Manufacturing, Antimicrobial Efficacy, and Falcon Pododermatitis Case Study

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Abstract

Background: Currently AgNP-based products are at a relatively high cost, with a lack of national generic alternatives.

Aim: The aim was to develop a cost-effective method to develop a local AgNP-based hydrogel and evaluate the antimicrobial efficacy of the product.

Methods: A large-scale quantity of AgNP was synthesized employing a wet chemical method with sodium borohydride as a strong reducing agent and polyvinyl pyrrolidone as a capping and stabilizing agent. The AgNP was extensively characterized for size, surface charge, and colloidal stability. AgNP were formulated into hydrogels by using Carbopol as a gelling agent, resulting in a clear, pale yellow hydrogel. This was then tested for their in vitro antimicrobial activity against MRSA and E.coli using SilverStat® Gel brand product as a positive control. Furthermore, in collaboration with Oryx Falcon Veterinary Clinic, we applied AgNP hydrogels to the feet of a falcon with ulcerative pododermatitis (bumblefoot) as part of our investigation.

Results: The nanoparticles exhibited uniformity in size, average hydrodynamic size of 86.93 nm, negative surface charge(-6.37 mV), outstanding resistance to aggregation, and consistent manufacturing reproducibility. AgNP hydrogels exhibited antimicrobial activity equivalent to the brand product when tested against *MRSA* and *E.coli* bacteria. Application to the falcon's feet accelerated the healing of advanced pododermatitis.

Conclusion: We developed a cost-effective, scalable process for high-quality AgNP hydrogels with excellent colloidal stability and antimicrobial efficacy against MRSA and E. coli. Their successful use in treating falcon pododermatitis underscores their clinical potential, addressing the high cost and limited availability of AgNP-based treatments.

Keywords: Silver Nanoparticles, hydrogel, wound healing, antimicrobial, falcons.

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Investigating Strategies to Enhance Aqueous Solubility of Ketamine HCl for Intranasal Delivery

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Abstract

Background: Ketamine HCl (KET), an FDA-approved therapeutic, is administered through various routes, including intranasal delivery. Administering an adequate therapeutic dose of intranasal (IN) KET is challenging due to the limited volume that can be delivered intranasally given the current commercially available concentrations.

Aims: This study explores solubilizing strategies to improve the aqueous solubility of KET by evaluating the effects of pH, co-solvents, and pharmaceutical surfactants.

Methods: The equilibrium solubility of KET was assessed in different pH conditions, organic co-solvents, and pharmaceutical surfactants. A UV-Vis spectroscopy method was developed and validated for ketamine HCl quantification.

Results: Solubility screening in organic co-solvents followed the order: water (158.58 ± 10.19 mg/mL)> propylene glycol (52.71+6.71 mg/mL) > dimethyl sulfoxide (21.59 ± 11.73 mg/mL)> ethanol (14.32± .13 mg/mL)>N-methyl-2-pyrrolidone (4.60± 0.64 mg/mL). KET solubility increased in acidic conditions, with pH 3.5 being optimal (204.3 ±2.0 mg/mL). Among surfactants tested (Tween 80, lecithin, poloxamer 188, and SDS), 1% SDS provided the highest solubility enhancement (256.1 ±15.4 mg/mL) via micelle formation.

Conclusion: Optimizing KET solubility is crucial for IN formulation. Among the tested conditions, pH 3.5 significantly enhances the solubility of KET, with 1% SDS being the most effective surfactant.

Keywords: ketamine; intranasal; drug delivery; spectroscopy

Boosting Intranasal Ketamine Delivery: Innovative Formulations with DDM and Poloxamer Thermoresponsive Gel

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Abstract

Background: Intranasal (IN) delivery of ketamine HCl (KET) presents several challenges, including pH-dependent solubility, high required dosage, poor bioavailability, and potential side effects on nasal tissues. Permeation enhancers (PEs), such as dodecyl maltoside (DDM), and thermoresponsive gelling systems, such as poloxamer (PLX), offer promising strategies to enhance KET delivery and bioavailability.

Aim: This study aims to formulate IN KET incorporating different levels of DDM and PLX thermoresponsive gel and to assess the physical and chemical characteristics of these formulations.

Methods: KET formulations containing varying concentrations of DDM and PLX (407 and 188 copolymers) were prepared and evaluated for homogeneity, stability, pH, and thermoresponsive behaviour. The gelling properties of PLX were optimized at 32°C by optimizing the ratio between PLX 407 and 188 copolymers to ensure suitability for nasal administration. Additionally, permeation and mucoadhesive properties were conducted to assess formulation performance.

Results: The prepared KET formulations exhibited homogeneous compositions with stable KET content and pH upon storage. The optimized PLX gelling system demonstrated appropriate thermoresponsive behaviour at 32°C. Increased DDM levels and the presence of PLX improved mucin binding (43.97 ± 1.03 %) properties in comparison to KET alone (15.67 ± 4.97%) and induced a time-dependent and controlled permeation of KET, enhancing formulation efficacy.

Conclusion: The combination of DDM and PLX in IN KET formulations effectively addresses key delivery challenges by improving stability, permeation, and mucosal interaction. These findings suggest potential for enhanced therapeutic outcomes with optimized IN KET delivery systems.

Keywords: ketamine; intranasal; drug delivery; poloxamer

Cytochrome P450 Epoxygenase as a Predictive Biomarker of Chemotherapy Resistance in Patients with Triple Negative Breast Cancer

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Abstract

Background: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer characterized by poor prognosis and a lack of targeted therapies. Anthracyclines are key treatments for TNBC, but chemoresistance frequently arises, negatively impacting patient outcomes. Arachidonic acid metabolites, specifically epoxyeicosatrienoic acids (EETs) produced by cytochrome P450 (CYP) epoxygenase enzymes, have been implicated in TNBC progression and anthracycline resistance. However, limited data exist on the role of CYP epoxygenase gene expression as predictive biomarkers for chemoresistance in TNBC.

Aim: To assess the extent of the involvement of CYP epoxygenase in the development of anthracyclines-induced chemoresistance among patients with TNBC.

Methods: This study investigated the role of CYP epoxygenase pathways in anthracycline resistance. TNBC patient samples were analyzed for gene expression levels of CYP epoxygenase enzymes. Predictive biomarker potential was assessed by correlating gene expression with responses to anthracycline treatment. Additionally, the effects of the CYP epoxygenase inhibitor MSPPOH in combination with doxorubicin (DOX) were evaluated in the TNBC cell line.

Results: Several CYP epoxygenase genes, including CYP2C8, CYP2C9, CYP2C19, and CYP2B6, were identified as potential biomarkers for predicting anthracycline resistance. The combination of MSPPOH, a CYP epoxygenase inhibitor, with DOX significantly reduced TNBC cell viability and increased apoptosis compared to DOX alone.

Conclusion: The CYP epoxygenase pathway plays a significant role in anthracycline resistance in TNBC, and specific CYP genes show potential as predictive biomarkers.

Keywords: breast cancer; CYP epoxygenase; chemoresistance; anthracycline

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Impact of Obesity on Rivaroxaban Pharmacokinetics: A Systematic Review

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Abstract

Background: Venous thromboembolism (VTE) is a leading cause of morbidity and mortality globally. Rivaroxaban is used for the treatment and prevention of VTE. Inconclusive evidence is surrounding the pharmacokinetics of rivaroxaban in obese subjects with VTE.

Aim: This systematic review synthesized the available evidence in the current literature pertaining to rivaroxaban pharmacokinetics in obese subjects.

Methods: Five databases were systematically searched, and studies investigating rivaroxaban pharmacokinetics in obese subjects were included in the review. Relevant data were extracted, including anthropometric parameters, rivaroxaban dosage regimen, pharmacokinetic parameters and model, and other outcome measures. The review protocol was registered in PROSPERO database: CRD42020177770.

Results: Eleven studies were included in this systematic review, which involved over 7,140 subjects who received rivaroxaban for different clinical indications. In general, rivaroxaban pharmacokinetic parameters in obese subjects demonstrated variability when compared with reference values in the general population. The volume of distribution reported values for obese subjects (73.4-82.8 L) showed some variability with the range of reported values for general population (59.4-104 L). Furthermore, some of the reported values of clearance in obese subjects (7.86-16.8 L.hr-1) do not fall within the range of values reported/calculated for general population (5.57-11.3 L.hr-1). The reported maximum plasma concentrations in obese vs. general population following 20 mg dose were 214-305 vs. 299-360 µg.L-1, respectively. The area under plasma concentration vs. time curves in obese subjects vs. general population following 10 and 20 mg dose were 1155 vs. 1029; and 1204-2800 vs. 3200 µg.h.L-1, respectively.

Conclusions: Studies indicate that obese subjects exhibit varying and inconsistent changes across different pharmacokinetic parameters of rivaroxaban when compared with general population. Additional well-designed studies are warranted to better characterize the pharmacokinetic profile of rivaroxaban in obese subjects.

Keywords: Rivaroxaban. Pharmacokinetics. Obesity.

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Molecular and biopharmaceutical characterisation of Ciprofloxacin ester salts for enhancing solubility and permeability

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Abstract

Background: Ciprofloxacin (CPR), a widely used Fluoroquinolone (FQ) antibiotic, has limited permeability. Enhancing permeability through esterification offers a promising approach to overcoming these limitations and improving therapeutic efficacy.

Aim: The aim was to analyze molecular descriptors and biopharmaceutical properties to understand ciprofloxacin ester salts' crystallization, physicochemical properties, and permeability.

Method: This study compared CPR with 37 other FQs, analyzing Log P against Log S, Gibbs Energy, Critical Volume, tPSA, and Henry's law. Norfloxacin (NOR) was found to be similar to CPR. While Temafloxacin (TEM), Pazufloxacin (PAZ), Rosxacin (ROS), and Prulifloxacin (PRU) were selected for their properties. A diverse molecular library was built by modelling the esters coupling selected FQs. 49 different alcohols were applied for each drug, resulting in 294 prodrugs. These aliphatic alcohols were chosen based on the substitution to evaluate how the length of the carbon chain and the degree of the branching, especially iso and tert-branching patterns, affect the physicochemical activity.

Results: The analysis revealed a strong negative correlation between Log S and LogP ($r = -0.7364$, $p < 0.001$), meaning as Log S increases, LogP decreases. Log S alone explained 54.2% of the variation in LogP. Critical volume showed a moderate influence, but its effect was not statistically significant. In the multiple linear regression model, the overall significance was confirmed ($F = 8.33$, $p = 0.007$), indicating that at least one of the predictors (Log S or critical volume) contributed meaningfully to predicting LogP. The combined predictors (Log S and critical volume) accounted for 19% of LogP's variability, with an adjusted R-squared of 0.17, suggesting a modest predictive ability. The intercept value was statistically significant ($p < 0.001$), with a 95% confidence interval ranging from 0.8534 to 1.6857, indicating strong reliability. Log S showed a significant negative relationship with LogP ($p = 0.009$), while the coefficient for critical volume was insignificant ($p > 0.05$). Overall, Log S emerged as the main predictor, with critical volume having little impact on LogP in this model.

Conclusion: Regression analysis identified Log S as the key predictor for LogP, showing a strong negative correlation between solubility and hydrophobicity. While factors like critical volume had weaker correlations, the model highlighted the significant role of solubility. These findings are valuable for optimizing the oral permeability of prodrugs and improving therapeutic efficacy, particularly for drugs like CPR.

Keywords: Prodrugs, Molecular descriptors, Solubility, Permeability, Fluoroquinolone Esters.

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A Controlled Clinical Trial of Single-Dose Rivaroxaban in Fed Obese Subjects: Pharmacokinetic and Pharmacodynamic Findings from the RIVOBESE-PK Study

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Abstract

Background: The evidence of rivaroxaban's pharmacokinetics in obese compared with nonobese populations remains inconclusive.

Aim: To compare the pharmacokinetic and the pharmacodynamic profiles of rivaroxaban between obese and non-obese populations under fed state.

Methods: Participants who met the study's eligibility criteria were assigned into one of two groups: obese (body mass index ≥35kg/m^2) or non-obese (body mass index 18.5–24.9kg/m^2). A single dose of rivaroxaban 20mg was orally administered to each participant. Total of 19 blood samples over 48h, and multiple urine samples over 18h were collected for pharmacokinetic and pharmacodynamic parameters determination. Samples were analyzed using ultra-performance liquid chromatography coupled with tandem mass detector for rivaroxaban concentration measurements.

Results: Thirty-six participants were recruited into the study. Pharmacokinetic parameters were determined using WinNonlin software. Insignificant decrease of 13.5% in peak plasma concentration was observed in obese compared with non-obese participants (339.7±84.2 vs. 392.9±78.9 ng/mL; p=0.059). No significant changes were observed between the two groups in time to reach peak plasma concentration, area under plasma concentration–time curve over 48h or to infinity, elimination rate constant, half-life, apparent volume of distribution, apparent clearance, and fraction of drug excreted unchanged in urine over 18h. Statistical analysis of pharmacodynamic parameters revealed significant difference between obese and non-obese groups with respect to prothrombin time measurements at 1h (13.72 vs. 15.58, p=0.013) and 4h (13.64 vs. 16.47, p=0.008).

Conclusions: In this prospective controlled clinical trial, the pharmacokinetic profile of single 20mg dose of rivaroxaban was largely comparable between obese and non-obese participants. Furthermore, key pharmacokinetic parameters, including overall rivaroxaban exposure, remained unaffected in obesity.

Taken together, these findings suggest that dose adjustments for rivaroxaban may not be necessary in obese populations.

Keywords: randomised controlled trial; rivaroxaban; pharmacokinetics;

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AMLODIPINE ORALLY DISSOLVING FILMS FOR CHILDREN: ENHANCED SOLUBILITY AND DRUG RELEASE

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Abstract

Background:

Orally dissolving films (ODF) offer significant benefits for children who have difficulty swallowing conventional tablets.

Aim:

This study aimed to optimize the formulation of orally dissolving films (ODF) for amlodipine using the solvent casting method to enhance drug solubility, ensure efficient drug release, and improve paediatric patient compliance.

Methods:

The optimized ODF formulation included hydroxypropyl methylcellulose (HPMC) Pharmacoat-606 as the primary film-forming polymer, polyvinylpyrrolidone (PVP) as a co-polymer and filler, and Tween-80 as a surfactant to enhance the solubility of amlodipine besylate. Glycerin was used as a plasticizer to improve flexibility, while citric acid enhanced taste and stimulated saliva production, aiding in rapid disintegration. The films were characterized for mechanical properties, disintegration time, pH, drug content uniformity, and drug release. Additional analyses included scanning electron microscopy (SEM) to assess film surface morphology and differential scanning calorimetry (DSC) to determine drug dispersion within the polymer matrix.

Results:

The optimized ODF exhibited desirable properties, including a folding endurance of 119±1.27, a disintegration time of 1.22±0.07 minutes, a pH of 3.12±0.08, a tensile strength of 3.53±0.29 N/cm², a percent elongation of 7.85±0.84%, and a film thickness of 0.11±0.01 µm. Drug content uniformity was 101.52±2.57%, and complete drug release was achieved within 5 minutes,

ensuring quick therapeutic action. SEM analysis revealed a uniform drug distribution with a smooth surface and porous structure, facilitating rapid disintegration and dissolution. DSC thermograms indicated no distinct melting peak for amlodipine besylate, suggesting its amorphous dispersion within the polymer matrix, which contributed to the rapid drug release.

Conclusion:

This study offers valuable insights into the formulation of ODF, highlighting advancements in drug solubility and delivery technology, particularly for paediatric antihypertensive treatments

Keywords: Orally dissolving films (ODF); paediatric drug delivery; antihypertensive; bioavailability

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Efficient Labelling of PLGA Nanocarriers with PLA-Capped Ultrasmall Gold Nanoprobes

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Abstract

Background: Polymeric nanocarriers, such as Poly(lactide-co-glycolide) (PLGA), have become pivotal in therapeutic delivery, but their distribution and interactions within biological systems are not fully understood. Fluorescence-based probes, commonly used to study PLGA nanoparticles, have inherent limitations such as leaching, photobleaching, and poor spatial resolution, leading to the need for alternative strategies. Gold nanoparticles (GNPs) offer tuneable optical properties, high stability, ability to visualize and quantify, making them ideal for studying PLGA nanocarriers in biological systems.

Aim: This study aims to develop novel PLA-capped ultrasmall gold nanoparticles (usGNPs) for efficient labelling, imaging, and quantification of PLGA nanocarriers.

Methods: usGNPs were synthesized using a reducing agent without the use of capping agents. Dynamic light scattering (DLS) and transmission electron microscopy (TEM) were employed to assess the size and structural morphology of the usGNPs. Thiolated polylactic acid (PLA-SH) was synthesized via ring-opening polymerization, with MALDI-TOF, 1H-NMR, and FTIR analysis used to confirm the polymer's structure, molecular weight, and thiol functionality. PLA-SH was then utilized to functionalize the surface of the usGNPs through a phase transfer method. The resulting PLA-usGNPs were encapsulated into PLGA nanocarriers using the nano-precipitation method.

Results: Characterization studies confirm that the usGNPs maintained stability without aggregation, with a particle size of 4–6 nm. MALDI-TOF confirmed the polymer's monomer structure with an Mw of 3337.52, and a PDI of 1.04. 1H-NMR and FTIR verified the successful synthesis of PLA-SH, confirming the presence of the lactide unit and thiol (-SH) functionality. The successful functionalization of usGNPs with PLA-SH improved surface coverage, enhancing nanoparticle stability, reducing aggregation, and providing precise functionalization. The PLA-usGNPs were efficiently encapsulated within PLGA nanocarriers, which will be further evaluated for visualization and quantification in cultured cells and living organisms.

Conclusion: We successfully developed PLA-capped usGNPs for efficient labelling and imaging of PLGA nanocarriers. The usGNPs exhibited excellent stability, with a controlled size of 4–6 nm, and were effectively functionalized with PLA-SH, enhancing their stability and reducing aggregation. The encapsulation of PLA-usGNPs within PLGA nanocarriers was achieved, paving the way for their future application in precise visualization and quantification in biological systems.

Keywords: Ultra-small gold nanoparticle, thiolated-PLA, PLGA nanoparticle, Encapsulation, Imaging

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Anthracyclines-Induced Vascular Endothelial Dysfunction in Cancer Patients and Survivors using Brachial flow-mediated dilation (FMD) tool: A Systematic Review and Meta-Analysis

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Abstract

Background: Anthracyclines are effective antineoplastic drugs used against various malignancies; however, their clinical use is constrained by dose-dependent cardiotoxicity. Endothelial dysfunction is recognized as an early, independent event in cardiovascular diseases and may precede and contribute to anthracycline-induced cardiotoxicity. Brachial flow-mediated dilation (FMD) is a non-invasive technique that is widely considered as the gold standard for evaluating endothelial function. **Aim:** This study aimed to evaluate the validity of evidence on anthracycline-induced vascular endothelial dysfunction in cancer patients and survivors using FMD. **Methods:** We performed a literature search using PubMed, Embase, and Scopus from inception to August 2024, including studies measuring FMD in active cancer patients or survivors exposed to anthracyclines. The primary outcome was the difference in FMD values between anthracycline-treated patients and healthy controls or pre-treatment baseline measurements. We performed the meta-analysis using a random-effects model and evaluated the certainty in effect estimates. **Results:** Out of 513 identified records, 18 studies involving 841 patients met the inclusion criteria. Our meta-analysis showed a non-significant change towards a decline in FMD when compared to baseline. However, a significant reduction in FMD was observed in anthracycline-treated patients compared to healthy controls (SMD: -0.7363; 95% CI: -0.9790 to -0.4935; $p < 0.0001$). Subgroup analyses revealed consistent significant reductions in FMD for childhood cancers (SMD: -0.7189; 95% CI: -0.9903 to -0.4476; $p < 0.0001$), while adult cancers showed no significant difference. No significant publication bias was detected overall for healthy control comparisons. High heterogeneity was observed in the included studies ($I^2 = 72.3635\%$ versus healthy controls and $I^2 = 75.6876\%$ for childhood cancers subgroup analysis). **Conclusions:** Our findings suggest that anthracyclines induce vascular endothelial dysfunction, as indicated by lower FMD in cancer patients and survivors, particularly among those with childhood cancers, who might be at risk of long-term cardiovascular complications.

Keywords: Systematic review; Anthracyclines; Cancer; cardiotoxicity

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"UNVEILING THE ANTIMICROBIAL POTENTIAL OF N, N-DIMETHYL BIGUANIDE ANALOGS: A NOVEL STRATEGY TO COMBAT RESISTANT *ESCHERICHIA COLI* INFECTIONS"

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Abstract

Background: Recently, Acquired Drug Resistance (ADR) and Antibiotic Multidrug Resistance (AMR) development against antibiotics is the new dilemma, the world is facing, due to extensive and irregular use of antibiotics, causative of resistance to multiple drugs. Among these, *Escherichia coli (E. coli)* has been an alarming concern, due to its propensity to allow the build-up of resistance genes mainly by horizontal gene transfer resulting in accession of gene coding for β-lactamases (cephalosporin resistance).

Aim: The aim of this study was to evaluate the antibacterial activity of novel analogs of N, N-dimethylbiguanide against multidrug-resistant (MDR) E. coli strains

Methodology: Firstly, *E.coli* resistant strains (n=5) were collected (urine samples), isolated by Culture Sensitivity testing, and characterized through a DNA extraction kit, followed by polymerization chain reaction (PCR) with resistant gene primers (bla_{TEM} and bla_{CTX}), and Gel Electrophoresis. N, N-dimethylbiguanide (Metformin), a drug of the biguanide class, possesses antidiabetic activity and has been under investigation for its antibacterial activity. These strains were then employed for antibacterial profiling of seven novel analogs of N, N-dimethylbiguanide (M01-M07) by implementing quantitative antimicrobial susceptibility testing (96-well plate minimum inhibitory concentration (MIC) determination method, using ELISA reader) against standard drug i.e. cefixime followed by MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) assay.

Results: All the isolated strains were characterized and found resistant indicated by the expression of bands on gel whereas, in non-resistant strains, bands were absent. All the studied compounds exhibit good antibacterial activity, while analog M07= 46.875 µg, M05= 93.75 µg, and M04 = 187.5 µg, by MTT assay method confirming through colorimetric image for identified MICs.

Conclusion: Analogs of N, N-dimethylbiguanide have shown proven antibacterial activity against multidrug *E.coli* resistance (MDR) strains that can be further evaluated for in-vivo studies to be marketed to overcome *E. coli* resistance worldwide.

Keywords: Multidrug resistance (MDR), N, N-dimethylbiguanide, 96-wellplate, ELISA, MTT assay.

Zoochemical Analysis, Antioxidative Activity Screening, and In Ovo Antiangiogenic Activity Assessment of Golden Kuhol (*Pomacea canaliculata*) Crude Methanolic Egg and Soft Body Extracts: A Preliminary Study

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Abstract

Background: Cancer remains a leading cause of death globally, with angiogenesis and oxidative stress as the main positive contributing factors in tumorigenesis and cancer development. *Pomacea canaliculata*, a freshwater snail, known for its notoriety as a pest in rice paddies is still to be studied with its potential therapeutic applications — unexplored.

Aim: This study aims to screen the zoochemicals present and evaluate potential antioxidant and antiangiogenic properties of methanolic extracts from *P. canaliculata* soft body parts (head and foot, gastrointestinal, and visceral regions) and eggs.

Methods: The extracts were subjected to zoochemical screening to identify various bioactive compounds. The antioxidant activity was evaluated using the DPPH radical scavenging assay, and the antiangiogenic potential was assessed through the duck embryo in ovo chorioallantoic membrane (CAM) assay.

Results: Zoochemical screening revealed the presence of alkaloids, flavonoids, saponins, sterols, carbohydrates, and proteins in all extracts. Polyphenols were identified only in certain soft body parts and absent in eggs. Antioxidant activity, assessed via the DPPH radical scavenging assay, showed weak to moderate effectiveness. The Snail Gastrointestinal Extract (2000 µg) achieved 33.63% radical scavenging, comparable to 12.5 µg ascorbic acid at 34.13%, with significant differences observed between controls and treatment groups. The CAM assay demonstrated that extracts from soft body parts and eggs inhibited blood vessel growth, with positive mean inhibition rates suggesting effective antiangiogenic properties. *P. canaliculata* egg extract showed the highest percent inhibition in both average vessel diameter (D_V) (42.00%) and total length (LT) (42.67%). No significant differences were found between the treatment groups and the quercetin in terms of inhibition rates in both parameters.

Conclusions: The study concludes that *P. canaliculata* extracts possess notable antioxidant and antiangiogenic activities. The extracts' bioactive compounds contribute to their therapeutic potential, particularly in cancer prevention and treatment.

Keywords: Antiangiogenic; Antioxidant; CAM Assay; *Pomacea canaliculata*; Golden Kuhol

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Population pharmacokinetics models of vancomycin among critically ill obese and non-obese adult patients: A systematic review

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Abstract

Background: Vancomycin, a glycopeptide antibiotic, holds significance in the treatment of gram-positive infections. Over the past decades, several population pharmacokinetic models for vancomycin have emerged.

Aim: This study aims to systematically review existing pharmacokinetic models, with specific objectives to (i) facilitate a comparative analysis of these models and (ii) provide a comprehensive investigation and summarization of factors influencing vancomycin pharmacokinetics.

Methods: Employing a systematic approach, a systematic literature review was conducted by scrutinizing the PubMed, PubMed Central, and SCOPUS databases for articles published from conception to June 2024. The focus was on population pharmacokinetic studies of vancomycin in critically ill obese and non-obese adult patients. The examples of exclusion criteria were: excluding in vitro and pre-in-vitro and pre-clinical research, review and meta-analysis, non-compartmental analyses, epidemiological, qualitative and survey-based studies. Information gathered encompassed research characteristics, patient demographics, clinical parameters, pharmacokinetic parameters, study outcomes, and software.

Results: The review incorporated findings from five studies, revealing a prevailing characterization of vancomycin pharmacokinetics as one-compartment in most investigations. Notably, significant interindividual variations in vancomycin pharmacokinetic parameters were consistently observed across the majority of studies. Factors influencing these variations encompassed age, sex, body weight, creatinine clearance, sever burn, albumin, and blood urea nitrogen. No effect was found for bacteraemia, sepsis , or septic shock. Notably, only one study undertook external validation to assess the predictive capabilities of the established models.

Conclusions: Despite the multitude of variables considered, a substantial degree of pharmacokinetic heterogeneity persists in vancomycin administration. Future advancements in this domain may be realized by incorporating a larger sample size and adopting a more rigorous sampling approach. Moreover, the refinement of population pharmacokinetic models can be achieved by integrating additional potential determinants, such as metabolic factors and significant drug-drug interactions. External validation of previously proposed models is recommended to ascertain their predictive accuracy.

Keywords: drug-drug interaction; vancomycin; systematic review; obese; critically ill

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Population pharmacokinetics model of vancomycin among critically ill obese adult Saudi populations

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Abstract

Background:

Vancomycin is still a drug of choice to treat several gram-positive infections. Vancomycin renal toxicity is a limiting factor for expanded and extended use. There is need to describe its pharmacokinetic (PK) parameters in critically ill obese patients due to potential nephrotoxicity.

Aim:

The purpose of this work is to develop a population pharmacokinetic model among obese critically ill obese patients.

Method:

This is a chart review retrospective analysis of 105 critically ill obese adult patients who were hospitalized in intensive critical care unit. Vancomycin concentrations were obtained from the patients' blood sample, measured at 1 hour and 419.97hours, as a part of therapeutic drug monitoring service in the Dr Suliman Al-Habib/Rayyan hospital. A population pharmacokinetic model of vancomycin was developed using nonlinear mixed effect modelling (NONMEM) software, involving the base and covariate model building. The likelihood ratio test was used to discriminate between models. The final model was chosen based on objective function value (OFV), goodness-of-fit, visual predictive checks and scientific plausibility.

Results:

The model fitted a first order, two-compartment structural model, with combined residual error. The value of vancomycin central clearance (CL) was 1.18 L/hr, central volume of distribution (Vd) 44.1 L, , inter-compartmental clearance 2.52 L/hr, and peripheral Vd 102 L. Central Vd was affected by gender and creatinine clearance. The Vd of peripheral compartment was affected by creatinine clearance. Vancomycin CL from central and peripheral compartments was not affected by any studied variable.

Conclusion:

The population PK model of vancomycin was successfully developed among critically ill obese adult Saudi population. Creatinine clearance was as a significant covariate for Vd in central and peripheral compartment. Gender is an additional significant covariate for Vd in central compartment.

Keywords: Critically ill; obese; pharmacokinetics; vancomycin

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Endothelial Sestrin2 Coordinates Multiple Protective Pathways to Maintain Angiogenic Function in Diabetes-Associated Endothelial Dysfunction

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Abstract

Background: Diabetes mellitus is a global health concern, with vascular complications accounting for over 70% of associated deaths. Methylglyoxal (MGO), a by-product of glycolysis, significantly contributes to vascular dysfunction in diabetes. Sestrin2 (SESN2), a stress-induced protein, regulates cellular homeostasis and stress responses, but its specific role in endothelial function under diabetic conditions remains unclear.

Aim: To investigate the role of SESN2 in preserving endothelial cell function and angiogenic capacity under diabetic conditions, particularly in response to MGO-induced stress.

Methods: SESN2 expression was modulated through silencing and overexpression techniques in EA.hy926 endothelial cells. Cells were then, exposed to MGO to simulate diabetic stress conditions. Angiogenic capacity was assessed through tubular network formation, zymography, proliferation, and invasion assays. Western blot and qPCR analyses were used to assess the key signaling pathways involved.

Results: The study reveals that SESN2 is a vital regulator of many protective pathways through both loss-of-function and gain-of-function methodologies in EA.hy926 endothelial cells. *SESN2* overexpression significantly maintained tubular network formation, proliferation, and invasive capability under MGO stress, whereas *SESN2* suppression exacerbated MGO-induced impairments. SESN2 was identified to orchestrate the activation of the NRF2/HO-1 antioxidant pathway while simultaneously enhancing VEGF-C expression, offering a dual strategy for cellular protection and angiogenesis enhancement. Moreover, SESN2 facilitated a regulated equilibrium of the AKT/mTOR signaling pathway, ensuring synchronized activation during stress conditions. SESN2 also regulated stress-activated MAPK pathways, diminishing P38 and ERK1/2 activation upon MGO exposure. Furthermore, SESN2 exhibited anti-apoptotic properties by positively modifying the BAX/BCL2 ratio and diminishing CASPASE3 cleavage during MGO-induced stress.

Conclusions: These findings establish SESN2 as a pivotal regulator of endothelial cell homeostasis and angiogenic activity under diabetes conditions. This study highlights the complex protective functions of SESN2, indicating its potential as a therapeutic target for addressing diabetic vascular complications and improving patient outcomes.

Keywords: Diabetes; endothelial dysfunction; Western blot; angiogenesis

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Sestrin2 Suppression Promotes Endothelial-Mesenchymal Transition and Exacerbates Methylglyoxal-induced Endothelial Dysfunction

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Abstract

Background: Sestrin2 (SESN2) is a stress-responsive protein recognized for its cytoprotective properties. Nonetheless, its role in diabetic vascular complications, especially in endothelial-mesenchymal transition (EndMT), remains unclear. Methylglyoxal (MGO), a reactive dicarbonyl compound increased in diabetes, causes endothelial dysfunction and facilitates EndMT.

Aim: The aim of this study was to examine the impact of SESN2 on MGO-induced EndMT and to elucidate its potential protective function in endothelial cells against vascular complications associated with diabetes.

Methods: Human endothelial cells (EA.hy926) were transfected with *SESN2* siRNA duplexes to downregulate SESN2 expression, followed by treatment with MGO (600 µM for 18 hours). The expression of endothelial and mesenchymal markers, oxidative stress indicators, inflammatory cytokines, and EndMT-related signaling pathways was then evaluated using Western blot analysis and quantitative PCR.

Results: *SESN2* knockdown markedly aggravated MGO-induced oxidative stress, as indicated by reduced expression of antioxidant markers including Nrf2 and elevated levels of Keap-1. Silencing *SESN2* enhanced the inflammatory response to MGO, as evidenced by elevated levels of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α. *SESN2* deficiency significantly facilitated EndMT, evidenced by elevated levels of mesenchymal markers (α-SMA, vimentin) and reduced levels of endothelial markers (VE-cadherin, PECAM-1). The study also revealed that *SESN2* knockdown exacerbated MGO-induced stimulation of TGF-β signaling and the overexpression of transcription factors including Snail, which are crucial mediators of EndMT.

Conclusions: These findings indicate that SESN2 has a vital protective function in endothelial cells against damage caused by MGO. The downregulation of *SESN2* may facilitate the pathophysiology of diabetic vascular complications by enhancing EndMT, elevating oxidative stress, and aggravating cellular inflammation. This study offers a new understanding of the molecular pathways associated with cardiovascular complications in diabetes and recognizes SESN2 as a possible therapeutic target for the prevention of endothelial dysfunction in diabetic patients.

Keywords: Sestrin2; methylglyoxal; endothelial dysfunction; endothelial-mesenchymal transition.

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Combination of Curcumin and Cisplatin Induces Apoptosis and Anti-migration Effect in Lung Adenocarcinoma through ERK/RSK and AKT/mTOR Pathways

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Abstract

Background: Lung cancer is a leading cause of mortality worldwide. Cisplatin is one of the most common anti-cancer drugs. However, cisplatin loses its sensitivity in the late stages of cancer and has severe side effects. This raises the need for an alternative treatment method such as combinations with natural products like curcumin.

Aim: This study aimed to investigate the effect of the combination of cisplatin and curcumin on inducing apoptosis and anti-migration effect in A549 lung cancer cell line, as well as their effect on the expressions of MAPK downstream mediators ERK1/2 and RSK1, as well as AKT/mTOR pathway.

Methods: Apoptosis effect was examined by measuring cell viability using MTT assay. Migration rate was measured by performing scratch migration assay, while the effect of the combination on the expression of the phosphorylated and the total proteins of ERK1/2, RSK1, AKT, and mTOR was examined by western blotting. Finally, flow cytometry was conducted to examine the effect of the combination on the cell cycle phases of A549 cells.

Results: This study showed that the combination of cisplatin and curcumin significantly decreased the cell viability of A549 cells compared to the single treatment of cisplatin or curcumin at 24hrs and 48hrs. Similar effect was observed in the scratch migration assay where the combination of cisplatin and curcumin significantly decreased the migration of A549 cells after 24hrs compared to the single treatment (80.3% 10µM cisplatin and 70.2% 30µM curcumin vs 37.9% combination group ± 2.64, $P<0.01$). The combination of cisplatin and curcumin could increase the expression of p-ERK/ERK and p-RSK/RSK, while it could decrease the expression of p-AKT/AKT and p-mTOR/mTOR at 48hrs. The combination resulted in significant cellular arrest at G2/M phase at 24hrs (22.6% NT vs 33.3% combination group ± 1.98, $P<0.05$), and significant cellular arrest at S phase at 48hrs (2.77% NT vs 32.06% combination group ± 1.81, $P<0.05$).

Conclusions: This project investigated the effect of the combination of cisplatin and curcumin on the A549 cells viability, migration, cell cycle phases, and its effect on the expression of ERK/RSK and AKT/mTOR pathways.

Keywords: cisplatin; curcumin; apoptosis; cancer

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Artificial Intelligence in synthesis and retro synthesis of therapeutic molecules: Paving the Way for Future Innovations

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Abstract

Background: Medicinal Chemistry is a field of science where artificial intelligence (AI) is encouraged with great expectations to identify new chemical entities with desirable properties efficiently. Machine learning (ML) and deep learning (DL) are widely used for various stages of drug discovery including lead identification, drug screening and design, and physio-chemical properties like interactions, toxicities, etc.

Objective: This abstract aims to identify the wide application of AI, in de novo synthesis and retro synthesis of therapeutic molecules by integrating various computational techniques and comprehending their effect in pharmaceutical development.

Methodology: A systematic research was carried out pertaining to the implications of AI in Medicinal Chemistry by examining various databases including PUBMED and CINAHL from inception until November 2024. The quest dwelled in the literature about the utilization of AI in Medicinal Chemistry and drug synthesis.

Results: The interim analysis revealed that 24 out of 200 studies met the inclusion criteria. ML, DL, Robotics, Machine Learning for Pharmaceutical Discovery and Synthesis (MLPDS) ,Computer aided synthesis planning (CASP),Computer Aided Drug Design (CADD), and artificial neural networks (ANNs) were the most relied upon AI techniques. These mainly focused on the various methodologies for lead identification, optimization, QSAR analysis, to speed up the initial phases of drug development. Furthermore, reverse compound formulation and on-the-fly autonomous process optimization were made feasible *in silico.* Additionally, it gives an insight into how AI algorithms are used to forecast molecular parameters including drug toxicity, drug–target interactions, and protein structures. Though AI has sped up the drug discovery process, challenges with data quality and technological restrictions persist.

Conclusion: AI algorithms are used for *de novo drug* synthesis and inverse formulation. It also aids to forecast molecular parameters including drug toxicity, drug–target interactions, and protein structures.

Keywords: Artificial Intelligence, Machine Learning, CADD, QSAR,*de novo* synthesis

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Eco-friendly Synthesis, Scale-up of silver nanoparticles using Andrographis paniculata root extract and evaluation of its Antimicrobial, Blood Anticoagulant activities and Cytotoxicity against HeLa and HaCaT cells

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Abstract

Background:

Silver nanoparticles are well known for their antimicrobial, antioxidants, anticancer and anti-inflammatory activities.

Aim:

This study aims to synthesize silver nanoparticle using root extract of *Androghraphis paniculata*, scale-up the production conditions, characterise their physiological properties and investigate their anticancer, antibacterial and antifungal activities.

Methods:

Silver nanoparticles (AgNPs) were synthesized using a cost-effective and eco-friendly method by optimizing extract concentration, temperature, $AgNO_3$ concentration, extract-to-$AgNO_3$ ratio, pH, and reaction time. Characterization was performed using UV-Vis spectroscopy (for optical properties), FT-IR spectroscopy (for functional groups), DLS (for particle size), XRD (for crystallinity), and FE-SEM/FE-TEM (for morphology).

In vitro cytotoxicity was evaluated against HeLa (cervical adenocarcinoma) and HaCaT (human keratinocyte) cells to assess anticancer potential and biocompatibility. Antibacterial activity was tested against Bacillus thuringiensis, Staphylococcus aureus, Escherichia coli, and Salmonella typhimurium, while antifungal activity was assessed using Candida albicans and Aspergillus niger. The blood anticoagulant properties of the synthesized AgNPs were also examined.

Results

The UV-Vis spectroscopy analysis showed a characteristic absorption peak between 420–442 nm, confirming the formation of AgNPs. FE-TEM analysis revealed that the nanoparticles were crystalline, spherical, and irregular in shape, with an average size of approximately 10 nm. Cytotoxicity studies showed that AgNPs exhibited strong anticancer activity, reducing the survival of

HeLa cells to 5–10%, while demonstrating very low toxicity to HaCaT cells, indicating good biocompatibility. Antibacterial assays confirmed significant antimicrobial activity against both Gram-positive and Gram-negative bacteria, and antifungal assays showed effectiveness against Candida albicans and *Aspergillus niger.* The synthesized AgNPs also demonstrated excellent blood anticoagulant properties, highlighting their potential applications in biomedical and nanotechnology industries.

Conclusion: This study demonstrated that silver nanoparticles (AgNPs) synthesized from A. paniculata exhibit strong anticancer, antimicrobial, and anticoagulant properties with good biocompatibility. These findings highlight their potential for biomedical applications, warranting further in vivo studies for clinical validation.

Key words: *Andrographis paniculata,* antimicrobial, HeLa cell, HaCaT cell, blood anticoagulant.

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Optimizing Thymoquinone-Loaded Hexosomes: A Novel Therapeutic Strategy to Address Autism-Like Deficits by Targeting Oxidative Stress in a Mouse Model of Autism

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Abstract

Background: Autism spectrum disorder (ASD), is a significant public health concern due to notable increase in prevalence with absence of any effective treatment due to unclear mechanisms underlying this condition. Yet research has recognized that neural oxidative stress and neuroinflammation are critical contributing factors.

Aim:

Thymoquinone (TQ), a well-established antioxidant, was loaded into a novel hexosomal nanoparticle to evaluate its potential to mitigate cognitive and social impairments as well as neural oxidative stress in the idiopathic autism model using BTBR mice.

Methods:

A 2^3 full factorial design was employed to optimize a novel TQ-loaded hexosomal nanoparticle formulation. The factorial design employed the varying concentrations of oil phase and stabilizer as independent with the entrapment efficiency, particle size, and zeta potential analyzed as dependent variables. The free and loaded TQ was evaluated through various behavioural assessments conducted using a battery of standard tests to evaluate parameters such as social behaviour, locomotor activity, and anxiety levels. Moreover, Biochemical analyses of oxidative stress markers in the cerebellum and hippocampus were also performed across treatment groups.

Results: The findings demonstrated significant improvements in sociability and social novelty preference in BTBR mice treated with TQ-loaded hexosomes (both $p<0.01$) and free TQ ($p<0.05$ and $p<0.01$, respectively). Additionally, TQ-loaded hexosomes treatment restored anxiety levels ($p<0.05$) and modulated hyperactivity parameters ($p<0.05$). Biochemical assessments revealed substantial reductions in neural oxidative stress, characterized by increased levels of antioxidant proteins such as reduced glutathione ($p<0.01$) and catalase ($p<0.01$), along with decreased levels of the oxidative stress by-product malondialdehyde ($p<0.01$).

Conclusion:

These preclinical results highlight the robust antioxidant potential of TQ and its promise as a therapeutic option for autism spectrum disorder (ASD). With further investigation, this study provides a foundation for transitioning TQ-loaded nanovesicle therapy into clinical trials.

Keywords: Autism; hexosomes; oxidative stress; thymoquinone

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Low-Intensity Aortic Baroreceptor Stimulation: A Novel Neuromodulation Strategy for Blood Pressure Reduction

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Abstract

Background: Carotid baroreceptor stimulation has shown promise as an antihypertensive therapy, yet the potential of aortic baroreceptor modulation remains clinically unexplored. Current approaches often rely on high-energy neuromodulation techniques, which are inefficient and may compromise long-term nerve viability.

Aim: This study aimed to identify optimal, low-energy stimulation parameters for the aortic baroreceptor afferents that effectively reduce mean arterial pressure (MAP) by ≈ 30 mmHg.

Methods: The aortic depressor nerve (ADN) was stimulated in anesthetized spontaneously hypertensive rats (SHRs). The depressor effects of low-frequency stimulation (1, 2.5, 5 Hz) across pulse amplitudes (0.2, 0.4, 0.6 mA) and widths (0.1, 0.2, 0.5 ms) for 20-second intervals were measured.

Results: A clear frequency-dependent depressor response was observed. At lower pulse amplitudes (0.2 mA), MAP dropped ≈ 18 mmHg across all pulse widths. Higher amplitudes (0.4 and 0.6 mA) achieved a consistent MAP reduction of ≈ 34 mmHg, with no additional benefit beyond 0.4 mA.

Conclusions: These findings demonstrate that low-intensity ADN stimulation provides a robust antihypertensive effect with minimal energy requirements, paving the way for more efficient and sustainable neuromodulation strategies. This approach holds promise for advancing clinical translation while preserving nerve integrity.

Keywords: Neuromodulation; Baroreceptor reflex; Aortic depressor nerve, Hypertension; Spontaneously Hypertensive Rats

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MiR-299-3p as a Modulator of Stemness and Anti-Tumour Immune Responses in Colorectal Cancer Stem Cells

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Abstract

Background: Cancer stem cells (CSCs) are rare cell subpopulations within tumours that exhibit self-renewal capabilities and stemness characteristics, contributing to tumour development, metastasis, recurrence, and therapeutic resistance. Nonetheless, the mechanisms underlying their tumorigenicity, immune evasion, and therapeutic resistance remain inadequately elucidated, especially regarding the function of miR-299-3p in CRC CSCs.

Aim

This study aimed to explore the role of miR-299-3p in colorectal cancer stem cells and assess its potential as a target for improving treatment and immune response in colorectal cancer.

Methods: This study utilized primary cell lines derived from CRC patients (CRC; N=10), comprising differentiated tumour cells and CSCs. Differentially expressed miRNAs between CRC-CSCs and differentiated tumour cells were identified using the nCounter platform. The expression of miR-299-3p in the cell lines was modulated using miRVana mimic and inhibitor by Neon electroporation. Subsequently, RNA sequencing (RNAseq) was conducted to identify key altered pathways and genes, followed by comprehensive molecular and functional validation, including cell proliferation assay, characterization of immune and stemness markers via flow cytometry, RT-qPCR, IDO-release assay, and co-culturing tumor cells with HLA-matched lymphocytes to evaluate their capacity to provoke antigen-specific T cell responses.

Results: MiR-299-3p was found to be elevated ($p<0.05$) in CRC-CSCs relative to their differentiated counterparts. The functional validation of the role of this miRNA was conducted via its overexpression in CRC cell lines, resulting in decreased cell proliferation, whereas its

inhibition promoted cell proliferation. RNAseq indicated that the modification of mir-299 dramatically affected genes associated with tumor development, invasion, and immune cell infiltration. Subsequent validation by RT-qPCR demonstrated that miR-299-3p mimics decreased the expression of critical genes, including VEGFA, CD47 and vimentin. Notably, untreated CSCs produced inadequate anti-tumor T-cell responses when co-cultured with PBMCs; however, transfection with miR-299-3p mimics significantly augmented their anti-tumor immune responses, as demonstrated by the elevated release of IFN-γ. These responses were associated with elevated HLA class-I expression and a slight reduction in IDO release.

Conclusion: Our results show that mir-299-3p can potentially serve as a therapeutic target for CRC.

Keywords: Colorectal cancer; Therapeutic resistance; Tumorigenicity

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Integrated gene expression data analysis and machine learning guided approaches to identify potential biomarkers and inhibitors for the treatment of Esophageal cancer

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Abstract

Background: Colorectal cancer (CRC) is one of the most common cancers and currently reported as a significant public health challenge globally. There is a need to improve screening programs, diagnostic methods, and treatment options to reduce mortality rates.

Aim

This study aims to develop an integrated framework combining network pharmacology, machine learning, and all-atom molecular simulations to identify novel biomarkers and design targeted therapies for colorectal cancer.

Methods: Here, a comprehensive, state-of-the-art approach with integration of network pharmacology, machine learning and all-atoms molecular simulations will be applied to the complex biology of colorectal cancer. **Results:** Network pharmacology for the key molecular targets and their interactions with proposed therapeutic agents, and machine learning improves biomarker discovery, providing high predictive accuracy. It is always beneficial to validate drug-target interactions at an atomic level, and the all-atoms simulations presented here will facilitate that by providing insights into the stability and efficacy of the drug molecule under different conditions. This integrated framework offers a powerful strategy for identifying novel biomarkers and designing targeted therapies for colorectal cancer. **Conclusion:** It supports personalized medicine by improving drug discovery pipelines and addressing gaps in CRC management, offering hope for more effective treatment strategies, particularly in Qatar where the disease's burden continues to grow.

Keywords: cancer; molecular target; machine learning; gene therapy

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Potential Cytotoxicity of Roundup® and Its Constituents on Human Skin Cells: Evidence from Two Different Colorimetric Assays

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Abstract

Background

The toxicity of glyphosate-based herbicides such as Roundup® has sparked an ongoing debate in the scientific community, due to concerns about their potential impact on human cells. Although earlier literature have reported the impact of Roundup® on different cell types, the results on a cultured HaCaT keratinocyte cell remain scarce.

Aim: This study aims to evaluate and compare the cytotoxicity of Roundup®, glyphosate, and the surfactant POEA on HaCaT cells by assessing cell viability across different concentrations.

Methods

An experimental approach was employed, and HaCaT cells were cultured in everyday settings. Cells were incubated in the presence of realistic exposure levels of Roundup® (up to 5%) glyphosate (up to 5000 µM) and POEA (4.5, 9, 13.6, 17.9, and 22.4 µM) for 24 hours. The cytotoxicity of the compounds was tested using a Crystal Violet assay and MTT assay, in which cell viability was measured in terms of absorbance and adherence.

Results

Roundup® was found to exhibit a cytotoxic effect, reducing cell viability to 47% + 3% at 0.05% ($p < 0.05$), compared to the negative control. By contrast, cell viability of glyphosate at concentrations of 5000 µM was > 85 % (minimal toxicity). Thus, POEA showed a concentration-dependent inhibition of cell growth starting at 13.6 µm, confirming this molecule's expected action to be the leading cause of the observed lethality with Roundup®.

Conclusions

Accordingly, current findings indicate that POEA, not glyphosate, is the primary cause of cytotoxicity in Roundup® on HaCaT cells. These results underscore the need for holistic safety investigations of formulated herbicides before they are administered to the public and that a possible alternative for POEA should be explored.

Keywords: Glyphosate, Roundup®, Cytotoxicity, Keratinocyte HaCaT cells, POEA

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Immune Checkpoints as Drivers of Colorectal Cancer Stem Cell Features: A Molecular Profiling Study

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Abstract

Background: Colorectal cancer (CRC) ranks among the most frequently diagnosed malignancies and is a leading cause of cancer-related deaths globally. Cancer stem cells (CSCs) are rare subpopulations within tumors that drive tumor development, metastasis, recurrence, and chemoresistance. However, the processes behind their tumorigenicity and therapeutic resistance are not entirely understood, especially the role and function of immune checkpoints (ICPs).

Aim: This study aims to a) perform extensive molecular profiling of colorectal CSCs, focusing on the differential expression of immunomodulatory markers, and b) identify new drug targets for the eradication of CSCs.

Methods: This study employed four CRC cell lines (HCT-116, HT-29, SW480, SW620) with normal colorectal cells (CCD841). CSCs were enriched by spheroid culture. Stemness marker and inhibitory ICP expression levels were assessed using real-time PCR and Western blotting. Besides, a comparative proteomic investigation of the entire colorectal CSC proteome versus their differentiated tumor counterparts was conducted utilizing a mass spectrometry-based label-free shotgun proteomics method.

Results: Cells grown in spheroid culture exhibited a significant elevation in the expression of stemness markers (e.g., ALDH, NANOG, CD133, SOX-9), increasing by 1.7-7.7 folds ($P<0.01$), thereby confirming the successful enrichment of the CSC subpopulation. This upregulation of stemness markers was accompanied by a corresponding increase in the expression of various inhibitory checkpoints (e.g., PD-L1, B7H3, CD47, CD155), increasing by 1.4-5.4 folds ($P<0.01$),

compared to their differentiated counterparts, suggesting a potential role of these ICPs in mediating CSC characteristics. The interaction between ICPs and stemness markers correlated with the dysregulation of many CSC proteins ($P<0.05$) involved in cancer progression and chemoresistance, as demonstrated by the KEGG-Reactome pathway analysis.

Conclusion: The distinctive immunological profile of the colorectal CSCs revealed in this study suggests that ICPs play a role in CSCs immune evasion and could represent a prime target for checkpoint blockade immunotherapy for CSC treatment.

Keywords: Colorectal Cancer, Immune Checkpoints, Cancer Stem Cells, Proteomics

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Thymoquinone Mediates Müller Cell Apoptosis via miR-29b/SP1 Pathway: A Potential Therapeutic Approach in Diabetic Retinopathy

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Background: Diabetes Mellitus (DM) is a major global health and economic challenge, leading to complications like diabetic retinopathy (DR), neuropathy, and nephropathy.

Aim: This study aims to explore the therapeutic potential of thymoquinone (TQ) in DR by assessing its effects on Müller cell apoptosis through modulation of the miR-29b/SP1 pathway in a diabetic animal model.

Methods: Healthy C57BL/6 mice (25g) were used in the study. Retinal samples were collected from both normal and diabetic mice: TQ (1mg/kg/day), glibenclamide (250 mg/kg/day), sitagliptin (10 mg/kg/day), and metformin (5 mg/kg/day) over a period of 28 days. The study measured miR-29b and SP1 mRNA levels using qRT-PCR. Protein expressions of SP1, Bax, and bcl-2 were analyzed through western blotting, while Caspase-3 activity using an ELISA assay kit, and apoptosis levels by annexin V.

Results: TQ administration resulted in a 52% reduction in blood glucose levels. Similarly, glibenclamide, sitagliptin, and metformin treatments reduced blood glucose by 60%, 57%, and 61%, respectively ($p<0.05$). In addition, TQ upregulated miR-29b by 51.28% and downregulated SP1 mRNA by 32.52% ($p<0.05$). Bax protein expression levels were decreased by 64.99%, while Bcl-2 protein expression increased by 62.92% in the TQ treatment group as compared to the untreated diabetic controls. Furthermore, Caspase-3 activity was downregulated by 40.03% with TQ treatment ($p<0.05$). Interestingly, the effect TQ on SP1 mRNA expression was inhibited by a miR-29b blocker, while an miR-29b mimic enhanced this effect; this was associated with a mitigation of apoptosis of retinal Müller cells as measured by flow cytometry ($p<0.05$).

Conclusions: These results indicate that TQ might be a possible option for DR *via* its effect on the miR-29b/SP1 pathway; and therefore, playing a significant role in the mechanism against cell death.

Keywords: Thymoquinone; Diabetic Retinopathy; microRNA-29b (miR-29b); Specificity Protein 1; Müller cell; Apoptosis.

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Surface-Coated Nanoparticles for Enhanced Paclitaxel Production in Taxus Callus Cultures

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Abstract

Background:
Paclitaxel (PTX) is an important chemotherapeutic agent, but its limited natural availability from yew trees requires alternative production methods. Plant cell cultures offer a sustainable solution, with nanoparticles (NPs) emerging as potential elicitors and carriers to optimize PTX biosynthesis. This study investigates the use of surface-coated nanoparticles, specifically chitosan conjugated with hydroxypropyl-β-cyclodextrin (CS-g-HPβCD), to enhance PTX production and interact with biosynthetic pathways in *Taxus* callus cultures.

Aim:
To evaluate the ability of surface-coated nanoparticles (CS-g-HPβCD) to improve PTX production in *Taxus* callus cultures by enhancing adsorption capacity and biosynthetic activity.

Methods:
CS-g-HPβCD nanoparticles were synthesized by conjugating chitosan (CS) with hydroxypropyl-β-cyclodextrin (HPβCD). Characterization was performed using dynamic light scattering (DLS), scanning electron microscopy (SEM), and Fourier-transform infrared spectroscopy (FTIR). The nanoparticles had an average size of 304.1 nm, with polydispersity indices (PDI) of 0.416 and 0.422 for chitosan and COMnp nanoparticles, respectively. *Taxus* callus cultures were exposed to fluorescently labeled nanoparticles, and localization was observed via confocal microscopy. PTX production was quantified by high-performance liquid chromatography (HPLC), and gene expression of key biosynthetic genes (*taxadiene synthase* [TXS] and *baccatin III hydroxylase* [DBAT]) was analyzed by qRT-PCR.

Results:
COMnp nanoparticles exhibited 50% adsorption efficiency for paclitaxel, with a total taxane recovery of 190 µg per 50 µL of nanoparticles. Confocal microscopy confirmed nanoparticle adherence to *Taxus* callus cells. Intracellular PTX production reached 33.12 ± 1.59 µg/mL, while extracellular PTX was 13.37 ± 1.85 µg/mL. Gene expression analysis revealed a 4.2-fold upregulation of TXS and a 3.8-fold increase in DBAT expression in nanoparticle-treated cells.

Conclusions:
Surface-coated nanoparticles, specifically CS-g-HPβCD, significantly enhance PTX production and secretion in *Taxus* callus cultures, suggesting their potential as dual-function elicitors and carriers for sustainable PTX production.

Keywords: Paclitaxel; drug delivery; cancer; nanotechnology

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Examining the effects of e-cigarette exposure with and without CDP-choline treatment on hormone levels and withdrawal-induced anxiety using a rat model

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Abstract

Background: Although the use of e-cigarettes is becoming more common, little is known about how it affects mental health, anxiety and hormones during withdrawal. Withdrawal symptoms may be lessened by the neuroprotective substance cytidine 5'-diphosphocholine (CDP-choline).
Aim: With an emphasis on blood levels of nicotine, cotinine, adrenaline, and beta-endorphins, this study investigates how CDP-choline affects withdrawal-induced anxiety and hormonal imbalances brought on by prolonged exposure to e-cigarettes.

Methods: Five groups of male Wistar rats were included in the study: control, e-cigarette-exposed, e-cigarette-exposed with CDP-choline, e-cigarette quitting with CDP-choline, and CDP-choline-only. For six weeks, rats were exposed to e-cigarettes for an hour, twice a day, five days a week, then the exposure was reduced for three weeks. At the beginning of week six, CDP-choline was given for three weeks. At baseline, during withdrawal, and after treatment, behavioral tests were performed, such as the light and dark box (LDB) test.

Results: Exposure to e-cigarettes increased anxiety-like behaviours and markedly increased serum levels of nicotine, cotinine, adrenaline, and beta-endorphins. Nicotine and cotinine levels were successfully decreased by CDP-choline treatment, especially in the quitting + CDP group ($p = 0.0416$) and the e-cigarette exposure + CDP group ($p = 0.0027$). Furthermore, CDP-choline significantly reduced beta-endorphin and adrenaline levels ($p < 0.0001$), which lessened withdrawal-related stress reactions.
Conclusion: In conclusion, by lowering hormonal imbalances and enhancing behavioural results, CDP-choline lessens the negative impacts of exposure to e-cigarettes. These results demonstrate its potential as an alternative for treating withdrawal symptoms caused by e-cigarettes.

Keywords: e-cigarettes; withdrawal; anxiety

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Formulation and characterization of Amorphous solid dispersion system of Celecoxib for improving its solubility and dissolution rate: An experimental and computational approaches

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Background

Celecoxib, a selective COX-2 inhibitor, commonly used for rheumatoid arthritis and osteoarthritis. However, its poor aqueous solubility and limited dissolution, results in low oral bioavailability and reduced efficacy.

Aim

This study aimed to predict and verify the compatibility of celecoxib with different polymer and formulate amorphous solid dispersion (ASD) to enhance its solubility and dissolution rate.

Methods

Molecular dynamics (MD) simulations using Material Studio 4.0 (Accelrys, San Diego, CA) predicted suitable carriers for Amorphous Solid Dispersions (ASDs) based on E_{mix} and E_{bs} analysis. ASDs were prepared with HPMC, PVP-K, Hydroxypropyl β-cyclodextrin (HP- βCD), and starch via freeze drying, labeled as SD1 - SD4. Characterization included solubility analysis, powder dissolution testing in pH 6.8 phosphate buffer at 37 ºC, FTIR, SEM, DSC-TGA and MD simulations parameters like radial distribution function (RDF), hydrogen bonding analysis of crystalline and amorphous system.

Results

The *in silico* results found that HP- βCD (E_{mix}: -8.70 kCal/mol, E_{bs}: -13.51 kCal/mol) is the most compatible carrier with celecoxib. The solubility and dissolution rates ranked as SD1 > SD2 > SD3 > SD4 > pure drug, indicating that SD1 exhibited the best solubility and dissolution activity. Broadening of OH (~3400 cm^{-1}), reduction in NH (~3325–3350 cm^{-1}) and C=O (~1650 cm^{-1}), and shift in S=O (~1248 cm^{-1}) in FTIR spectrums of freeze-dried ASDs indicated hydrogen bonding, complex formation. SEM showed that reduced the crystal size of celecoxib and altered its crystalline morphology, while DSC revealed broader endothermic peak in SD (160–170°C) indicated reduced crystallinity and confirming drug-polymer miscibility. Detailed MD simulations provide molecular insights into the molecular interaction by Radial distribution function and hydrogen bonding analysis of amorphous solid dispersion systems.

Conclusions

This combined experimental and computational approach optimized Celecoxib-HP-βCD dispersions, significantly improving solubility and dissolution rates while minimizing physical stability testing for enabling rational formulation development.

Keywords: celecoxib; ASD; polymer; drug development

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Revolutionizing Skin Rejuvenation Therapy: Design and Structural Elucidation of Mesoporous Silica Nanoparticles Loaded with Kojic Acid for Enhanced Topical Drug Delivery

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Abstract

Background: Excessive exposure of skin to UV irradiation leads to photoaging and triggers an overproduction of melanin, causing skin darkening and visible alterations in appearance. Effective dermal drug delivery systems are essential to enhance anti-pigmentation therapy by improving the stability and bioavailability of therapeutic agents.

Aim: This study aimed to design and evaluate mesoporous silica nanoparticles (MSNs) encapsulating kojic acid as a stable and efficient drug delivery system for enhancing anti-pigmentation therapy.

Methods: The synthesis of mesoporous silica nanoparticles involved the use of tetraethyl orthosilicate and cetyltrimethylammonium ammonium bromide (as a surfactant) through sol–gel methodology. Subsequent processes, including acid extraction and drug loading, were comprehensively characterized through size analysis, polydispersity index, zeta potential, entrapment efficiency (EE%), field emission scanning electron microscopy (FE-SEM), X-ray diffraction (XRD), Brunauer-Emmett-Teller (BET) technique, thermogravimetric analysis (TGA), Fourier transform infrared (FT-IR) spectroscopy, and differential scanning calorimetry (DSC). Cosmetic potential was evaluated through DPPH antioxidant assay and tyrosinase inhibition assay.

Results: The loaded MSNs exhibited an impressive EE of 90.013%. FE-SEM revealed the spherical and porous nature of the MSNs. Results demonstrated that the particle size of kojic acid-loaded MSNs was 240.8 nm, with a pore size of 2.63 nm. XRD analysis indicated the absence of crystallinity in KA-MSN, confirming its incorporation into MSNs carriers in an amorphous state. Ex-vivo rat skin permeation studies conducted in a phosphate buffer (pH=5.5) unveiled a biphasic release pattern, with drug-loaded mesoporous silica nanoparticles releasing 70.62% of their content after 24 hours, exhibiting a more rapid release in the initial four hours.

Conclusion: These findings substantiate the effectiveness of the synthesized mesoporous silica nanoparticles as a promising carrier for kojic acid, showcasing enhanced drug loading and skin permeation capabilities.

Keywords: Kojic Acid; nanotechnology; skin pigmentation; topical

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Novel Chalcone Analogues for Liposome-Targeted Therapy in Triple Negative Breast Cancer Using a Proliposome Technology

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Abstract

Background: Triple Negative Breast Cancer (TNBC) is an aggressive subtype with limited treatment options. Chalcone compounds exhibit anticancer potential by targeting key pathways in cancer progression, but their poor solubility and stability hinder clinical application. Liposomes, as nanocarriers, enhance drug delivery by improving solubility, stability, and selectivity. This study investigates novel pyridine-based chalcone analogues and their incorporation into proliposomes for improved TNBC treatment.

Aim: This study aims to evaluate the anticancer potential of pyridine-based chalcone compounds against TNBC cells and enhance their stability and efficacy through ethanol-based proliposomal formulations.

Methods: Chalcone compounds were prepared as stock solutions and tested on TNBC cell lines (MDA-MB-231, BT-20). Cell viability was assessed using the alamarBlue assay, while morphological changes were observed via stereomicroscopy. The soft agar colony formation assay was conducted, and the scratch assay measured cancer cell migration. Proliposomes were prepared using the ethanol-based proliposome method, and the resulting small unilamellar vesicles (SUVs) were characterized for size and surface charge using a Zetasizer.

Results: Chalcone compounds significantly reduced TNBC cell viability by 50% at 2 µM (MDA-MB-231) and 1.5 µM (BT-20). They induced notable morphological changes, inhibited 99% of colony formation, and suppressed cancer cell migration. The, these compounds were incorporated into a proliposomal formulation, generating SUVs with a hydrodynamic size below 100 nm, a polydispersity index of 0.1, and slightly negative zeta potential values.

Conclusion: This study demonstrates the potential of combining chalcone analogues with liposomal formulations to improve TNBC treatment. These findings support further in vivo investigations to develop effective, targeted therapies for this aggressive breast cancer subtype.

Keywords: Triple-Negative Breast Cancer, Chalcone Compounds, Anticancer Activity, Proliposomal Formulation

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Establishing Neratinib-Resistant HER2-Positive Breast Cancer Cell Lines: A Model for Investigating Resistance Mechanisms and Novel Therapeutic Strategies

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Abstract

Background: HER2-positive breast cancer accounts for approximately 20% of all breast cancer cases and is characterized by aggressive growth and poor prognosis. Neratinib, an irreversible tyrosine kinase inhibitor, has shown efficacy in this subset of patients. However, acquired resistance to neratinib remains a significant clinical challenge, limiting its long-term effectiveness.

Aim: This study aimed to establish neratinib-resistant HER2-positive breast cancer cell lines to provide a robust *in-vitro* model for investigating mechanisms of resistance and exploring novel therapeutic strategies, including the use of metformin to overcome resistance.

Methods: Neratinib-resistant cell lines (SNR and HNR) were developed from parental HER2-positive breast cancer cell lines (SKBR3 and HCC1954) through the dose-escalating method. Cell viability assay was conducted to confirm resistance. Cell proliferation and protein expression levels were compared between the resistant and parental cells. Additionally, the potential of metformin to re-sensitize resistant cells to neratinib was assessed using combination treatment assays.

Results:
The generated neratinib-resistant cell lines (SNR and HNR) exhibited a significant increase in IC_{50} values compared to parental cells (SKBR3 and HCC1954), confirming acquired resistance. The proliferation rate was significantly reduced in resistant cells compared to parental ones ($P<0.05$). Further, resistant cells demonstrated a major increase in EGFR, HER2, HER3, and IGF-1R levels compared to parental cells. Protein expression profiling also revealed upregulation of alternative signaling pathways, such as PI3K/AKT and MAPK. Importantly, combination treatment with metformin significantly re-sensitized resistant cells to neratinib, restoring their response ($P<0.05$).

Conclusion:
Our established neratinib-resistant cell lines provide a valuable tool for elucidating the molecular mechanisms driving resistance in HER2-positive breast cancer. Furthermore, the observed re-sensitization of resistant cells by metformin highlights its potential as a combination therapy to overcome resistance and improve clinical outcomes. Future studies will focus on leveraging these findings to optimize therapeutic strategies for patients with neratinib-resistant HER2-positive breast cancer.

Keywords: Breast cancer; in-vitro model; drug resistance; chemotherapy;

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The effect of pre-treatment with polyethylene glycol on the pharmacokinetics of PEGylated gold nanoparticles in rats.

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Abstract

Background: PEGylated gold nanoparticles (PEG-AuNPs) hold great promise for targeted drug delivery and chemotherapy due to their ability to evade the immune system. However, repeated administration of PEGylated formulations triggers accelerated blood clearance (ABC) phenomenon, which decreases their circulation time, alters pharmacokinetic parameters, and potentially impacts therapeutic efficacy and safety.

Aim: To synthesize PEG-AuNPs and assess the effect of pre-treatment with free-PEG on the pharmacokinetics of PEG-AuNPs when administered shortly before the second dose.

Methods: AuNPs were synthesized using the Turkevich–Frens method, PEGylated, and characterized by UV-VIS spectroscopy, Zeta sizer, and TEM. Male Wistar rats were divided into three groups. Groups 1 and 2 received two PEG-AuNPs IV injections (0.7 mg/kg) with a 7-day interval. Group-2 was pre-treated with free-PEG (20 kDa, 120 mg/kg) 30 minutes before the second dose. Blood samples were collected at 5, 15, 30, 45 min, 1, 2, 4, 6, and 24 h post-dose. At 24 h, liver and spleen were harvested. Group-3 received a single dose of PEG-AuNPs, and organs were harvested 24 h later. Samples were analyzed for gold via ICP-MS. All experiments were approved by the Animal Care and Use Committee (ACUC) of Jordan University of Science and Technology / approval number 20240570.

Results: The synthesized PEG-AuNPs were spherical (33.7±0.439 nm). The concentration-time profiles confirmed the ABC phenomenon, comparing the first and the second doses. However, free-PEG pre-treatment in group-2 did not significantly alter the pharmacokinetic parameters (C_{max}, t_{max}, , and $t_{0.5}$; $p > 0.05$) compared to Group-1. Liver and spleen accumulation of AuNPs increased (6-7) and (2-3)-fold, respectively, after the second dose, compared to the single dose, consistent with the ABC phenomenon.

Conclusions: Under conditions of this study, pre-treatment with free-PEG did not significantly mitigate the ABC phenomenon.

Keywords: Gold nanoparticles, Polyethylene glycol, Accelerated blood clearance, Pharmacokinetics.

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The Role of Environmental Toxins and Microbiome-Derived Formate in Colorectal Cancer Progression via the Aryl Hydrocarbon Receptor and β-catenin Pathways

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Abstract

Background: Colorectal cancer (CRC) is a leading cause of cancer-related deaths. Cancer stem cells (CSCs), a subpopulation of cancer cells, drive chemoresistance through self-renewal and immune evasion. Environmental carcinogens, including polycyclic aromatic hydrocarbons like benzo[a]pyrene (B[a]P), and bacterial infections exacerbate CRC progression, largely through activating the aryl hydrocarbon receptor (AhR) pathway. Formate, a bacterial fermentation product of *Fusobacterium nucleatum* (Fn), has emerged as a potential modulator of CRC. Nevertheless, the mechanism of action of formate requires further investigation.

Aim: This study aims to investigate whether formate plays a role in CRC progression by promoting CSC expansion and immune evasion through activation of AhR/β-catenin pathways.

Methods: HCT116 cells were treated with B[a]P or formate in the presence and absence of CH223191, an AhR inhibitor, or FH535, a β-catenin/TCF inhibitor. The mRNA and protein expression levels of AhR target genes, stemness markers, and immune evasion markers were evaluated using real-time PCR and Western Blot, respectively.

Results: Treatment with either B[a]P or formate significantly upregulated AhR and β-catenin pathways. This activation was accompanied by upregulation of stemness markers (CD133, CD166, SOX9, ALDH1A1, and c-Myc), suggesting AhR promotes CSC expansion. Immune evasion markers (PD-L1, B7H3) were also significantly elevated. CH223191 and FH535 both abrogated these effects, confirming the AhR-dependent and β-catenin-dependent nature of these processes.

Conclusion: Formate, a known *Fn* metabolite, activated AhR in a manner akin to B[a]P, acting through AhR- and β-catenin-dependent pathways to promote CSC expansion and immune evasion. These findings are the first to highlight the dual impact of environmental and microbial factors on CRC progression through AhR activation, providing insights into potential therapeutic and chemopreventive strategies to improve patient outcomes. Future studies will elucidate the broader implications of these mechanisms through proteomic and transcriptomic profiling.

Keywords: Colorectal cancer; environmental toxins; Formate

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Formulation, Optimization, and Pharmacological Evaluation of Nanostructured Lipid Carriers for Enhanced Bioavailability of Curcumin in Rheumatoid Arthritis

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Abstract

Background:
Rheumatoid arthritis (RA) is a debilitating autoimmune disease characterized by chronic inflammation and joint degradation, necessitating innovative therapeutic approaches. Curcumin, a natural polyphenol with potent anti-inflammatory and antioxidant properties, faces challenges of low bioavailability due to poor solubility and rapid metabolism.

Aim:
This study aimed to develop and evaluate nanostructured lipid carriers (NLCs) to enhance curcumin's therapeutic efficacy in RA management.

Methods:

The study employed a collagen-induced arthritis (CIA) model in rats (i.e. Wistar species, IACUC clearance body, approval number: 1297/PO/RE/S09/CPCSEA) to evaluate pharmacological efficacy. The NLCs were formulated using a systematic Design of Experiments (DoE) approach and optimized for critical parameters including particle size (~120 nm), entrapment efficiency (92%), and sustained drug release over 24 hours.

Results:
The optimized curcumin-loaded NLCs significantly reduced paw edema, inflammatory cytokines, and oxidative stress markers compared to conventional curcumin formulations in the CIA model. These results indicate improved anti-inflammatory and antioxidant activity.

Conclusion:
The findings suggest that curcumin loaded NLCs are a promising formulation for enhancing curcumin's therapeutic potential, offering a novel approach for managing rheumatoid arthritis.

Keywords: Nanostructured Lipid Carriers, Curcumin, Rheumatoid Arthritis, Bioavailability, Anti-inflammatory Therapy.

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Cytochrome P450 Epoxygenases could be a Potential Target For Reducing The Cardiotoxicity Caused By Doxorubicin

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Abstract

Background: Cardiotoxicity is a major concern limiting the therapeutic potential of the widely used antineoplastic anthracycline doxorubicin (DOX). Consequently, discerning the pathway involved may help minimize the risk-to-benefit ratio and improve life quality in chemotherapy patients. Recent literature suggests that Endothelial-to-Mesenchymal transition (EndMT) may be a new target for understanding the progression of DOX-induced cardiotoxicity.

Objective: Given that Arachidonic Acid (AA) and associated Cytochrome P450 (CYP) epoxygenases have been implicated in cardiac and endothelial function, we aimed to examine the effect of an epoxygenases inhibitor, MSPPOH, on DOX-induced cardiotoxicity in vitro and in vivo.

Methods: To investigate this, EA. hy926 cells were treated with DOX, with or without MSPPOH. Subsequently, the gene expression of EndMT, inflammatory and apoptotic markers was measured, along with the morphology, cytotoxicity and proteomic profile of differentially expressed proteins across the treatments. We also used the zebrafish model to investigate the in vivo effect of MSPPOH in morphology, cardiovascular parameters, and gene expression with the treatment of DOX.

Results: Our results indicated that MSPPOH significantly elevated the ratio of EndMT, the expression of inflammation markers like ICAM, and apoptosis markers like Caspase-7 in endothelial cells incubated with DOX by approximately 180%, 200% and 160%, respectively. Furthermore, MSPPOH increased the size of cardiac edema by 150%, lowered blood flow velocity by 30%, and further upregulated the expression of cardiac injury markers like myh7 by 170% in the zebrafish model of DOX-induced cardiotoxicity.

Conclusion: In conclusion, blocking CYP epoxygenases exacerbates cardiotoxicity caused by DOX through the initiation of EndMT. From a drug development perspective, CYP epoxygenases may prove to be a potential target in alleviating DOX-induced cardiotoxicity.

Keywords: Doxorubicin, Endothelial, Mesenchymal, Cytochrome p450, Epoxyeicosatrienoic acids

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Formulation and Characterization of Meropenem-Based Ointments: A Comprehensive In Vitro and In Vivo Study

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Abstract

Background:

Meropenem is a broad-spectrum antibiotic, but its instability to light and humidity poses significant challenges in dermal application. Combining Meropenem with Arginine through crystal engineering enhances its solubility, maintains a skin-friendly pH, and may improve wound healing by promoting collagen synthesis and tissue perfusion by adding arginine.

Aim:

This study aims to formulate and evaluate Meropenem and Meropenem-Arginine ointments using oleaginous and water-soluble bases, focusing on their stability, drug release profiles, and wound healing efficacy.

Methods:

Two ointment bases (oleaginous and water-soluble) were prepared with Meropenem alone and as a co-amorphous complex (Meropenem-Arginine). Stability was evaluated at 4°C, 25°C, and 40°C using FTIR and HPLC for drug retention analysis. Drug release profiles were assessed using dialysis bag diffusion, while antimicrobial efficacy was tested against three bacterial strains: Staphylococcus aureus (ATCC 25923), Escherichia coli (ATCC 25922), and Pseudomonas aeruginosa (ATCC 27853) using the well agar method. Wound healing efficacy was evaluated in vivo on mouse models (BALB/c male mice) by tracking wound closure over fourteen days. The study followed ethical guidelines by the Department of Pharmacology, Faculty of Pharmacy, Damascus University and EU Directive 2010/63.

Results:

Oleaginous formulations demonstrated greater stability at refrigerated temperatures, retaining up to 90.6% of Meropenem, compared to 78.4% in water-soluble bases. In vitro drug release studies revealed faster release from water-soluble ointments (72.4% within 4 hours) compared to oleaginous bases (32.9% within 4 hours). However, in vivo experiments showed superior wound healing with the oleaginous Meropenem-Arginine ointment, achieving over 90% wound closure within 5 days, compared to 11 days for other formulations.

Conclusions:

The oleaginous Meropenem-Arginine ointment demonstrates excellent stability, sustained drug release, and effective wound healing, making it a strong candidate for treating infected wounds, burns, and diabetic ulcers. Further research is recommended to refine its clinical applications.

Keywords: wound; diabetic ulcer; meropenem; ointment;

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Aptamer-Guided Nanomedicines for Targeted Drug Delivery into Cancer

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Abstract

Background: Cancer is a major health problem affecting millions annually and is associated with a very high mortality rate. Although many drugs have been explored and have shown promising anti-tumor efficacy, most of these drugs belong to a class of molecules that suffer from low aqueous solubility and poor cellular uptake, leading to a lack of therapeutic efficacy and unwanted side effects. Most nanomedicines still present the inconvenience of lacking specificity toward their target cells. This is why a promising approach in this field consists of designing functionalized drug nanocarriers utilizing molecular ligands such as aptamers, targeting unique or overexpressed tumor biomarkers in a specific manner.

Objective: To develop and characterize aptamer-functionalized drug nanocarriers specifically designed for the targeted delivery of anti-NOTCH1 siRNA and hydrophobic anti-cancer drugs (Echinomycine and Curcumin) into cancer cells, followed by investigating these nanocarrier formulations for stability, specificity, and therapeutic efficacy.

Methods: Different approaches were applied, including thiol–maleimide “click” reactions and post-insertion technique to functionalize nanocarriers with aptamers to guide these nanocarriers loaded with siRNA, Echinomycin, and curcumin into cancer cells. Targeting selectivity and therapeutic potency were evaluated in different cancers.

Results: In our studies, we successfully loaded various therapeutic payloads, including anti-NOTCH1 siRNA and hydrophobic anti-cancer drugs (Echinomycine and Curcumin) into nanocarriers. These nanocarriers were then functionalized with aptamers targeting overexpressed tumor biomarkers, specifically CD44 and nucleolin receptors. The results showed higher selectivity and uptake by targeted tumor cells overexpressing these markers, demonstrating higher cytotoxicity and improved therapeutic efficacy.

Conclusions: Integrating aptamers into nanomedicines addresses major limitations in cancer drug delivery, offering a robust platform for targeted therapies. The findings of our studies highlight the potential of precise, effective treatments tailored to combat resistant cancers.

Keywords: nanotechnology; drug delivery; aptamers; cancer

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Evaluating the Biodistribution, Toxicity, and Metabolomic Profiles of Gold and Silver Nanoparticles in Rat Upon Intravenous Administration

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Abstract

Background: Nanoparticles (NP) have gained significant attention in biomedical research due to their unique properties and potential applications in drug delivery, imaging, and diagnostics. Gold (AuNPs) and silver (AgNPs) NPs are among the important nanoplatforms that received extensive attention recently for various biomedical applications. Understanding the complex interaction of these NP in biological systems is essential to unveil their pharmacological, Pharmacokinetic and toxicological attributes. However, there is a lack of understanding regarding the biodistribution and acute toxicity of these nanoparticles when utilized simultaneously in vivo.

Aim: This study aims to investigate the biodistribution and evaluate the potential toxicity of surface modified AuNP and AgNP in rat models following intravenous injection.

Methods: In this work, spherical polyethylene glycol (PEG) modified AuNPs and AgNPs were synthesized and dosed into rats via intravenous route. Rats were divided into four groups: Control, AuNPs, AgNPs, and Mixed (receiving both AuNP and AgNP), to mimic potential biomedical exposure scenarios. Organ tissues and serum samples were collected 24hr post-dosing, and comprehensive biodistribution and metabolite profiling was performed using inductive coupled plasma- mass spectrometry (ICP-MS), liquid chromatography-mass spectrometry (LC-MS/MS) and real time-polymerase chain reaction (RT-PCR)

Results: indicated that AuNPs and AgNP were significantly accumulated in the blood, liver and spleen after 24 h of IV injection. Toxicity and metabolomics profiling demonstrated no toxicity observed in any of the groups at the protein and gene level. Thus, co-administration of NPs did not influence the biodistribution or toxicity.

Conclusion: This study demonstrated that PEG-modified AuNPs and AgNPs primarily accumulate in the blood, liver, and spleen without inducing acute toxicity at the protein or gene level. Co-administration of these nanoparticles did not alter their biodistribution or toxicity, supporting their potential biocompatibility for biomedical applications.

Keywords: nanotechnology; Silver nanoparticles (AgNPs); Gold nanoparticles (AuNPs)

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Intravenous Administration of Gold Nanoparticles in Rats Exhibit Alterations in Sphingomyelins, Bile Acids, Sphingolipids, and Cholesterol Esters Levels

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Abstract

Background: Nanoparticles (NP) have gained significant attention in biomedical research due to their unique properties and potential applications in drug delivery, imaging, and diagnostics. Gold (AuNPs) and silver (AgNPs) NPs are among the important nanoplatforms that received extensive attention recently for various biomedical applications. Understanding the complex interaction of these NP in biological systems is essential to unveil their pharmacological, Pharmacokinetic and toxicological attributes. Metabolomics has proven invaluable in providing detailed insights into NP's biodistribution, metabolic effects, and potential toxicity.

Aim: This study aims to investigate the underlying metabolic pathways affected by in vivo exposure to NP using a robust metabolomics approach.

Methods: In this work, spherical polyethylene glycol (PEG) modified AuNPs (13 nm, diameter) or AgNPs (20 nm, diameter) were synthesized and dosed into rats via intravenous route to study the associated metabolic changes. Rats were divided into three groups: Control, AuNPs and AgNPs, to mimic potential biomedical exposure scenarios. Organ tissues and serum samples were collected 24hr post-dosing, and comprehensive biodistribution and metabolite profiling was performed using inductive coupled plasma-mass spectrometry (ICP-MS), liquid chromatography-mass spectrometry (LC-MS/MS) and flow injection analysis-mass spectrometry (FIA-MS/MS).

Results: AuNPs treatment significantly impacted several metabolic pathways. Notably, there was an increase in sphingomyelin SM 34:2 (FRD= 0.069), a decrease in glycochenodeoxycholic acid levels (FRD= 0.066), and significant alterations in cholesterol ester levels. These metabolic changes suggest that gold nanoparticles can disrupt fatty acid metabolism, pyrimidine/purine metabolism, and amino acid synthesis.

Conclusion: This study demonstrates that AuNP exposure significantly alters metabolic pathways, particularly affecting lipid metabolism, bile acid homeostasis, and nucleotide synthesis. The observed changes, including increased sphingomyelin and disrupted cholesterol ester levels, highlight potential metabolic disruptions caused by AuNPs. These findings provide valuable insights into the pharmacological and toxicological effects of nanoparticles, emphasizing the importance of metabolomics in assessing their biological impact.

Keywords: nanotechnology; silver nanoparticles; gold nanoparticles; drug delivery

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Microsecond simulations to investigate the structural mechanism of super resistant double mutations in BTK to covalent inhibitor Ibrutinib in multiple leukaemia

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Abstract

Background: Bruton's tyrosine kinase (BTK) plays a pivotal role in chronic lymphocytic leukemia (CLL). Covalent BTK inhibitors such as ibrutinib, enhance CLL patients' survival. However, mutations at the C481 residue diminish ibrutinib's efficacy, leading to drug resistance. Recently, super-resistant mutants i.e., T474M-C481S and T474I-C481S were reported to cause manifold resistance to ibrutinib. Understanding the mechanism of this drug resistance could guide novel effective therapeutics.

Aim: We investigated the impact of the BTK mutations, T474M-C481S and T474I-C481S, on ibrutinib binding to elucidate the structural and biophysical mechanisms contributing to drug resistance.

Methods: Microsecond-scale molecular dynamics simulations were conducted to analyze structural dynamics, residue flexibility, and binding interactions of ibrutinib. Total binding free energy (TBE) calculations were performed using MM-GBSA and MM-PBSA methods. Furthermore, principal component analysis (PCA), and free energy landscape (FEL) analysis assessed dynamic variations in the wild-type and mutant systems.

Results: T474M-C481S and T474I-C481S mutations disrupt essential hydrogen bonds and the covalent interaction with the C481 residue, weakening thus ibrutinib binding. Molecular dynamics simulations indicated dynamic instability in regions 432-439 and 545-559, characterized by transitions between helix and loop structures. Structural compactness and residue flexibility analyses showed significant differences between wild-type and mutant trajectories. Using the MM-PBSA approach, the TBE was -42.65±0.08 kcal/mol for the wild type, -38.81±0.18 kcal/mol for the T474M-C481S mutant, and -33.04±0.13 kcal/mol for the T474I-C481S mutant. Similarly, MM-GBSA results confirmed that mutants have lower TBE values compared to the wild-type. PCA and FEL analyses further highlighted the dynamic variations caused by the mutations.

Conclusions: The T474M-C481S and T474I-C481S mutations significantly reduce ibrutinib binding by disrupting critical interactions and altering the structural dynamics of BTK. These findings underscore the importance of the T474 and C481 residues in BTK-ibrutinib interactions and provide valuable insights for designing novel therapeutics to overcome resistance.

Keywords: chronic lymphocytic leukaemia; tyrosine kinase; ibrutinib

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Assessment of Native Myocardial T1 Mapping for Early Detection of Anthracycline-Induced Cardiotoxicity in Cancer Patients: a Systematic Review and Meta-analysis

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Abstract

Background: Anthracyclines are among the most effective anti-tumor drugs. However, they are associated with dose-dependent cardiotoxicity, which may progress to heart failure. Utilizing a sensitive predictor, such as native myocardial T1 mapping, could help with the early detection of cardiac dysfunction. Thus, facilitating timely diagnosis and initiating protective interventions.

Aim: To evaluate the current evidence supporting the use of T1 mapping to detect early myocardial changes in patients treated with anthracyclines.

Methods: This is a systematic review conducted in accordance with the PRISMA guidelines. Four electronic databases (PubMed, EMBASE, SCOPUS, Web of Sciences) were searched till November 2022. Clinical studies published in the English language assessing T1 mapping use for early detection of anthracyclines-induced cardiac dysfunction were included. Screening, data extraction, and quality assessment, were performed by three independent reviewers. A standardized mean difference with a 95% confidence interval using a fixed-effects model was calculated. Heterogeneity was assessed using the I^2 parameter by Chi-squared test. Publication bias was assessed using funnel plot analysis and Egger's test.

Results: A total of nine studies were included. Five studies assessed T1 mapping in healthy controls compared to cancer patients, while five studies, one of which assessed both contexts, evaluated baseline T1 mapping in cancer patients before anthracyclines exposure. Significant elevation of native myocardial T1 mapping from baseline (95% CI 0.1121 to 0.5802; $p = 0.0037$) as well as compared to healthy control patients (95% CI 0.2925 to 0.7448; $p < 0.0001$) was associated with anthracyclines exposure. No significant publication bias was noted on the assessment of the funnel plot and Egger's test. No significant heterogeneity in the included studies was observed ($I^2 = 0.0000\%$ versus healthy controls and $I^2 = 14.0666\%$ versus baseline).

Conclusion: Native myocardial T1 mapping is useful tool for detecting anthracycline-induced cardiotoxicity in cancer patients.

Keywords: cardiotoxicity; anthracycline; meta-analysis; cancer

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IN SILICO PHARMACOLOGICAL EVALUATION TO EXPLORE THE BIO- ACTIVE COMPOUNDS OF PHOENIX DACTYLIFERA ON POLYCYSTIC OVARIAN SYNDROME

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Abstract

Background

Polycystic ovary syndrome (PCOS) is a prevalent gynaecological disorder affecting women of reproductive age, characterized by disruptions in androgen and estrogen secretion and metabolism. Given the increasing incidence of PCOS and its associated physical and mental health complications, there is a need for effective therapeutic interventions targeting hormonal imbalances. Phoenix dactylifera (date palm) contains bioactive compounds with potential pharmacological effects, which may offer therapeutic benefits for PCOS management.

Aim

This study aimed to evaluate the pharmacological potential of bioactive compounds from Phoenix dactylifera for treating PCOS using in silico approaches.

Methods

A literature review and PhytochemDB database were used to identify bioactive compounds in Phoenix dactylifera. The selected compounds underwent ADMET (Absorption, Distribution, Metabolism, Elimination, and Toxicity) analysis to assess their pharmacokinetic properties. Protein targets related to PCOS were extracted from the RCSB PDB database. Molecular docking studies were conducted using AutoDock PyRx, screening compounds based on their binding affinity and biological activity against PCOS-related proteins.

Results

Seven bioactive compounds from Phoenix dactylifera met the required ADMET criteria. Further molecular docking analysis confirmed that four compounds exhibited excellent biological activity against PCOS-related targets, indicating strong potential for therapeutic application.

Conclusion

This study identified four druggable compounds from Phoenix dactylifera with potential therapeutic efficacy against PCOS and elucidated their possible mechanism of action. These findings provide a basis for further experimental validation and drug development for PCOS treatment.

Keywords: estrogen; PCOS; Women’s health

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3D printed skyscraper electrochemical biosensor for the detection of tumour necrosis factor alpha (TNFα) in faeces

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Abstract

Background: Tumour necrosis factor alpha (TNFα) is an important inflammatory mediator in the body and thus, is considered an important biomarker in a host of inflammatory disorders such as ulcerative colitis. Many biosensing strategies have been developed however, they are expensive, time consuming and use complex fabrication approaches.

Aim: This study aimed to develop a simple yet robust TNFα biosensor, which could conduct measurement within biological environments.

Method: 3D printing was utilised to fabricate an electrode with skyscraper (SS) structures to provide increased surface area thus enhancing the performance of the purposed sensor. The probe was made by covalent immobilization of anti-TNFα onto carboxylic acid bearing conducting polymer thiophene-2-carboxylic (Th2CA) after electrodeposition of gold nanoparticles (AuNPs) onto the SS electrode.

Results: The development of the biosensor was characterised using field emission scanning electron microscopy, X-ray photoelectron spectroscopy and electrochemical impedance spectroscopy. The linear range for TNFα was from 160 to 1820 pg/ml with a limit of detection of 44.5 pg/ml on the skyscraper (SS) immunosensor. The probe was selective for the detection of TNFα when compared to other commonly found extracellular biological molecules.

Conclusions: The sensor was able to monitor levels of TNFα from faecal pellets, where an increase in TNFα was observed with increasing age. These findings highlight that 3D printing could be used to make a simple yet robust immunosensor for the detection of a host of key biomolecules providing the potential for vital diagnostic tools.

Keywords: biosensor; 3D printing; Tumour necrosis factor

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Polyphenols as Promising Biologically Active Compounds with Therapeutic Applications

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Abstract

Background: Polyphenols possess antioxidant, anti-inflammatory, and therapeutic properties; however, their low bioavailability has led to increasing interest in nano formulations for improved delivery.

Aim: The purpose of this study was to explore the antioxidant, wound-healing, cardioprotective and anti-inflammatory effects of polyphenol-rich formulations from cucurbitaceae family members, including Cucurbita pepo, C. moschata, and C. maxima, on rat models.

Methods: The initial crude extracts from the selected cucurbits were further fractioned into hexane, chloroform, ethyl acetate, butanol, and aqueous ethanol fractions, labelled as HEF, CHF, EAF, BUF, and AEF, respectively. To enhance the solubility, stability and to increase the bioavailability of polyphenols, the potent fraction was subjected for nano encapsulation using spray dryers. The polyphenol niosomes were prepared using span-60 and cholesterol. To evaluate the wound-healing potential of polyphenols, the nanomembrane was prepared using electrospinning method and characterized using scanning electron microscopy and particle size analyser. Doses of 250 and 500 mg/kg body weight of cucurbit formulation were administered orally to evaluate the cardioprotective effects and apply the nano-membrane to evaluate the wound healing potentials. Oxidative status assessments were conducted by measuring the levels of malondialdehyde (MDA), superoxide dismutase (SOD), reduced glutathione (GSH), nitric oxide (NO), and total antioxidant capacity (TAC) and anti-inflammatory potential by assessing the TN-α and IL-6.

Results:

AEF yielded the highest amount, followed by BUF, HEF, EAF, and CHF in descending order. Notably, EAF contained the greatest concentration of total phenolics, flavonoids, and flavonols. In terms of antioxidant activity, EAF demonstrated the most potent DPPH radical scavenging capability. EAF also exhibited the strongest reducing potential among the fractions. RP-HPLC analysis identified various phenolic acids and flavonoids across the cucurbit fractions, including ferulic acid, vanillic acid, p-coumeric acid, gallic acid, p-hydroxybenzoic acid, chlorogenic acid, catechin, rutin, quercetin, myricetin, and kaempferol. Results showed that EAF of cucurbits significantly enhanced endogenous antioxidant levels, and showed cardioprotective effects as reflected by amelioration of troponin in treated rat groups. Furthermore, the results showed that the polyphenol-loaded niosome-PVA nanomembranes supported faster and more efficient wound healing compared to traditional dressings.

Conclusion: It is that concluded that EAF of cucurbits showed high antioxidant potential and the polyphenol-loaded niosome-PVA membrane showed wound healing potential.

Keywords: Quercetin, Ferulic acid, Gradient elusion, Oxidative stress, SOD, TNF-α, IL-6