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目　录

Extraction of polypeptides from residues of *Oplopanax elatus* adventitious roots

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Abstract:

Ethanolic extraction of *Oplopanax elatus* adventitious roots can produce large amounts of residues, leading to resource waste and environment pollution. To address this issue, this study focused on reusing these residues by employing a flash extraction-assisted enzymolysis method. The extraction process was optimized using response surface methodology, with polypeptide yield as the evaluation index. Further purification of the extract was conducted through macroporous resin adsorption. The optimized extraction conditions were: 0.9% enzyme addition, enzymatic hydrolysis pH 11, liquid-to-material ratio 60.95 mL/g, and hydrolysis temperature 56.1°C, resulting in polypeptide yield 3.36%. The purification process revealed that the optimal conditions were sample concentration 0.8 mg/mL, sample volume 2.16 BV, eluent concentration 42.3%, and elution volume 0.93 BV, achieving polypeptide content 261.97 mg/g. Finally, the pharmacological evaluation showed that the purified polypeptides exhibited high antioxidant activity and promoted probiotic growth. In conclusion, the findings of this study present an efficient approach for residue utilization, offering valuable insights into the comprehensive use of *O. elatus* adventitious roots.

Keywords: *Oplopanax elatus* adventitious roots; Residues; Flash extraction-assisted enzymolysis, Purification of polypeptides

Eupalinolide B targets DEK and PANoptosis through E3 ubiquitin ligases RNF149 and RNF170 to negatively regulate asthma

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Abstract:

We investigated the mechanism by which eupalinolide B (EB) regulates DEK protein ubiquitination and degradation, and its impact on DEK-mediated RIPK1-PANoptosis pathway in allergic asthma. *In vitro*, EB could bind to DEK. RNF149 and RNF170 were identified as regulatory factors of DEK, polyubiquitinating the K349 site in the DEK CDS region 270-350 through K48 linkages and leading to its degradation. RNA sequencing showed that DEK overexpression upregulated the expression of genes such as RIPK1, FADD, and Caspase 8. Treatment with siDEK or EB reduced the activation of the RIPK1-PANoptosis pathway in BEAS-2B-DEK cells. *In vivo*, EB significantly reduced the levels of DEK in house dust mite-induced mice and alleviated pulmonary inflammatory cell infiltration, goblet cell hyperplasia, collagen fiber deposition, and eosinophil proportion in BALF. Knocking out the DEK gene reduced RIPK1-induced PANoptosis, and inhibited airway inflammation and cell apoptosis. EB promotes the degradation of DEK by RNF149 and RNF170, inhibits the RIPK1-PANoptosis pathway, and may effectively suppress asthma. EB may become a potential drug for treating airway inflammation in asthma.

Keywords: EB; DEK; RNF149/170; PANoptosis; Asthma.

Mechanism of NMDARs in sensory stimulation-evoked MF-GrC long-term plasticity

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Abstract:

N-methyl-D-aspartate receptors (NMDAR) are involved in important physiological and pathological processes in the neural circuits of the cerebellar cortex. NMDAR is highly expressed in granule cells (GrC) of the cerebellum and participates in the synaptic transmission between mossy fibers and granule cells (MF-GrC) in the cerebellar cortex. This study aims to clarify the mechanism of NMDAR on the synaptic transmission and long-term plasticity of MF-GrC induced by sensory stimulation in cerebellar cortex. Methods: This study employs techniques such as in vivo electrophysiological recordings, immunohistochemistry, pharmacology, microinjections into the cerebellar cortex, and behavioral assays, analyzing data to investigate the role of NMDAR in MF-GrC synaptic transmission induced by facial stimulation in urethane-anesthetized mice. Results: In the presence of $GABA_A$ receptor antagonists, 20 Hz facial stimulation could induce a LTP of MF-GrC in cerebellar granular layer. However, blocking NMDARs, 20 Hz facial stimulation failed to induce MF-GrC LTP in cerebellar granular layer. Under the condition of blocking NMDARs containing GluN2A subunit, 20 Hz facial stimulation could not induce MF-GrC LTP in cerebellar granular layer. However, blocking NMDARs containing GluN 2B or GluN 2C/D subunit had no effect on 20Hz facial stimulation-induced MF-GrC LTP in the cerebellar granular layer. In addition, activation of NMDARs containing GluN2A subunit could induce MF-GrC LTP, and lead to sensory stimulation can't further induce MF-GrC LTP. The application of nitric oxide synthase (NOS) inhibitor could eliminate the MF-GrC LTP induced by facial stimulation in mouse cerebellar cortex. The application of NO donor, SNOP could not only induce the production of MF-GrC LTP, but also block the 20 Hz stimulation to further induce MF-GrC LTP. Intracellular signaling mechanism of MF-GrC LTP in cerebellar granular layer induced by 20 Hz facial stimulation. Inhibiting protein kinase A (PKA) or blocking PKC signaling pathway could lead to the inability of facial stimulation to induce MF-GrC LTP in the mouse cerebellar cortex. In addition, the depletion of intracellular Ca^{2+} led to the failure of facial stimulation to induce MF-GrC LTP in the mouse cerebellar cortex. Conclusion: NMDAR containing GluN2A subunit exists in GrCs of mouse cerebellar cortex. MF-GrC LTP induced by facial sensory stimulation depends on the NMDAR containing GluN2A subunit / NO cascade, which is co-mediated by PKA and PKC signaling pathways

and requires the participation of intracellular calcium ions. The present results suggest that NMDAR containing GluN2A subunit, control the long-term plasticity of MF-GrC synaptic transmission, which may play a key role in motor learning of animals.

Keywords: N-methyl-D-aspartate receptor; cerebellar cortex; MF-GrC synapse; In vivo electrophysiological recording; neuropharmacology.

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Cucurbitacin B prevents LPS-induced skeletal muscle atrophy via regulating protein synthesis/degradation pathway

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Abstract:

Background and Purpose： Increasing evidence suggests systemic inflammationcaused skeletal muscle atrophy as a major clinical feature of cachexia. Cucurbitacin B obtained from Cucumis melo L. possesses potent anti-inflammatory and immunosuppressive effects. The present study aims to evaluate the protective effects and molecular mechanisms of Cucurbitacin B on inflammation-induced skeletal muscle atrophy.

Experimental Approach： The effects of Cucurbitacin B on skeletal muscle atrophy were investigated in LPS-treated C2C12 myotubes and C57BL/6 mice. Protein expressions were analysed by western blot, respectively. Skeletal muscle mass, volume and strength were measured by histological analysis and grip strength, respectively.

Key Results： Cucurbitacin B (0.3–3 μM) up-regulated protein synthesis signals (IGF-1/p-IGF-1R/IRS-1/p-Akt/p-mTOR) and down-regulated protein degradation signal atrogin-1 in C2C12 myotubes. In LPS -treated C2C12 myotubes, Cucurbitacin B up-regulated MyHC, IGF-1, p-IGF-1R, IRS-1 and p-Akt. Cucurbitacin B also down-regulated ubiquitin-proteasome molecules (n-FoxO3a/atrogin-1/MuRF1), proteasome activity, autophagy-lysosomal molecules (LC3-II/LC3-I、Becline 1 and p62). In LPS-challenged mice, Cucurbitacin B (0.05 and 0.25 mg/kg, i.g.) increased skeletal muscle volume, cross-sectional area of myofibers, weights of the gastrocnemius and tibialis anterior muscles, forelimb grip strength and locomotion.

Conclusions and Implications： These findings reveal that Cucurbitacin B prevented LPS-induced inflammation and skeletal muscle atrophy and have implications for the discovery of novel agents for preventing muscle wasting.

Keywords: anti-inflammation, autophagy-lysosomal pathway, skeletal muscle atrophy, Cucurbitacin B, ubiquitin-proteasome system

Panaxadiol mitigates DSS-induced colitis by inhibiting NLRP3 inflammasomes, regulating intestinal microbiota, and protecting the intestinal barrier

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Abstract:

Panaxadiol (PD), a triterpenoid sapogenin monomer extracted from the rhizome of Panax ginseng, has been reported to exhibit anti-inflammatory, antitumor, and neuroprotective effects. Inflammatory bowel disease (IBD) is a chronic inflammatory condition that affects the intestines and poses a significant threat to patients' health. The exact pathogenesis of IBD remains unclear. While numerous medications are available for its treatment, their serious adverse effects often restrict their use. Consequently, there is a pressing need to identify a highly effective and low-toxicity drug for the management of inflammatory bowel disease. Our objective was to examine whether PD could exert a therapeutic effect on inflammatory bowel disease (IBD) and to explore its mechanism of action. THP-1 cells and bone marrow-derived macrophages (BMDMs) were utilized for in vitro experiments, while dextran sulfate sodium (DSS)-induced colitis mice served as an in vivo model. PD can inhibit the activation of the NLRP3 inflammasome induced by lipopolysaccharide (LPS) and adenosine triphosphate (ATP), decrease the release of pro-inflammatory factors, and thereby protect the integrity of the intestinal barrier. Additionally, PD partially restored the gut microbiota. Our results indicate that PD can protect the intestinal barrier by inhibiting NLRP3 inflammasomes and reducing the release of inflammatory factors. Additionally, PD could modulate gut microbiota, which may offer new candidates for the treatment of IBD.

Keywords: Panaxadiol; NLRP3 inflammasome; Intestinal flora; Intestinal barrier.

Targeting RXFP1 by Ligustilide: A novel therapeutic approach for alcoholic hepatic steatosis

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Abstract:

Purpose: Ligustilide (Lig) is the main active ingredient of *Umbelliferae Angelicae Sinensis Radix* (Chinese Angelica) and *Chuanxiong Rhizoma* (Sichuan lovase rhizome). Lig possesses various pharmacological properties and could treat obesity by regulating energy metabolism. However, the impact and regulatory mechanism of Lig on alcoholic hepatic steatosis remains unclear. This study aimed to explore the therapeutic effect of Lig on alcoholic hepatic steatosis and its related pharmacological mechanism.

Methods: 1. Different cells (HepG2, AML12, MPM, and BMDM) were given LPS combined with ATP stimulation, and the expression of RXFP1 and its downstream signaling-related proteins were observed by immunocy to fluorescence and Western blotting; The supernatant of Relaxin-2 pretreated BMDM was incubated with LPS combined with ATP stimulation. The expression levels of SREBP1 in AML12 cells were observed by immunofluorescence after the interaction between BMDM and AML12 for 24 h. The expression levels of SREBP1 in AML12 cells were observed by immunofluorescence after the interaction between BMDM and AML12.

2. MPM was selected to simulate the in vitro immune response and to investigate the therapeutic effect of drugs on the inflammatory response in AFLD. MPM was pretreated with different concentrations of ligustilide and inhibitors, followed by LPS combined with ATP to stimulate the cells, and the cell supernatant and intracellular proteins were collected, and the content of IL-1β in the supernatant was measured by ELISA and Western blotting. The expression of NLRP3 inflammatory vesicle-associated protein and HMGB 1 and IL-1β were analyzed by Western blotting.

3. AML12 cells were selected to construct an in vitro experimental model of AFLD, and AML12 cells were given different concentrations of drug pretreatment, followed by alcohol stimulation, visualization of lipid accumulation by oil red O staining, and observation of intracellular expression of PPARα and SREBP1.

4. In vivo model of alcoholic fatty liver in mice was established by randomly dividing male C57BL/6 mice into 7 groups, chronic alcohol feeding for 10 days and acute alcohol gavage on day 11, serum was collected and biochemical indexes (ALT, AST and TG) and TG content in liver were detected; histopathological changes in mouse liver were observed by H&E staining and oil red O staining, ELISA was used to detect IL-1β in serum, Tnf mRNA

expression level in mouse liver tissues by qPCR, and RXFP1, lipid metabolism (SREBP1, PPARα), inflammatory factors (HMGB1, Caspase-1, ASC, IL-1β), NETs-related (NE, PR3, Cathepsin G) protein expression levels; the expression of lipid metabolism (SREBP1, PPARα) and RXFP1 was observed by immunohistochemical staining; the expression sites and trends of RXFP1 were determined by immunofluorescence double-staining of F4/80 and RXFP1 expression.

Results: With chronic and binge ethanol feeding, liver tissue damage and lipid accumulation in mice suffering alcoholic hepatic steatosis were significantly improved after Lig treatment. Lig effectively regulated the expression levels of lipid metabolism-related proteins in alcoholic hepatic steatosis. In addition, Lig reduced RXFP1 expression, inhibited the activation of NLRP3 inflammasome, and blocked NET formation. Lig reduced the infiltration of immune cells to the liver and the further prevented the occurrence of alcohol-stimulated inflammatory response in liver. Lig significantly regulated lipid accumulation in alcohol exposed AML12 cells via modulating PPARα and SREBP1. In MPMs, Lig decreased the expression of RXFP1, inhibited the activation of NLRP3 in macrophages stimulated by LPS/ATP, and slowed down the occurrence of inflammatory response.

Conclusion: Lig sustained lipid metabolism homeostasis in alcoholic hepatic steatosis, through inhibiting the activation of NLRP3 inflammasomes and the formation of NETs, especially targeting RXFP1 in macrophages.

Keywords: Alcoholic hepatic steatosis, RXFP1, Lipid metabolism, Inflammatory response, Ligustilide

Ginsenoside RG3 combined with near infrared photothermal therapy reverses TAM/M2 polarization to inhibit TNBC progression

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Abstract:

Background：Ginsenoside Rg3, a prominent bioactive constituent derived from ginseng, has gained significant recognition for its remarkable anticancer properties. Meanwhile, near-infrared photothermal therapy (NIR) has become an adjunctive therapy in tumor treatment. However, studies on the role and mechanism of ginsenoside RG3-NIR to inhibit triple-negative breast cancer (TNBC) are unknown. Specifically, we aimed to elucidate whether this combination therapy exerts inhibitory effects by reversing the M2 polarization of tumor-associated macrophages (TAM) within the TNBC microenvironment. Furthermore, we aimed to unravel the underlying mechanisms by which this therapeutic approach operates.

Methods： MTT and clone formation assays were utilized to determine the inhibitory activity of RG3-NIR on TNBC cells. In addition, Annexin V-FITC apoptosis assay, transwell, Endothelial cell tube formation assay, immunofluorescence, cell co-culture techniques and western blotting, and a TNBC nude mouse subcutaneous graft tumour model were established and analyzed to elucidate the possible mechanisms.

Results： RG3-NIR inhibits TNBC cell proliferation, migration, invasion, EMT process and promotes TNBC cell apoptosis, and when co-cultured with macrophages, it can produce anti-tumour effects by inhibiting the entry of P-STAT3 into the nucleus of the cells, which reverses the polarization of TAM/M2 and promotes the polarization of TAM/M1.

Conclusion：RG3-NIR reverses TAM/M2 polarization by inhibiting P-STAT3 entry into the nucleus and inhibits TNBC malignant evolution by inhibiting the PI3K-AKT-mTOR pathway.

Keywords: Ginsenoside RG3; Near infrared photothermal therapy; Triple negative breast cancer; Tumor-associated macrophage polarization.

Synthesis and anti-inflammatory activity evaluation of derivatives of cycloastragenol

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Abstract:

Inflammation is a basic pathological process in which biological tissues are stimulated by various injury factors, such as trauma and infection, with a defense response as the main response. It is a defense response of living tissues of the vascular system to various injury factors, and plays an extremely important role in the occurrence and development of many major diseases in the human body. Its local manifestations include redness, swelling, heat, pain, and functional impairment, as well as systemic reactions such as fever and changes in peripheral white blood cell count. Due to the significant adverse reactions of existing chemically synthesized anti-inflammatory drugs, people have increasingly focused on finding and developing anti-inflammatory drugs from natural products in recent years. Previous studies have mainly focused on the anti-inflammatory mechanism of natural medicines, but there have been few reports on the anti-inflammatory active ingredients in natural medicines. We found from previous research that the hydrolysis product of astragaloside, the main component of astragalus membranaceus, has excellent anti-inflammatory activity. This article takes cycloastragenol as the parent compound, introduces some phenyltetrazole fragments into the hydroxyl groups at positions 3 and 6, and modifies the parent compound to synthesize a total of 29 compounds. The anti-inflammatory activity is evaluated to find compounds with lower toxicity and better activity, providing ideas for natural product derivatives as anti-inflammatory drugs.

Keywords: cycloastragaloside, derivative, anti-inflammatory activity

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Study on the Mechanism of Traditional Chinese Korean Ethnic Medicine Formula of Lurong Dabu Decoction in the Treatment of Asthma

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Abstract:

Asthma is a syndrome characterized by airway inflammation, airway hyperresponsiveness and airflow obstruction. Lurong Dabu decoction is a typical prescription of Korean medicine. It has the effects of enhancing lung function, relieving cough, benefiting body and nourishing essence and blood which recorded in the ancient traditional Chinese Korean ethnic medicine prescription book "Donguisusebowon". In this study, a rat asthma model was established based on UHPLC-HRMS metabonomics technology and network pharmacology method. Comprehensive evaluation of curative effect of Lurong Dabu decoction on asthma to provide scientific basis and theoretical support for the development of Korean medicine.

Based on UHPLC-HRMS technology and Compound Discoverer small molecular compound platform, 122 chemical constituents were identified in Lurong Dabu decoction and eight kinds of single drugs. Metabolic components in plasma, heart, liver, spleen, lung and kidney of SD rats fed with Lurong Dabu decoction include the main metabolites pathways are dehydration, desaturation, oxidation, reduction (i), hydroxylation. PPI network analysis showed 20 key targets that might be regulated by Lurong Dabu decoction include SRC, MAPK3, MAPK1, EGFR, AKT1. The enrichment pathways include PI3K-Akt signaling pathway, arachidonic acid metabolism, steroid hormone biosynthesis and NF-κB signaling. In the light of this, to establish a rat model of asthma induced by OVA. Using non-targeted metabonomics, it was found that the metabolites of Lurong Dabu Decoction in the treatment of asthma were mainly concentrated in glycerophosphate metabolism, steroid hormone biosynthesis, retinol metabolism and arachidonic acid metabolism. Finally, levels of IL-4, IL-5 and IL-13 in BALF were detected by ELISA through PI3K/AKT/NF-κB/NLRP3 signal pathway. The pathological changes of lung tissue were observed by HE and Masson staining techniques. Observe its expression in lung tissue and protein expression level.

This study provides an important perspective for clarifying the mechanism of Lurong Dabu decoction in treating asthma. It lays a solid scientific data foundation for the follow-up study of the Korean medical prescription Lurong Dabu decoction.

Keywords: Lurong Dabu decoction; asthma; material basis; mechanism of action; Sasang medicine

Rutin Enhances the Sensitivity of Breast Cancer to THP Therapy and Alleviates THP-Induced Cardiomyotoxicity through the lncRNA Miat/miR-124-3p.1/Adcy1 Axis

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Abstract:

Breast cancer stands as the leading cause of cancer-related deaths among women globally, with its high metastatic potential and rapid proliferation often leading to poor clinical outcomes. Chemotherapy, particularly with anthracycline drugs represented by pirarubicin (THP), constitutes a primary treatment strategy for breast cancer. However, the severe myocardial damage induced by long-term THP administration significantly limits its widespread clinical application. Recent research has unveiled a novel therapeutic approach utilizing the active ingredient rutin (RUT) from traditional Chinese medicine to enhance THP's cytotoxic effect on breast cancer cells while mitigating THP-induced myocardial injury. Furthermore, bioinformatics and network pharmacological studies have indicated that the ceRNA (competing endogenous RNA) network formed among long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and messenger RNAs (mRNAs) plays a crucial role in breast cancer progression. Through bioinformatics analysis and in-depth mechanistic studies, this research elucidates that lncRNA Miat can sponge and regulate mmu-miR-124-3p.1, thereby upregulating the expression level of adenylate cyclase 1 (Adcy1). Additionally, rutin has been found to effectively inhibit the proliferation and metastasis of breast cancer cells through this ceRNA network, significantly potentiate THP's antitumor effects, and alleviate THP-induced myocardial damage. This discovery not only unveils the potential value of rutin in breast cancer treatment but also provides robust experimental evidence and theoretical support for the development of novel breast cancer treatment strategies based on the ceRNA network.

Keywords: Breast cancer，lncRNA Miat，Rutin，Pirarubicin，ceRNA，Cardiomyotoxicity

Palmatine, a protoberberine alkaloid from *Phellodendron amurense* Rupr., ameliorated gouty inflammation by inhibiting pyroptosis via NLRP3 inflammasome

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Abstract:

Aim of the study: Gout is a common metabolic inflammatory disease caused by the deposition of MSU crystals (MSU) in joints and non-articulation structures. Given the multiple toxic side effects of clinical anti-gout medications, there is a need to find a safe and effective alternative. We investigated the therapeutic effects of Palmatine, one of the primary active protoberberine alkaloids from Phellodendron amurense Rupr., on MSU crystal-induced acute gouty inflammation, targeting the NLRP3 inflammasome mediated pyroptosis.

Materials and methods: In vitro, mouse peritoneal macrophages (MPM) and rat articular chondrocytes were stimulated with LPS plus MSU in the presence or absence of Palmatine. In vivo, arthritis models include the acute gouty arthritis model by injecting MSU crystals in the paws of mice and the air pouch acute gout model by injecting MSU crystals into the mouse subcutaneous tissue of the back. Expression of NLRP3 inflammasome activation and NETosis formation was determined by Western blot, ELISA kit, immunohistochemistry, and immunofluorescence. In addition, the anti-cartilage damage of Palmatine on MSU-induced arthritis mice were also evaluated.

Results: Pal (25, 50 and 100 μM) dose-dependently decreased levels of NLRP3 inflammasome activation related proteins NLRP3, ASC, caspase-1, IL-1β, HMGB1 and Cathepsin B. The NETosis protein levels of caspase-11, histone3, PR3 and PAD4 were remarkably reduced by Pal. Pal effectively blocked the activation of NLRP3 inflammasome, attenuated the caspase-11 mediated noncanonical NLRP3 inflammasome avtivation and intervened the formation of NETs, thereby inhibiting the pyroptosis. In vivo, Pal attenuated MSU-induced inflammation in gouty arthritis and protect the articular cartilage through inhibiting the pyroptosis of proteins NLRP3, ASC, caspase-1, IL-1β, HMGB1 and Cathepsin B, reducing levels of NETosis relevant proteins caspase-11, histone3, PR3 and PAD4 and up-regulating expression of protein MMP-3.

Conclusion: Palmatine ameliorated gouty inflammation by inhibiting pyroptosis via NLRP3 inflammasome.

Keywords: gout; Palmatine; inflammations; pyrotosis; NETs

Extraction and isolation of the components from ragweed flower and the evaluation of their anti-lymphoma cell activity

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Abstract:

Ragweed is one of the typical invasive alien plants, which originated from the Sonoran desert in North America and was introduced into China in the early 1930s. The existing research results show that ragweed and ragweed extracts have a wide range of application value in many disciplines such as agriculture, pharmacy, biology and ecological environment. In addition, the flowers and pollen of ragweed contain a large number of sesquiterpenoids, so some chemical components extracted from this natural plant have certain value and role in the treatment of some diseases. In this study, the flowers and pollen of ragweed were first selected as the research objects, and then four organic solvents of different polarity, including petroleum ether, were used to extract the ethanol extracts of ragweed flowers in turn. The dichloromethane layer extracts with more extracts and less pigments were gradient elutated, and a total of 14 components were obtained. Then, the anticancer cell activity of 7 components was determined. The experimental results show that: All components had strong inhibitory effects on SU-DHL-10 cells and RaJi cells. Fr.P 2, Fr.P 5, and Fr.P8 showed lower inhibitory rates on L-02 cells, but higher inhibitory rates on RaJi cells and SU-DHL-10 cells, so these components are expected to be the candidates for anti-tumor cells.

Keywords：Ragweed flowers ; Extractive; Antitumor activity; Selectivity index

Table 1：Proliferation inhibition rate (%) of the components at 100 μg/mL

Component	L-02	SU-DHL-10	RaJi	SIHA
Fr.P 2	42.91	74.18	70.15	37.50
Fr.P 4	60.64	67.32	75.28	57.19
Fr.P 5	18.73	53.53	57.44	23.23
Fr.P 8	15.28	51.75	50.02	36.46
Fr.P 9	62.85	72.47	76.32	62.43
Fr.P 11	62.08	70.25	72.09	51.25
Fr.P 12	60.77	63.04	74.65	55.76

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Synthesis and evaluation of selective anticancer activity of novel isoalantolactone derivatives

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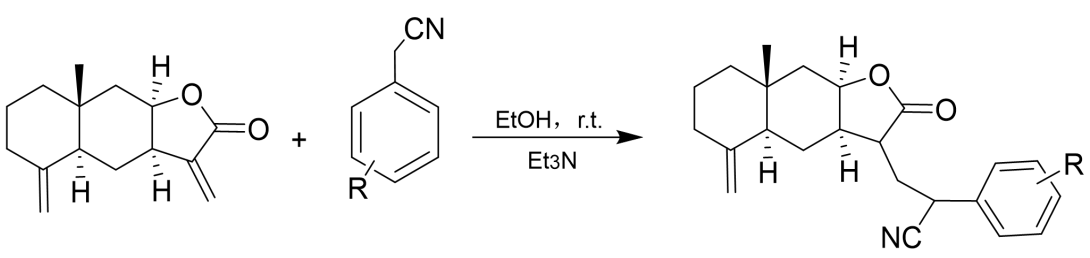
Abstract:

Sesquiterpene is a class of natural compounds containing 15 carbon progeny in the molecule, and its structure contains three isoprene units. It has many kinds of bone structure such as chain and ring. The sesquiterpene compounds previously known are artemisinin, chrysolactone, and parthenolide. Isoalantolactone has many physiological activities such as anti-insect, anti-bacterial and anti-tumor. The structure modification of ester is an effective way to improve its activity. At present, the structural modification of isoalantolactone is mainly focused on the Michael reaction of conjugate double bond with lactone. Michael addition is a reaction in which the active methylene compound forms a carbanion in the presence of a base, and then performs 1, 4-addition with an α, β-unsaturated carbonyl compound. This reaction is a common method for growing carbon chains and is widely used in organic synthesis. Many important organic intermediates can be synthesized through the Michael addition reaction. This experimental group will introduce cyanogroup for the first time to modify the structure of isoalantolactone, which is believed to be of great significance for the discovery of bioactive isoalantolactone derivatives. It is believed that it is of great significance to enrich the structural modification of isocodenolactone and to find bioactive isocodenolactone derivatives. The results of MTT assay showed that the isoalantolactone derivatives containing cyanyl group had a good inhibitory effect on the above cancer cells.Against HepG-2 human liver cancer cells, compound B and D expressed good inhibitory activities, with IC50 values of 28.9 and 26.6 μmol/L, respectively. And, compound A and B showed significant inhibitory activities against the SiHa cancer cells, with IC50 values of 26.3 and 10.9 μmol/L, respectively. The anti proliferative activity of compound A is significant for RaJi lymphoma cells, and for another type of lymphoma cell SU-DHL-10, compound C has good activity, the IC50 values are 29.6 and 25.8 μmol/L, respectively.

Keywords: isoalantolactone derivatives; Michael reaction; antitumor activity



A: R=2-chloro-4-fluorophenyl

B: R=3-chloro-4-fluorophenyl

C: R=2-cyanophenyl

D: R=3-trifluoromethylphenyl

Scheme 1: Synthesis route of compound A-D.

Table 1: The IC_{50} values of compounds for 4 types of cancer cells (μmol/L)

Compound	HepG-2	SiHa	RaJi	SU-DHL-10
A	ND	26.3±1.7	29.6±5.3	ND
B	28.9±1.6	10.9±0.3	ND	ND
C	ND	ND	ND	25.8±0.9
D	26.6±2.4	ND	ND	ND
isoalantolactone	ND	ND	ND	ND

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Investigations into the chemical constituents present in the EtOAc extract of *Alnus mandshurica* (Callier) Hand.-Mazz.

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Abstract:

A phytochemical study of *Alnus mandshurica* (Callier) Hand.-Mazz. (dried stem bark) led to the isolation of 23 compounds, including twelve simple phenols and simple phenol glycosides (**1**–**9**), eleven flavonoids (**13**–**18**), among them, compounds 13, 15, 17, 18, and 23 are flavan-3-ols compounds, two coumarins (**19** and **20**), one diarylheptanoid (**21**), one lupine triterpenoid (**22**), one sterol (**23**). The structures of these isolated compounds were identified using NMR spectroscopy (^{1}H and ^{13}C) by comparison with previously reported data. Compounds **2**, **5**–**11**, **15**, **17**, **20**–**22** were isolated from *A. mandshurica* for the first time

Keywords: *Alnus mandshurica*; Chemical composition

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Mechanism of Maslinic acid Improving Non-alcoholic fatty liver disease by Tyloxapol through NF-κB Signaling Pathway

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Abstract:

Objective: To study the mechanism of Maslinic acid (MA) improving Non-alcoholic fatty liver disease (NAFLD) through NF-κB signaling pathway, which provided theoretical support for the treatment or prevention of NAFLD related diseases.

Results:In vivo experiments, MA significantly reduced TG, TC and LDL-C levels and increased HDL-C levels in TY induced hyperlipidemia mice in a dose-dependent manner.Western blotting showed that MA significantly up-regulated the expression levels of lipid metabolis-related proteins (p-AMPK, p-ACC, ATGL, and p-HSL) and down-regulated the expression levels of fatty acid synthesis-related proteins (SREBP1c, FAS, SCD1, and Lipin1). Maslinic acid may improve HLP and NAFLD in the liver of Tyloxapor mice through NF-κB signaling pathways.

Conclusion:Maslinic acid may improve NAFLD in the liver of Tyloxapol mice through NF-κB signaling pathways.

Keywords: Hyperlipidemia; Maslinic acid; Tyloxapol

Pterostilbene exerts cytotoxicity on activated hepatic stellate cells by inhibiting excessive proliferation through the crosstalk of Sirt1 and STAT3 pathways

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Abstract:

Pterostilbene (PTE), a natural analogue of resveratrol, abundantly exists in blueberries and grapes and has several beneficial potentials against oxidative stress, inflammation, and cancer. In current study, we investigated the effects of PTE on hepatic fibrosis in vitro and in vivo. Activation of hepatic stellate cells (HSCs) is an initiating event in the initiation of hepatic fibrosis. MTT assay revealed that PTE (3.125–12.5 μM) displayed cytotoxicity on activated HSCs, no cytotoxicity on AML-12 and quiescent HSCs. PTE significantly inhibited the expressions of α-SMA, collagen I and TIMP-1/MMP13 ratio; suppressed inflammatory cascade activation to reduce inflammatory cytokines release, such as Caspase-1, IL-1β and IL-6. PTE activated Sirt1 and decreased STAT3 phosphorylation, functioning as SRT1720 and Niclosamide. Sirt1 deficiency significantly elevated p-STAT3 expression, while STAT3 deficiency resulted in Sirt1 increasing and inhibited fibrosis and inflammatory cytokines expressions. In mice with hepatic fibrosis induced by thioacetamide (TAA), PTE significantly decreased ALT and AST activities, reduced fibrosis markers, STAT3 phosphorylation and activated Sirt1 expression. PTE showed cytotoxicity on activated HSCs to ameliorate hepatic fibrosis via regulating fibrogenesis, energy metabolism and inflammation and targeting the crosstalk of Sirt1 and STAT3. In conclusion, PTE could be potentially beneficial as a natural plant metabolite in preventing and treating hepatic fibrosis.

Keywords: Pterostilbene; cytotoxicity; hepatic fibrosis; energy metabolism; inflammation

Simultaneous determination of free DL-amino acids in human hair with a novel DBD-M-Pro derivatization by UHPLC-HRMS: An application in diabetes patients

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Abstract:

Human hair is a non-invasive biological sample that is easy to collect and store and can reflect long-term body health. However, the correlation between DL-amino acids and metabolic diseases in hair samples has not been studied. Therefore, we propose a novel UHPLC-HRMS method for analyzing seven free chiral amino acids (DL-Thr, DL-Glu, DL-Ala, DL-Val, DL-Pro, DL-Leu, and DL-Phe) simultaneously in hair samples by derivatization of chiral probe 4-(N, N-dmethylaminosulfonyl)-2,1,3-benzoxadiazole-trans-2-methyl-L-proline (DBD-M-Pro) labeled with targeted amino functional groups.

Gradient elution was carried out using an ACQUITY^{TM} BEH C_{18} (100×2.1 mm,1.7 μm) column with a mobile phase of 0.15% formic acid (FA) in 10 mM ammonium acetate (CH_3-$COONH_4$) and 0.2% FA in acetonitrile. The labelled DL-amino acid diastereoisomers could be completely separated, with a resolution (Rs) of 1.59–11.44. These amino acids show a great linear correlation within the range of 3.1 to 99.2 pmol ($R^2 \geq 0.9990$). The limit of detection ranged from 0.29 to 2.11 pmol. Intraday and interday precision was 1.87%–14.87%. The average recovery was 96.12%–105.33%. We employed the method to determine the concentration of free chiral amino acids in hair samples from 30 healthy volunteers (HVs) and 30 diabetes patients (DPs) male diabetes patients had significantly higher levels of L-Thr, L-Val, L-Leu ($p < 0.05$), and D-Ala ($p < 0.01$) in their hair samples than male healthy volunteers and female diabetes patients had significantly higher levels of D-Ala ($p < 0.05$) in their hair samples than female healthy volunteers.

This study evaluated the feasibility of free chiral amino acids in human hair in early warning of diabetes for the first time. It provides a new method for the detection of trace free DL- amino acids in human hair samples and a new strategy for diabetes screening. In the future, we will use more hair samples of diabetic patients for further determination to confirm the clinical effectiveness of this method.

Keywords: Hair; Diabetes; Free chiral amino acid; Diastereomer; UHPLC-HRMS

含咪唑并噻二唑结构的吡唑类衍生物的合成及其抗菌活性的研究

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摘要：

2022 年《柳叶刀》杂志的一项研究报道指出目前细菌感染是全球第二大死亡原因。细菌感染伴随出现的细菌耐药性问题近年来已经发展到了非常严重的地步。目前，每年由细菌耐药性造成的死亡人数大约是 70 万例，预计到 2050 年能达到 1000 万例[1]。WHO 的全球抗菌素耐药性和使用监测系统（GLASS）2021 年的报告指出大肠杆菌对第三代头孢菌素的耐药率对不同国家显示出了显著的差异[2]。在低收入国家显示的耐药性为 58.3%，而高收入国家中显示的耐药性是 17.53%。因此，开发可耐药的新型抗菌药物迫在眉睫。

根据前期研究，发现在吡唑环与苯环之间引入甲酰基能够提升化合物的抗菌活性。因此，本研究在保留甲酰基的基础上。设计合成化合物 **3a-i**，探究不同取代基化合物对抑菌活性的影响。为了进一步确认吡唑环上的甲酰胺基对抑菌活性的影响，在吡唑环上引入了磺酰基设计了化合物 **4a-g**。并评价了其对金黄色葡萄球菌 ATCC 6538、大肠埃希氏菌 ATCC 25922、铜绿假单 胞菌 CMCC 10211、耐甲氧西林金黄色葡萄球菌 ATCC 43300、白色念珠菌 CMCC 98001、啤酒酵母菌 ATCC 9763 的体外抗菌活性。药理活性结果显示有一半的化合物显示中等或较高的抗菌活性，其中化合物 **4g**（MIC = 4 μg/mL）和 **4c**（MIC = 4 μg/mL）其活性与阳性对照化合物加替沙星（MIC = 1 μg/mL）接近。

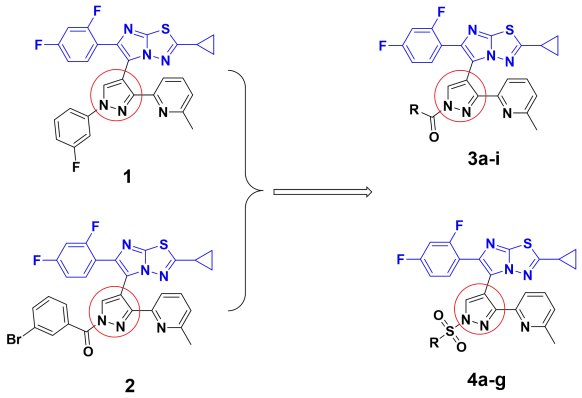

图 1 3a-i 和 **4a-g** 的设计思路

通过本研究发现的化合物 **4c** 和 **4g** 作为抗细菌候选化合物，具有进一步研究价值，为吡唑类抗菌药物设计与研究提供理论依据。

关键词：咪唑；噻二唑；吡唑；抗菌

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Artemetin targets the ABCG2/RAB7A axis to inhibit mitochondrial dysFunction in asthma

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Abstract:

Background:Artemetin, a natural flavonoid, is well-known for its significant anti-inflammatory and antioxidant properties, but its mechanisms in asthma are still unclear.

Purpose:This study aims to explore the therapeutic potential of Artemetin in mitigating airway inflammation and mitochondrial dysfunction via ABCG2/RAB7A signaling pathway.

Methods:An HDM-induced mouse asthma model and HDM-treated BEAS-2B cell model were established. Methods utilized included bioinformatics, molecular docking, Drug Affinity Responsive Target Stability (DARTS), and Cellular Thermal Shift Assay (CETSA), flow cytometry, Western blot, co-immunoprecipitation (CO-IP), immunohistochemistry, and immunofluorescence staining.

Results:Artemetin significantly alleviates the proportion of eosinophils and pro-inflammatory cytokines in BALF, IgE levels in serum, airway epithelial mucus secretion, inflammatory cell infiltration, and collagen fiber deposition. ABCG2 was identified as a core binding target of Artemetin. When Artemetin was labeled with Biotin, further experiments confirmed its interaction and upregulation of ABCG2. Overexpression of ABCG2 (OV-ABCG2) enhances antioxidant capacity by upregulating Nrf2, HO-1, SOD, and CAT, mitigating mitochondrial oxidative stress (mtROS), improving mitochondrial membrane potential (MMP), and reducing DRP-1-mediated mitochondrial fission while enhancing MFN2-mediated fusion. Furthermore, ABCG2 was found to interact with and downregulate RAB7A. Both Artemetin and siRNA-RAB7A notably inhibit p-DRP1 and mitochondrial translocation of DRP1, thereby promoting mitochondrial fusion, reducing mtROS, and increasing MMP. Gene Ontology (GO) analysis revealed that ABCG2 is closely linked to apoptosis. Artemetin, OV-ABCG2, and RAB7A knockdown all alleviated HDM-induced PANoptosis by decreasing ZBP1, GSDMD, Caspase-8, FADD, BAX, and RIPK1 while increasing anti-apoptotic protein Bcl-2.

Conclusion:Artemetin significantly improves airway inflammation, oxidative stress, and mitochondrial dysfunction in asthma by modulating the ABCG2/RAB7A axis and PANoptosis. Artemetin presents new possibilities for adjunctive therapy in the management of asthma.

Keywords: Artemetin; ABCG2; RAB7A; mitochondria; asthma

Study on the intervention effect of salidroside on the APP enzymatic cleavage pathway in dementia model neurons and its impact on mitochondrial abnormal protein aggregation

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Abstract:

Objective: To investigate the effect of salidroside on the enzymatic cleavage pathway of Amyloid Precursor Protein (APP) in an Alzheimer's disease (AD) model, as well as its potential regulatory effect on mitochondrial function and abnormal protein aggregation.

Methods: Fifty 2-month-old male Kunming mice were randomly divided into five groups (10 mice per group) using a random number method: Control group (CT), Model group (AE),Low-Salidroside, Medium-dose Salidroside , and High-Salidroside. For 50 consecutive days, the mice were intraperitoneally injected with 120 mg/kg of D-galactose and 20 mg/kg of AlCl3 at scheduled intervals each day. The mice in the low, medium, and high salidroside groups received oral gavage treatment with salidroside at doses of 25, 50, and 100 mg/kg, respectively. Behavioral experiments, including the Morris water maze, dark avoidance test, and platform jumping test, were conducted to assess the effect of salidroside on learning and memory in the aging model mice. Within 24 hours, the mitochondrial indicators (Complex I, Complex III, Cyt-C, β-CTF, ATPase) isolated from the mouse brain tissue were measured, along with α-Secretase, β-Secretase, γ-Secretase, Aβ1-42, and sAPPα in the brain tissue lysate.

Results: The salidroside groups showed a significant improvement($P < 0.05$) in the behavioral experiments (reduced errors and shorter latency) compared to the AD model group. The levels of Aβ1-42 and β-CTF in the isolated mitochondria of the brain tissue were significantly reduced in the salidroside treatment groups compared to the AD model group. In contrast, the levels of Complex I, Complex III, and Cyt-C were significantly increased in the salidroside treatment groups, with the high-dose group performing better than the low-dose group ($P<0.05$).

Conclusion:1.Salidroside can significantly reduce the generation of Aβ1-42 in the APP enzymatic cleavage pathway.2.Salidroside can protect cells by inhibiting β-secretase activity, thereby reducing the production of C99, decreasing Aβ accumulation, and mitigating oxidative stress, which helps maintain the integrity of mitochondrial membrane function. It also inhibits apoptosis triggered by mitochondrial cytochrome C. Moreover, salidroside can suppress the production of β-CTF, directly alleviating the inhibitory effect of β-CTF on ATP production efficiency.3.It is hypothesized that salidroside may slow down the pathological progression of AD by improving mitochondrial function, and this hypothesis is supported.

Keywords: Salidroside, APP enzymatic pathway, mitochondria, Alzheimer's disease

Taraxerol targeting Nrf2/GPX4 axis exhibits anti-tumor activity through inducing ferroptosis in Breast cancer

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Abstract:

Background: Breast cancer (BC) is the second most common malignant tumour worldwide and has become the most harmful cancer to women's health. Ferroptosis, a novel form of programmed cell death driven by iron-mediated lipid peroxidation, represents a promising avenue for BC treatment by targeting ferroptosis to eliminate tumours. Taraxerol, a natural triterpenoid compound derived from dandelions, has demonstrated antitumour effects in breast cancer. However, it remains unclear whether its anti-breast cancer activity is related to the ferroptosis mechanism.

Methods: The effects of taraxerol on cell proliferation and apoptosis, iron accumulation, lipid peroxidation, glutathione (GSH) and malondialdehyde (MDA) were examined using SK-BR-3 and MDA-MB-468 cells. Western blot was used to detect the changes in the expression of Nrf2, GPX4 and SLC7A11 in the regulation of Taraxerol-mediated cell ferroptosis and their significance The mechanism of Taraxerol regulating cell ferroptosis-related signal pathways and specific protein regulation was explored through network pharmacology and molecular docking technology. In vivo, the antitumor effect mediated by Taraxerol and Nrf2 was explored through a xenograft tumor model.

Results: Taraxerol significantly inhibited the growth of breast cancer tumours both in vivo and in vitro. In this study, we found that Taraxerol increased lipid peroxidation and Fe^{2+} levels and decreased GSH levels in BC. This regulatory effect could be partially reversed by DFO. In addition, overexpression of Nrf2 reversed the ferroptotic effect induced by Taraxerol. In vivo, it was demonstrated that Nrf2 plays a role in the regulation of taraxerol-induced ferroptosis in breast cancer tumours.

Conclusion: Our findings for the first to demonstrate that Taraxerol mediates ferroptosis in BC through the Nrf2/GPX4 axis, and it is expected to provide promising drug candidates for the treatment of BC.

Key words: Taraxerol; Breast cancer; ferroptosis; Nrf2

Preparation of flavonoid derivatives and their anticancer activities by microwave-promoted Wolff rearrangement reaction

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Abstract:

Wolff rearrangement reaction has important research significance in the fields of organic chemistry and medicinal chemistry, however, the conversion from α-diazoketone to vinyl ketone in the Wolff rearrangement reaction restricts the application of vinyl ketone due to its excessive reactivity in the preparation. Microwave reaction technology is characterized by fast heating rate, homogeneity, high thermal energy utilization and sensitive reaction. Wolff rearrangement of diazo compounds, the conventional method involves the risk of instability and explosiveness, toxicity and potential carcinogenicity with high energy release, however, these problems can be avoided in microwave reactor by releasing only nitrogen, less reaction time and less energy required, which demonstrates its simplicity and sustainability. Flavonoids are an important class of medicinal compounds extracted from various natural plants with a variety of pharmacological properties, including antioxidant, anti-inflammatory, anticancer, antihypertensive and other bioactivities, which are of great value in biomedicine. In the present work, a series of flavonoid derivatives were designed and synthesized in order to find efficient and low-toxicity anticancer drugs by using microwave reaction technology, applying green thinking and innovative ideas in drug design, and their anticancer properties were investigated. This paper is divided into four parts, the first part in the microwave reaction conditions through methodology, screening of temperature, time and solvent for condition optimization to get the optimum reaction conditions. The second part of the substrate range was studied to expand the diazo compound substrates. The third part of diazo compounds and flavonols in Wolff rearrangement reaction to complete the esterification reaction in micro by optimal reaction conditions. The fourth part completes the compounds of flavonoid ester series to carry out experiments related to anticancer cell proliferation activity, expecting to get good pharmacological activity.

Keywords: wolff rearrangement reaction, enones, flavonoid ester derivatives, antitumor cell proliferative activity

Efficient degradation and enhanced anticomplementary activity of *Belamcanda chinensis* (L.) DC. polysaccharides via trifluoroacetic acid

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Abstract:

Belamcanda chinensis (L.) DC. rhizomes have been traditionally employed in Chinese medicine owing to their efficacy in heat clearance, detoxification, phlegm alleviation, throat health promotion, and polysaccharides as the main active constituents in decoction have been highly valued. The polysaccharides from rhizomes of *B. chinensis* (BCPs) were found to potent anticomplementary activity. These polysaccharides possessed a disadvantage in the form of high molecular weight, exceeding 2×10^7 g/mol, which could lead to poor solubility. Consequently, their poor solubility, combined with the challenge of traversing cell membrane barriers, restricted their ability to be effectively absorbed and utilized by the body. To solve this problem, five different concentrations (1~5 mol/L) of trifluoroacetic acid (TFA) were used to degrade BCPs, followed by purification and isolation to obtain DBCP-1, DBCP-2, DBCP-3, DBCP-4, and DBCP-5 with increasing TFA concentration. Subsequently, the structural characteristics of degradation BCPs (DBCPs) were investigated through a series of physical and chemical methods. Finally, the complement inhibition ability and blocking targets of DBCPs were evaluated by an immune hemolysis assay, and the structure-activity relationship was explored using Pearson correlation analysis. The findings revealed a notable reduction in the molecular weight of BCPs, from an initial value of 2.622×10^5 g/mol to a final value of 6.255×10^4 g/mol, and the water solubility index increased from 90.66 ± 0.42 % to 97.78 ± 0.43 %. The DBCPs were acidic polysaccharides composed of Man, GalA, Glc, Gal, and Ara with different molar ratios. As the concentration of TFA increased, the degradation rate constant increased from 1.468×10^{-3} to 5.943×10^{-3}, and the process followed the first-order degradation kinetic model ($R^2 > 0.97$) and the random fracture model ($R^2 > 0.96$). Furthermore, the five degraded polysaccharides still exhibit good thermal stability. *In vitro* experiments showed that DBCP-3 (0.029 ± 0.011 mg/mL) exhibited more potent anticomplementary activity than the BCPs (0.096 ± 0.013 mg/mL) and positive drugs (0.144 ± 0.017 mg/mL), which was strongly correlated with its Mw (r = 0.6-0.8), inhibiting complement activation by blocking C2 and C4. These results indicated that TFA degradation has a positive effect on polysaccharides, of which DBCP-3 is expected to treat diseases involving hyperactivation of the complement system.

Keywords: *Belamcanda chinensis* (L.) DC. Rhizomes; TFA degradation; Polysaccharides; Anticomplementary activity

Analysis of Three Thiol Compounds in Wine Labeled with NCS-OTPP Based on Mass Spectrometry Probe and Monitoring of Urine Metabolism Dynamics after Wine Consumption

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Abstract:

Monitoring the change of chiral thiol compounds in human body is important for the early diagnosis of oxidative stress-related diseases and to explore their pathogenesis. In order to solve this problem, a new isotope spectrum probe, labeled (R)-(5-(3-isothiocyanatepyrrolidine-1-yl)-5-oxypentyl)triphenylphosphorus (NCS-OTPP), has been synthesized and its parent structure is triphenylphosphine. In this study, we established a new method based on NCS-OTPP derivatization for simultaneous detection and chiral separation of DL- thiol compounds in wine, and monitored the metabolic dynamics of chiral thiol compounds in human urine after drinking wine.

First, a novel UHPLC-HRMS method based on NCS-OTPP derivatization was developed for simultaneous detection and chiral separation of three DL-thiol compounds (DL-GSH, DL-Cys, DL-Hcy) in wine. Results The three chiral thiol compounds observed separation degrees (Rs) ranging from 1.70 to 1.83 in 25 min, R^2≥0.9992 in linearity, 0.83-4.06% in intraday precision and 85.90-108.43% in average recovery rate. The method was applied to the detection of DL-thiol compounds in ten different wines, and the content of DL-thiol compounds varied with different wine types. In addition, the content of DL-thiol compounds can be used as the identification index of wine raw materials by PCA separation and identification.

We also monitored the dynamics of L-GSH, DL-Cys and DL-Hcy in urine of 12 healthy volunteers (5 men and 5 women) after drinking wine and purified water. We generated fitting curves and investigated the change trend of chiral thiol compounds in vivo. The content of DL-thiol compounds in purified water was found to be decreasing, while that of DL-thiol compounds in wine and sake was increasing first and then decreasing.

Based on the derivation of NCS-OTPP, a new method of UHPLC-HRMS was established to isolate and detect DL-thiol compounds in wine, and it was successfully applied to the analysis of DL-thiol compounds.

Key words: Chiral thiol compounds; Wine; NCS-OTPP; UHPLC-HRMS

Structural characterization of an ammonia adduct of "peptide-hemin/DNA" hybrid complex

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Abstract:

G-quadruplex DNAs (G4s) are involved in key biological processes such as regulation of oncogene expression and maintenance of telomeric repeats upon cell division.[1] G4 is composed of stacked G-quartets, each of which involves a planar association of four guanine bases circularly connected through Hoogsteen type base-pairings. The size and planarity of the G-quartet are well-suited for interaction with iron(III)-protoporphyrin IX complex (hemin).[2] However, the interaction mechanism between hemin and G4 is not clear. Recently, we prepared a water-soluble hemin-peptide known as *N*-acetylated microperoxidase-11 (AcMP11), which offers the significant advantage of possessing a proximal histidine ligand that can bind to hemin iron to give a five co-ordination structure, leaving a distal open hemin-plan and constructed novel "peptide-hemin/DNA" hybrid-complex mediated by interaction between the open hemin-plan of AcMP11 and G-quartet of parallel-stranded [d(TTAGGG)$_4$].[3]

Here, we constructed an ammonia adducted "peptide-hemin/DNA" hybrid complex. NMR studies revealed that the AcMP11 binds to the 3'-terminal G-quartet of the [d(TTAGGG)$_4$] through a π-π stacking interaction between the porphyrin moiety of the hemin and the G-quartet. In this unique hybrid complex, the hemin(Fe^{3+}) exhibits features characteristic of low-spin species (S = 1/2), which indicating the Fe-bound NH_3 accommodated between the hemin and G-quartet planes. Absorption spectroscopic studies revealed the binding constant (K_a) of 41183 ± 6695 M^{-1}, and a 1:1 stoichiometric ratio between the "peptide-hemin/DNA" hybrid complex and NH_3. The K_a value obtained for the hybrid complex is significantly larger than the AcMP11, *i.e.*, K_a = 1864 ± 516 M^{-1}. These findings provide novel insights as to the design of novel DNA enzymes possessing metalloporphyrins as prosthetic groups.

Keywords: G-quadruplex DNA; Hemin; Hybrid-complex

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Ginsenoside RG3 synergizes with STING agonist to reverse cisplatin resistance in gastric cancer

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Abstract:

This study investigates the inhibitory effects of the combination of the stimulator of interferon genes (STING) agonist cyclic diadenylate monophosphate (c-di-AMP) and ginsenoside RG3 on cisplatin (DDP)-resistant gastric cancer (GC) cells. The objective is to provide new therapeutic targets and insights for the clinical management of DDP resistance. Materials and Methods: We employed various techniques, including Western blot, MTT assay, colony formation assay, scratch assay, Transwell assay, tubule formation assay, flow cytometry, Hoechst 33342 fluorescence staining, and in vivo experiments, to explore the effects of the combined application of the STING agonist and ginsenoside RG3 on reversing cisplatin resistance in gastric cancer. Results: The combination of the STING agonist and RG3 significantly inhibited the proliferation, migration, invasion, and angiogenesis of SGC-7901/DDP cells. Furthermore, this treatment suppressed the epithelial-mesenchymal transition (EMT) process and stem cell-like characteristics of the SGC-7901/DDP cells, while downregulating the expression of resistance-related proteins. Conclusion: The STING agonist hinders the growth and proliferation of gastric cancer cells. Ginsenoside RG3, recognized for its antioxidant, anti-aging, and anti-cancer properties, is widely used in cancer treatment and in managing chemotherapy-related side effects. Additionally, RG3 enhances anti-tumor immunity through the regulation of signal transduction. This study conducted a series of in vitro and in vivo experiments to examine the impact of the combined use of the STING agonist and RG3 on gastric cancer drug resistance. The results indicate that this combined treatment significantly inhibits the malignant progression of gastric cancer and reverses drug resistance, providing a theoretical foundation for clinical applications and new therapeutic targets.

Keywords: Gastric cancer; cisplatin resistance; STING agonist; ginsenoside RG3; immunotherapy

Sesamol as a potential candidate for the treatment of hepatic fibrosis, based on its regulation of FXR/LXR axis-mediated inhibition of autophagy through crosstalk between hepatic cells and macrophage

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Abstract:

Sesamol (SEM), a natural lignan compound isolated from sesame, has strong anti-oxidant property, regulating lipid metabolism, decreasing cholesterol and hepatoprotection. However, its anti-hepatic fibrosis effect and mechanisms have not been comprehensively elucidated. C57BL/6 mice with hepatic fibrosis were induced by TAA, then administrated with SEM or curcumin, respectively. Hepatic stellate cells (HSCs) were stimulated by TGF-β or conditioned medium, and then cultured with SEM, GW4064, GW3965, Rapamycin (RA) or 3-methyladenine (3-MA), respectively. Mice with hepatic fibrosis also were administrated with SEM, RA or 3-MA to estimate the effect of SEM on autophagy. In *vitro*, SEM significantly inhibited extracellular matrix deposition, P2×7R-NLRP3, and inflammatory cytokines. SEM increased farnesoid X receptor (FXR) and liver X receptor α/β (LXRα/β) expressions and decreased MAPLC3α/β and P62 expressions, functioning as 3-MA (autophagy inhibitor). In *vivo*, SEM reduced serum transaminase, histopathology changes, fibrogenesis, autophagy markers and inflammatory cytokines caused by TAA. LX-2 were activated with conditioned medium from LPS-primed THP-1, which resulted in significant enhance of autophagy markers and inflammatory cytokines and decrease of FXR and LXRα/β expressions. SEM could reverse above these changes and function as 3-MA, GW4064, or GW3965. Deficiency of FXR or LXR attenuated the regulation of SEM on α-SMA, MAPLC3α/β, P62 and IL-1β in activated LX-2. In activated THP-1, deficiency of FXR could decrease the expression of LXR, and vice versa. Deficiency of FXR or LXR in activated macrophage (MΦ) decreased the expressions of FXR and LXR in activated LX-2. Deficiency FXR or LXR in activated MΦ also attenuated the regulation of SEM on α-SMA, MAPLC3α/β, P62, caspase-1 and IL-1β. In *vivo*, SEM significantly reversed hepatic fibrosis via FXR/LXR and autophagy. SEM could regulate hepatic fibrosis by inhibiting fibrogenesis, autophagy and inflammation. FXR/ LXR axis-mediated inhibition of autophagy contributed to the regulation of SEM against hepatic fibrosis, especially based on involving in the crosstalk of HSCs-macrophage. SEM might be a prospective therapeutic candidate, and its mechanism would be a new direction or strategy for hepatic fibrosis treatment.

Keywords: Sesamol; Hepatic fibrosis; Liver microenvironment; Inflammation

Study on the anti-Toxoplasma gondii effect of Minocycline and the mechanism of inhibiting microglia activation

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Abstract:

Neuronal damage caused by *Toxoplasma gondii*（*T. gondii*） infection is related to neuroinflammation caused by excessive activation of microglia. Studies have shown that Minocycline can effectively inhibit the activation of microglia, reduce the production of inflammatory factors, and has anti-inflammatory, neuroprotective and other pharmacological effects. However, the specific molecular mechanism by which Minocycline inhibits microglial activation remains unclear. In this study, BV2 cells were infected with tachyzoites of *T. gondii* to establish an *in vitro* microglia activation model and mice were infected with tachyzoites of *T. gondii* to establish an *in vivo* infection model to explore the molecular mechanism of Minocycline in the treatment of brain injury caused by *T. gondii* infection.In this experiment, MTT assay was used to detect the effect of different concentrations of Minocycline on the proliferation of BV2 cells and the optimal concentration was selected. The effects of Minocycline on the proliferation of *T. gondii* in BV2 cells were evaluated by Q-PCR, Trypan blue staining and double Immunofluorescence staining. The results showed that Minocycline reduced the number of intracellular *T. gondii* , increased cell survival rate, and significantly reduced the expression level of B-1, which directly and indirectly inhibited the proliferation of *T. gondii* in vitro. The same results were also confirmed in vivo by clinical scores, body weight changes in mice and Q-PCR experiments. The pathogenesis of neuronal injury is related to the activation of microglia. In vitro, we detected the fluorescence expression intensity and protein expression of Iba-1 in BV2 cells by Immunofluorescence and Western blot. The results showed that compared with the model group, the fluorescence intensity of Iba-1 was down-regulated and the protein expression of Iba-1 was decreased in the Minocycline treatment group, and Minocycline inhibited the activation of microglia. Western blotting of Iba-1 in mouse brain tissue also showed the same conclusion. Studies have found that TLR4/NF-κB signaling pathway plays a key role in neuronal damage caused by *T. gondii* infection. Next, we analyzed the effects of Minocycline on the expression of TLR4/NF-κB pathway proteins and their downstream inflammatory factors (iNOS, HMGB1 and TNF-α) in BV2 cells by Western blot. At the same time, the effect of Minocycline on NF-κB nuclear translocation and the expression and localization of inflammatory factor HMGB1 were observed by Immunofluorescence assay.The results showed that Minocycline inhibited the expression of TLR4, MyD88 and NF-κB pathway proteins (p-NF-κB p65 and p-IκBα),

inhibited NF-κB nuclear translocation, and reduced the production of inflammatory factors (iNOS, HMGB1 and TNF-α). In vivo, the expression of inflammatory factors in mouse brain tissue was detected by Western blot, and the expression of TLR4 and p-NF-κB p65 in mouse prefrontal cortex microglia was evaluated by double Immunohistochemical staining. The results were consistent with the results of in vitro experiments. The co-culture model of microglia and primary neurons was established, and the purity of neurons and the effect of Minocycline on neuronal apoptosis were detected by Immunofluorescence assay. The results showed that Minocycline inhibited the activation of microglia and reduced the apoptosis of neurons in the co-culture system with neurons, which had a positive effect on the protection of neurons. The neuronal damage in the brain tissue of mice was further verified by Nissl staining and Immunohistochemistry. The results showed that the degree of neuronal damage was restored after Minocycline treatment, and the number of Nissl bodies increased significantly.In summary, in vitro and in vivo studies have shown that Minocycline treatment can significantly inhibit the proliferation of *T. gondii*. Minocycline blocks the activation of microglia through the TLR4/NF-κB signaling pathway, reduces the release of inflammatory mediators, and improves neuronal damage. This reveals the potential of Minocycline against *T. gondii* infection, and provides an effective basis for the clinical treatment of Toxoplasmosis encephalitis, which helps to further save resources and realize the new use of old drugs.

Keywords: Microglia; Inflammation; *Toxoplasma gondii*; Minocycline; TLR4

Chemical constituents from *Picea jezoensis var.komarovii* and their chemotaxonomic significance

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Abstract:

The Pinaceae is the most diverse and widely distributed group of gymnosperms and the main forest tree species, with great ecological and economic value. *Picea jezoensis var. komarovii*, commonly known as *Picea Jezoensis* is a spruce tree that belongs to the pine family and is primarily distributed in the Changbai Mountain area and the Korean Peninsula, at elevations ranging from 1100 to 1800m above sea level. The chemical constituents in the Picea are mainly flavonoids, tannins, terpenoids, lignans, etc. Modern pharmacological studies indicate that this plant exhibits anti-tumor, anti-bacterial, anti-inflammatory, and anthelmintic properties .

In this study, 24 compounds were isolated from *P. jezoensis.*, including seven flavonoids (**1**-**7**), four phenols (**8**, **10**, **11**, **17**), one stilbene (**9**), two phenolic glycosides (**12**, **19**), one coumarin (**13**), one organic acid (**14**), two lipids (**15**, **21**), one aromatic glycoside (**16**), two acetophenone glycosides (**18**, **20**), three glycosides (**22**-**24**). The chemical structures of these metabolites were elucidated by NMR spectroscopy and compared with previously reported literature data. Compounds **1**, **13**-**16**, **23**-**24** were isolated for the first time from the Picea, and compounds**19**, **20**, **22** were isolated for the first time from the Pinaceae. Moreover, the chemotaxonomic significance of these compounds was investigated.

Keywords: *P. jezoensis*, Flavonoid; Phenol, Chemotaxonomy

Research progress on the relationship between the structure of natural polysaccharides and their hypoglycemic activity

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Abstract:

Diabetes is a metabolic disease characterized by hyperglycemia.According to statistics, the incidence rate and mortality of diabetes worldwide are increasing year by year.The treatment method based on western medicine has some side effects, which urges researchers to focus on natural active substances in the treatment of diabetes.Natural polysaccharides are safe, low toxic, and possess various biological activities, including hypoglycemic activity, with great potential for development.A systematic review of the latest research progress on natural polysaccharides and their possible molecular mechanisms of hypoglycemic effects is of great significance for a better understanding of natural polysaccharides.This article systematically summarizes the relationship between the hypoglycemic activity of polysaccharides and their structure from the aspects of molecular weight, monosaccharide composition, glycosidic bonds, etc., and reviews the molecular mechanisms of their hypoglycemic activity, providing valuable insights and important guidance for further research on the hypoglycemic mechanism of natural polysaccharides.

Keywords: Natural polysaccharides;Structure;Hypoglycemic effect;Hypoglycemic mechanism

Baicalin induces renal tubular epithelial cell autophagy to prevent renal fibrosis via the GSK3β/Nrf2/HO-1 pathway

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Abstract:

Baicalin is a flavonoid from the root of Scutellaria baicalensis Georgi, which has the function of relieving kidney diseases.However, the mechanisms underlying the effects of baicalin on diabetic nephropathy (DN) remain incompletely understood.In this study, DN models were established using high fat diet (HFD)+Streptozocin (STZ)-induced rats and high glucose (HG)-induced HK-2 cells.In vivo, the effect of baicalin on DN rats were evaluated by detecting the biochemical indexes of blood and urine,renal function. In vitro, the expression of epithelial-mesenchymal transition (EMT) and extracellular matrix (ECM) marker protein, autophagy marker protein and GSK3β/Nrf2/HO-1 signaling pathway protein were detected by Western blotting.Our results showed that baicalin can reduce renal fibrosis in patients with diabetic nephropathy.Baicalin can improve the general symptoms of DN rats,reduce renal function and pathological impairment. Regulating the GSK3 β /Nrf2/HO-1 pathway and enhancing the autophagy activity of HK-2 cells, thereby reducing the accumulation of EMT and ECM.

Keywords: Baicalin；Diabetic nephropathy；Autophagy；HK-2；GSK3 β /Nrf2/HO-1

Platycodin D targets ZNF70 to inhibit NLRP3 inflammasome and STAT3 signaling pathway in colitis

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Abstract:

Background: Ulcerative colitis is a chronic idiopathic inflammatory bowel disease that primarily involves the lining of the colon, leading to ulceration and inflammatory reactions in the colonic mucosa. It is an autoimmune disease, the exact cause of which has not been fully defined and is characterized by a relapsing and remitting course. Symptoms of ulcerative colitis include abdominal pain, diarrhea, blood in the stool, weight loss, and fatigue. The incidence of ulcerative colitis has been gradually increasing worldwide in recent years, and the main risk factors include genetics, environmental factors, autoimmunity, and gut microbiota. The current treatment is oral medications such as mesalazine and dexamethasone, but prolonged oral administration may lead to serious side effects. In severe cases or in patients for whom medication is ineffective, surgical treatment, such as partial or total colectomy, may be necessary. Therefore, there is an urgent need for safer and more effective drugs to control UC.

In traditional Chinese medicine, Platycodon grandiflorum is a genuine medicinal material in Yanbian area, which has the effects of dispersing lung, expelling phlegm, expelling pus and promoting pharynx. Its chemical constituents mainly include oleanolic acid pentacyclic triterpenoid saponins, polysaccharides, flavonoids, phenols, sterols, fatty acids, etc. Platycodin D（PLD） is a triterpenoid saponin extracted from Platycodon grandiflorum, which has anti-inflammatory, anti-tumor, and other pharmacological effects. The most valuable point is that it has almost no normal cytotoxicity while exerting anti-tumor activity and cooperating with various anti-cancer chemotherapeutic drugs. However, its anti-inflammatory molecular mechanism is still unclear. Therefore, in-depth exploration of the anti-inflammatory effect and potential mechanism of PLD plays an important role in the further development of anti-inflammatory drugs.

NLRP3 inflammasome is a cytoplasmic multiprotein complex that senses the presence of pathogens and triggers an inflammatory response. Excessive activation of inflammasomes can promote the development of autoimmune inflammatory diseases, cancer, etc. NLRP3 inflammasome can be activated by various stimuli, including ion flux, mitochondrial dysfunction, production of reactive oxygen species, and lysosomal damage. Inflammasome activation is a two-step process. The first process is to initiate the inflammasome, and the second process is to activate the inflammasome. Startup has two functions. The first function is to up-regulate the expression of pro-IL-1β, NLRP3 and Caspase-1 inflammasome components. The up-regulation of inflammasome components can be induced by identifying

various pathogen-associated molecular patterns (PAMP) or risk-associated molecular patterns (DAMP), participating in PRR nucleotide binding to protein 2 containing oligomerization domain, Toll-like receptors, or induced by cytokines, such as IL-1β and tumor necrosis factor, leading to NF-κB activation and gene transcription. The second function of is to induce the post-translational modification of NLRP3. Stabilize NLRP3 in an automatically suppressed inactive but signaling state. Several post-translational modifications of NLRP3 have been described, including methylation, ubiquitination, and phosphorylation.

Zinc finger protein 70 (ZNF70) is a member of the zinc finger protein family which is rarely studied [3]. As a protein present in the human body, it can bind to some deoxyribonucleic acid or some ribonucleic acid and play an important role in some biochemical reactions in the human body such as cell differentiation and the growth and development of pregnant mothers and fetuses. It has been reported to participate in a variety of biological processes, including the secretion of inflammasomes. The literature shows that zinc finger protein 70 is involved in the secretion of NLRP3 inflammasome.

Objective: NLRP3 inflammasome plays an important role in the occurrence and development of inflammation-related diseases. Studying the mechanism of NLRP3 inflammasome not only helps to deepen the understanding of the occurrence and development of inflammatory diseases, but also provides new ideas for the development of new drugs for such diseases. The aim of this study was to investigate whether PLD inhibits colitis by regulating NLRP3 inflammasome and STAT3 activation in macrophages through ZNF70.

Methods: In vitro, the effect of PLD on cytotoxicity was detected by MTT assay. The release of IL-1β was measured by ELISA. The protein expression of ZNF70, pro-IL-1β and NLRP3 inflammasome components in cells was analyzed by Western blot. The mRNA expression of ZNF70, pro-IL-1β and NLRP3 inflammasome components in cells was detected by RT-PCR. The effects of PLD on the formation of NLRP3 inflammasome complex were detected and analyzed by immunofluorescence and co-immunoprecipitation experiments. The effect of PLD on STAT3 signaling pathway was detected by Western blot. In vivo experiments, the AAV-mediated ZNF70 gene silencing genetic method was combined with the DSS model to explore the effect of PLD on colitis.

Results: In LPS and ATP-induced THP-1 cells, we found that PLD inhibited IL-1β production by down-regulating ZNF70. At the same time, PLD inhibited the expression of NLRP3 inflammasome components and the formation of inflammasome complex by down-regulating ZNF70. In addition, PLD inhibits Src / STAT3 signaling pathway through ZNF70. In vivo experiments, we also found that ZNF70 knockdown could improve DSS-induced colitis in mice, and the effect of drug treatment was similar. ZNF70 knockdown group and drug group significantly inhibited the expression of pro-IL-1β, NLRP3 inflammasome, p-stat3, p-JAK1 and p-Src in colon tissue of mice and inhibited the secretion of IL-1β in serum, which further confirmed the results of in vitro observation.

Conclusion: PLD inhibits colitis by interfering with NLRP3 inflammasome and STAT3 signaling pathway in macrophages through ZNF70, suggesting that ZNF70 may be a promising therapeutic target for the intervention of colitis.

Keywords: ZNF70; NLRP3 inflammasome; STAT3 signaling pathway; colitis

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25-hydroxycholesterol promotes the proliferation and migration of colorectal cancer via the miR-7-5p/OSBPL3/SREBP1 axis

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Abstract：

Colorectal cancer (CRC) is the third most common malignant tumor worldwide. It is well known that hypercholesterolemia is closely associated with a high incidence of CRC, but the exact mechanism is not clear. Our experiments found that treatment with exogenous 25-hydroxycholesterol (25-HC) promoted the proliferation, migration and EMT process of CRC cells, and suppressed the level of miR-7-5p and upregulated the expression level of its target gene OSBPL3. Overexpression of OSBPL3 promoted the proliferation, migration and lipid synthesis of CRC cells, and was closely related to the activation of AMPK/SREBP signaling pathway, and these effects were reversed by the cholesterol inhibitor simvastatin. In vivo xenograft experiments showed the same results. In conclusion, 25-HC regulates lipid synthesis through miR-7-5p/OSBPL3/SREBP1 signaling pathway, and lipids further affect the malignant progression of CRC. This signaling loop may become an important target for the treatment of CRC and provide new therapeutic strategies for the clinic.

Key words: Colorectal cancer; miR-7-5p; OSBPL3; lipid metabolism; SREBP1

Usnic Acid alleviates pulmonary fibrosis in vitro and in vivo by inhibiting the ZNF70-Mediated Wnt/β-Catenin signaling pathway

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Abstract：

Background: Pulmonary fibrosis is a serious interstitial lung disease, which is caused by chronic pulmonary inflammation and infection. Zinc finger protein 70 plays a key role in cancer and inflammatory diseases. Usnic acid a dibenzofuran natural compound, has been shown to have certain anticancer activity and excellent anti-inflammatory ability. However, it has not been elucidated that usnic acid exerts anti-fibrotic effects by targeting ZNF70 and Wnt/β-catenin signaling pathway.

Purpose: This study aims to elucidate whether usnic acid mediates ZNF70 to regulate the activation of Wnt/β-catenin signaling pathway, nuclear translocation of β-catenin and the process of EMT, and its mechanism of inhibiting pulmonary fibrosis in vivo and in vitro.

Methods: (1) In vitro experiments, MTT, Western blot and immunofluorescence experiments were used to explore the effect of UA on the expression of EMT-related proteins; (2) To investigate the relationship between UA and ZNF70, the activation of Wnt / β-catenin signaling pathway and the effect of β-catenin nuclear translocation; (3) The mechanism of UA targeting ZNF70 on EMT-related protein expression was explored by plasmid transfection, Western blot and immunofluorescence experiments, as well as the effect of UA-mediated ZNF70 regulation of Wnt / β-catenin signaling pathway activation and β-catenin nuclear translocation; (4) To verify the effect of UA on the proliferation and migration of A549 cells induced by TGF-β; (5) In vivo experiments, AAV-mediated ZNF70 knockdown mouse model was used in combination with BLM-induced animal pulmonary fibrosis model. The therapeutic effect of UA on pulmonary fibrosis, the effect of fibrosis markers, and the expression of ZNF70 and Wnt/β-catenin signaling pathway-related proteins were evaluated by H&E, Masson, Sirius red staining, IHC, immunofluorescence, and protein immunization.

Results&Conclusion: For the first time, it was confirmed that usnic acid exerted anti-fibrotic activity by targeting ZNF70 to regulate the activation of Wnt/β-catenin signaling pathway and the activation of EMT process. These conclusions highlight the anti-pulmonary fibrosis effect of usnic acid, and provide new ideas and theoretical basis for the development of new anti-pulmonary fibrosis treatment programs targeting ZNF70 with usnic acid as a lead compound.

Keywords: Pulmonary fibrosis; Usnic acid; ZNF70; Wnt/β-catenin

Fed-batch culture of Rhodiola sachalinensis cells: Selecting feeding time and harvesting duration

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Abstract:

Rhodiola sachalinensis A. Bor., a perennial medicinal plant primarily found in the Changbai Mountain area of Jilin Province. Cell culture of *R. sachalinensis* has significant potential for metabolite production, with characteristics that overcome seasonal and geographical limitations. Fed-batch culture (FBC), an advanced method closely related to batch culture, is an effective system for increasing metabolite yields. Key factors influencing the FBC system include the composition of the initial culture medium, feeding strategy, and harvesting duration. In this study, we examined the effects of feeding time and harvesting duration on cell biomass and the accumulation of bioactive compounds, including salidroside, total polysaccharides, total polypeptides, total phenolics, and total flavonoids based on pre- and prost-feeding kinetic profiles. Pre-feeding kinetic analysis indicated that day 20 was the optimal feeding date to maximize both cell biomass and bioactive compound accumulation. Post-feeding kinetic analysis showed that a harvesting duration of 35 days was suitable, yielding 485.60 mg/L salidroside and 2.92 g/L polysaccharides. Compared to the roots of field-grown plants, the levels of bioactive compounds were significantly higher in the FBC cells. The findings of this study provide a strong foundation for the large-scale production of *R. sachalinensis* cells and have important implications for the conservation, development, and utilization of *R. sachalinensis* resources.

Keywords: *Rhodiola sachalinensis*; Fde-batch culture; Kinetic study; Bioreactor; Bioactive compounds

Synthesis and Anti-toxoplasma Activity in Vitro of Arctigenin Derivatives

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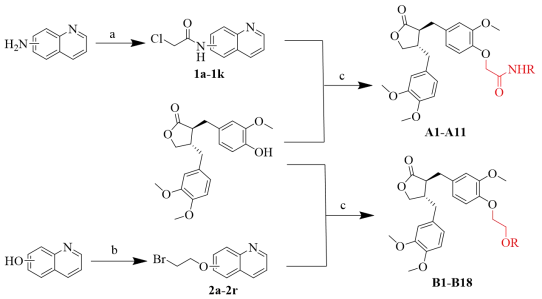
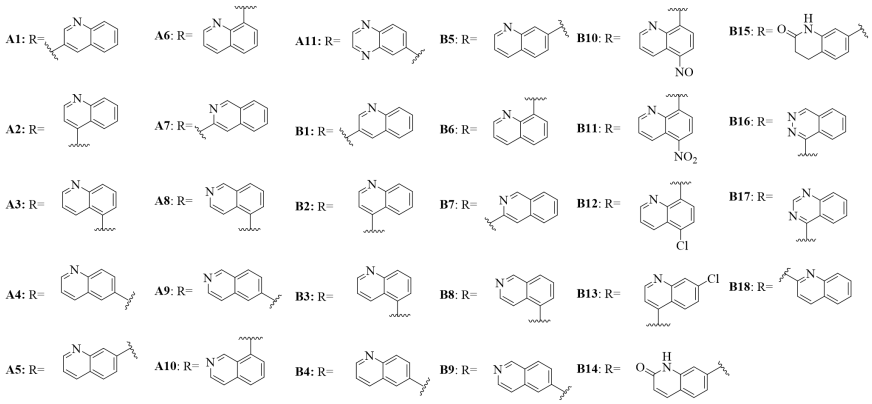
Abstract:

At present, the therapeutic drugs for *Toxoplasmosis* have serious side effects and limitations in application, so it is urgent to develop low toxicity and high efficiency drugs. A series of quinoline groups were introduced into the phenolic hydroxyl group at the C-22 position of arctigenin compound, 29 novel arctigenin derivatives were designed and synthesized. The chemical structures were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS spectra. The cytotoxicity of all compounds to host cells (HeLa) and the half inhibitory concentration of HeLa cells infected with *Toxoplasma gondii* were determined by the MTT assay, and the selectivity index (SI) was calculated. The selectivity index of compound **B8** and **B12** was 1.45, indicating that the anti-*toxoplasma* activity of compound **B8** and **B12** was higher than that of the lead compound arctigenin(SI= 0.99) and the positive control drug spiramycin(SI= 0.92). This offers valuable guidance for the subsequent screening of more effective anti-*Toxoplasma* drugs.



Reagents and conditions: (a) Chloroacetyl chloride, CH_2Cl_2, triethylamine,0°C, 12 hours; (b) 1,2-dibromoethane, MeCN, K_2CO_3, 80°C, 24 hours; (c) DMF,K_2CO_3, 60°C,10 hours.



Keywords: arctigenin derivatives; synthesis; anti-*toxoplasma* activity

A network pharmacology-based study on the mechanism of the action of Chao medicine SZDTT in relieving allergic rhinitis

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Abstract:

Objective To study the mechanism of action of CHAO medicine SZDTT in relieving allergic rhinitis based on network pharmacology.**METHODS** The active ingredients and potential targets of SZDTT were obtained through the TCM Systematic Pharmacology Database and Analysis Platform (TCMSP) by screening with oral bioavailability (OB) ≥30% and drug likeness (DL) ≥0.18 as the filtering conditions.We searched for allergic rhinitis related targets through DISGENT database and Genecards database, screened the intersecting targets using Veeny platform, mapped the PPI protein interaction network through STRING database and Cytoscape 3.9.1 software, and finally performed gene ontology (Go) and Kyoto Gene and GenomeFinally, gene ontology (Go) and Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis were performed.**RESULTS** We screened 1029 targets of the active ingredients of SZDTT, including luteolin, β-sitosterol, Stigmasterol, Eucalyptoll, Sinensetin, and quercetin, and 1121 disease targets, of which a total of 185 were common targets, including MMP2, TLR4, ERBB4, ADRA2C, CXCR4, and PLAU, two free targets, AMY1A andMTNR1A, 35 core targets such as TNF, IL-6, IL-1B, STAT3, etc. GO functional enrichment analysis yielded 2315 biological processes, and KEGG pathway enrichment analysis yielded 188 signaling pathways.**CONCLUSIONS** Chao medicine SZDTT can alleviate the inflammatory response of allergic rhinitis by regulating IL-6, STAT3, HIF-1α, NF-Kb, TNF-α, and TNFR1 signaling pathways.

Keywords: SZDTT, allergic rhinitis, network pharmacology, mechanism of action, targets

Octa-arginine conjugated liposomal nimodipine incorporated in temperature-responsive gel for nasoencephalic delivery

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Abstract:

Nimodipine is the primary clinical drug used to treat cerebral vasospasm following subarachnoid hemorrhage (SAH). Currently, tablets have low bioavailability when taken orally, and injections contain ethanol. Therefore, we investigated a new method of nimodipine administration, namely nasoencephalic administration. Nasal administration of nimodipine was carried out by attaching the cell-penetrating peptide octa-arginine (R8) to liposomes of nimodipine and incorporating it into a temperature-sensitive in situ gel. The prepared liposomes and gels underwent separate evaluations for in vitro characterization. In vitro release exhibited a significant slow-release effect. In vitro toad maxillary cilia model, RPMI 2650 cytotoxicity and in vivo SD rat pathological histotoxicity experiments showed that all the dosage form groups had no significant toxicity to toad maxillary cilia, RPMI 2650 cells and SD rat tissues and organs, and the cilia continued to oscillate up to 694 ± 10.15 minutes, with the survival rate of the cells being above 85%. Transwell nasal mucosa cell model and an isolated porcine nasal mucosa model were established, and the results showed that the osmolality of R8 modified nimodipine liposomal gel to nasal mucosal cells and isolated porcine nasal mucosa was 30.41±2.14 μg/mL and 65.9±7.34 μg/mL, respectively, which was significantly higher than that of the NM-Solution and PEGylated Nimodipine Liposome Gel groups. Animal fluorescence imaging studies revealed that the R8-modified nimodipine liposomal gel displayed increased brain fluorescence intensity compared to the normal liposomal gel. Pharmacokinetic results showed that after transnasal administration, the $AUC_{(0-\infty)}$ of R8-modified nimodipine liposomal gel was 11.662±1.97 $\mu g \cdot mL^{-1}$, which was significantly higher than that of plain nimodipine liposomal gel (5.499±2.89 $\mu g \cdot mL^{-1}$). Brain-targeting experiments showed that the brain-targeting efficiencies of PEGylated Nimodipine Liposome Gel and R8-modified PEGylated nimodipine liposome gels were 20.44 and 33.45, respectively, suggesting that R8/PEG/Lip-NM-TSG significantly increased the brain-targeting of the drug.

Keywords: Cell-penetrating peptide, Nimodipine liposomes, Temperature-sensitive gel, Nasal mucous membrane cells, Nasal-brain delivery mechanism

Chemical consituents from EtOAc fraction of the leaves of *Ulmus pumila* L.

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Abstract:

Ulmus pumila L. belongs to the *Ulmus* genus in the Ulmaceae family, which is widely distributed in China. It has been reported that the leaves of this plant have a variety of pharmacological effects, including antioxidant, antibacterial, antitumor, and other pharmacological effects. Previous studies have found that the EtOAc part of 75% ethanol extract from the leaves of this plant had certain inhibitory effects on human liver cancer cells (HepG-2) and staphylococcus aureus (6538) (Figure. 1). To further elucidate the basis of material basis and provide a theoretical basis for its follow-up research and development, the chemical compositions of the plant was investigated. The chemical structures of the compounds were determined by the physical and chemical properties, spectral analysis (^{1}H-NMR and ^{13}C-NMR) and related literature, including fourteen flavonoids (**1**–**14**), four phenols (**15**–**18**), seven terpenes (**19**–**23**), four sugars (**24**–**27**), two aromatic (**28**–**29**), one lignan (**30**), one sterol (**31**), and one fatty acid (**32**) (Figure. 2). Among them, compounds **1**, **7**, **11**–**13**, **15**–**22**, **24**–**25**, **27**–**28**, and **31**–**32** were firstly isolated from the Ulmaceae family. Compounds **2** were reported from genus *Ulmus* for the first time and compounds **3**, **5**, **14**, and **29** were obtained from this plant for the first time.

Keyword: *Ulmus pumila* L.; Chemical constituents; Structural identification

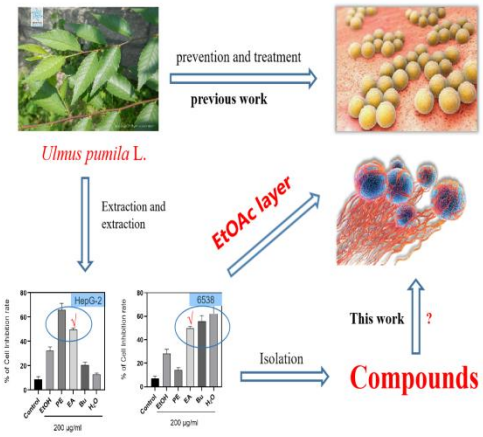

Figure1. Technical route

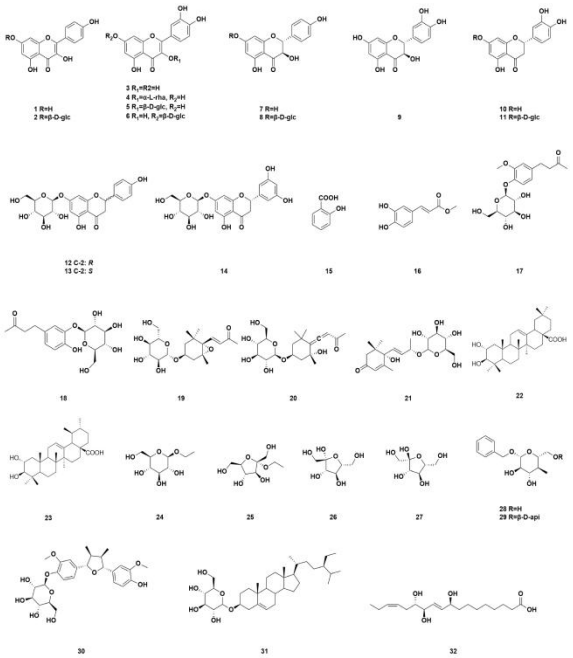

Figure 2. Chemical constituents isolated from EtOAc fraction of the leaves of *Ulmus pumila*

Research progress of anti-fatigue animal model

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Abstract:

Fatigue is a complex physiological phenomenon, which often appears in people's life and work, and seriously affects people's life quality. In recent years, research on it has increased, and it has been found that fatigue can be caused by many reasons, including overwork, lack of sleep, malnutrition, chronic diseases and psychological stress. In order to relieve fatigue symptoms, improve work efficiency and quality of life, it is urgent to find safe and effective treatment methods. At present, the relevant experimental studies are mostly carried out in rodents. This paper mainly collated and analyzed the animal models of anti-fatigue studies in recent years, and divided them into physiological, psychological, pathological and comprehensive fatigue animal models to provide theoretical reference for future anti-fatigue studies.

Key words: anti-fatigue; Physiological fatigue; Psychological fatigue; Pathological fatigue; Animal model

The mechanism of action of Lu Rong Da bu decoction in relieving allergic asthma through the IL-6 / JAK2 / STAT3 signaling pathway

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Abstract:

Objective: To investigate the mechanism of Lu Rong Da Bu decoction in the treatment of allergic asthma.Methods 40 male BALB/c Mice were randomly divided into a normal group (CON), model group (OVA), velvet antler tonic soup HIGH dose group (HIGH), velvet antler tonic soup LOW dose group (LOW), and dexamethasone (DEX).Through the injection of ovalbumin (OVA), aluminum hydroxide solution and atomization inhalation arouse cough to create Allergic asthma, Allergic asthma, AA) model.The mice were dissected within 24 h after the last stimulation, and their alveolar lavage fluid (BALF) and lung tissue were taken.Using immunosorbent (ELISA) method for determination of inflammatory cells in BALF types and levels of inflammatory cytokines,In the middle of the left lung, HE staining and Masson staining, observed the pathological changes;Using immunohistochemical staining method to observe the lung tissue of IL - 6, the expression of JAK2 and STAT3 protein distribution;The protein levels of IL-6, STAT3 and JAK2 in lung tissue were detected by Western blot.Immunofluorescence was used to detect the fluorescence intensity of IL-6, STAT3 and JAK2 in lung tissue.IL-4 and IFN- γ were detected by flow cytometry in lung tissue of mice.Results Lu Rong Da Bu decoction decoction could improve airway inflammation, inhibit collagen fiber deposition, reduce IL-4, IL-5, IL-13 content in BALF, inhibit the protein expression of IL-6, STAT3, JAK2 in lung tissue, increase the level of IFN-γ in lung tissue, and reduce the level of IL-4. Conclusion Lu Rong Da Bu Decoction may inhibit the occurrence of allergic asthma through the IL-6, STAT3, and JAK2 signaling pathways.

Keywords: Allergic asthma；Imperial medicine；Lu Rong Da Bu decoction

Advances in cellular and animal models of hyperuricemia and related complications

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Abstract:

As a typical metabolic disease, hyperuricemia (HUA) is a disorder of purine metabolism in the body, mainly due to the excess production or excretion of uric acid, which is regarded as a key contributing factor to cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, and many other health threats. Since the 21st century, the research field of HUA has been expanding, and its modeling strategies have become increasingly rich but not yet close enough to the complexity of clinical practice, and there is a lack of a unified and standardized assessment system in the field. Therefore, the purpose of this paper is to review the establishment of cellular and animal models of HUA and related complications, in order to lay a solid theoretical foundation and experimental reference for an in-depth understanding of the pathogenesis of the disease and the exploration of innovative therapeutic pathways.

Keywords: Hyperuricemia; Cellular model; Animal model

Study and Application of Dioscin, an Active Component of Dioscorea polystachya, on LPS Induced Inflammatory Acute Lung Injury

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Abstract:

Methods: In *in vitro* experiments were conducted using MTT, ELISA, Western blot, Immunofluorescence, ROS Assay Kit, and Mitochondrial membrane potential assay kit to analyze the anti-inflammatory mechanism of Dioscin (Dio) and its impact on the SIRT1 signaling pathway. In *in vivo* experiments, mice were treated with the SIRT1 inhibitor EX527 via gastric administration, and the effects of Dio on LPS-induced acute lung injury(ALI) and inflammatory signaling pathways were evaluated using ELISA, HE staining, Western blot, and Tissue fluorescence assays.

Results: In LPS-induced J774A.1 cells, Dio was found to inhibit IL-1β production by upregulating SIRT1. Additionally, Dio dose-dependently inhibited the acetylation of HMGB1, reduced oxidative stress in LPS-induced cells, and promoted autophagy, thereby improving ALI. The use of the SIRT1 inhibitor EX527 *in vivo* demonstrated effects opposite to those of the drug treatment, further confirming the *in vitro* observations.

Conclusion: Dioscin, the active component of yam, treats ALI by promoting SIRT1 to inhibit the acetylation of HMGB1, reduce oxidative stress in LPS-induced cells, and enhance autophagy. This suggests that SIRT1 could serve as a promising new target for intervening in inflammatory acute lung injury.

Keywords: Dioscin; Acute kidney injury; SIRT1; Inflammation; HMGB1

Effect of *Angelica dahurica* extract and imperatorin on gouty arthritis

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Abstract:

To investigate the effects of *Angelica dahurica* extract and imperatorin on gouty arthritis induced by monosodium urate (MSU) crystal. The model of gouty arthritis was established by injecting MSU crystals into the left ankle of rats. The degree of ankle swelling was measured at 0-24 h in rats. The histopathological changes of synovial tissues were observed. Meanwhile the mRNA and protein expression levels of Nod-like receptor protein 3 (NLRP3), interleukin-1β (IL-1β), cysteinyl aspartate specific proteinase-1 (caspase-1), interleukin-1 receptor type 1 (IL-1R1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) were detected by Western blot and RT-PCR in synovial tissues. *Angelica dahurica* extract and imperatorin significantly reduced MSU induced left ankle swelling in rats, and improved inflammatory infiltration in synovial tissues. The expression of NLRP3, IL-1B, caspase-1, IL-1R1, IL-6, TNF-α protein or mRNA in synovial tissues decreased significantly. *Angelica dahurica* extract and its active component imperatorin could ameliorate gouty arthritis, which supplies basic data support for its clinical application.

Keywords: gouty arthritis; imperatorin; inflammatory reaction; NLRP3; monosodium urate

Synthesis and comparative mechanism analysis of thiazole isomers J-1155 and J-1156 as anti-liver fibrosis agents targeting ALK5 against inflammation

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Abstract:

Liver fibrosis is a critical stage in the remission and treatment of cirrhosis and liver cancer, but the precision treatment of liver fibrosis is currently bottlenecked by its vague underlying molecular mechanisms. ALK5, a common target for interfering with the TGF-β signaling pathway, has emerged as an engaging molecular target for the treatment of fibrotic disorders. In this paper, two thiazole derivatives (J-1155 and J-1156) containing enantiomer amino acids were synthesized and evaluated activin receptor like kinase 5 (ALK5) in the enzymatic assay. Furthermore, we delved into the antagonistic effects of J-1155 and J-1156 on TGF-β-induced hepatic stellate cell activation and TAA-induced liver fibrosis in mice. Our data revealed that J-1155 and J-1156 circumvented the development of hepatic fibrosis through the inhibition of ALK5, which is likely related to the inhibition of TGF-β/Smad signaling pathway as well as the blockade of P2X7R-NLRP3 signaling axis. In comparison, J-1156 had a better overall therapeutic effect than J-1155 in antifibrosis, whereas J-1155 modulated Smurf2 better than J-1156. Collectively, our observations suggest that J-1155 and J-1156 might both serve as novel therapeutic synthetic agents to combat hepatic fibrosis.

Keywords: Liver fibrosis; Thiazole derivatives; TGF-β; Smad; Inflammation

Mechanism of Ginsenoside Rh2 in the treatment of pulmonary fibrosis based on network pharmacology and molecular docking

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Abstract:

In order to explore the mechanism of Ginsenoside Rh2 in the treatment of pulmonary fibrosis, using network pharmacology and molecular docking technique to predict the potential targets. The results of network pharmacology show that Ginsenoside Rh2 has 70 targets, pulmonary fibrosis has 2963 targets, 50 intersecting genes and 10 core targets for drug treatment of disease. Ginsenoside Rh2 has 122 biological pathways and 361 functional analyses in the treatment of pulmonary fibrosis. The results of molecular docking show that Ginsenoside Rh2 exhibit stable binding activity with the nine core targets. These studies suggests that Ginsenoside Rh2 may participate in the treatment of pulmonary fibrosis through multiple targets and pathways, and the results of this study can provide references for the subsequent investigation of Ginsenoside Rh2 treatment of pulmonary fibrosis.

Keywords：Network pharmacology；Molecular docking technology；Ginsenoside Rh2；Pulmonary fibrosis

The Effects And Mechanism Of Virgin Coconut Oil(VCO) On Learning And Memory Impairment And Amyloid Precursor Protein(APP) Processing Pathway In Aging Mice.

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Abstract:

Objective To study the effects and mechanism of Virgin Coconut Oil(VCO) on learning and memory impairment and amyloid precursor protein(APP) processing pathway in aging mice.

Methods Fifty two-month-old male Kunming mice were divided into 5 groups randomly: normal control, aging model, aging+ low dose of VCO,aging+medium dose of VCO,aging+high dose of VCO groups.The aging model was established by sub cutaneous injection after neck of D-galactose(100mg/ml) for 90 days. The learning and memory abilities of mice were observed by Morris water maze and behavioral measurements.Enzyme-linked immunosorbent assay(ELISA) was used to detect the expressions of disintegrin-Metalloprotease10(ADAM10), β-secretase1(BACE1), Presenilin1(PS1).

Results Behavioral test showed that the learning and memory abilities of mice were consolidated and strengthened,and the memory impairment of aging mice was improved with the increasing of the concentration of VCO. Compared with the aging model group, biochemistry showed that the VCO enhance the activity of α-secretase, inhibit the activity of β, γ-secretase and decrease the content of $A\beta_{1-40}$ in brain tissue.Western blot analysis showed the expressions of BACE1 was up-regulated and the levels of ADAM10 was down-regulated in the aging model group, compared with the normal control group. Compared with the aging group,the expression levels of ADAM10 in VCOgroup were significantly higher,while the expressions of BACE1 and PS1 were significantly lower.

Conclusions Virgin Coconut oil is protective aganist the APP processing and alleviates the learning and memory deficit in aged mice.

Key words: Virgin Coconut oil;Alzhemer's Disease;ADAM10;BACE1;PS1

Chemical constituents of *Acer tegmentosum* Maxim and their chemotaxonomic significance

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Abstract:

A phytochemical study of *Acer tegmentosum* Maxim (the dried stem bark of *Acer tegmentosum* Maxim) led to the isolation of **28** compounds, including thirteen phenols, five coumarins, four benzoate esters, three tetracyclic triterpenoids, one carbohydrate, one hydrocarbon and one lignan. The structures of these isolated compounds were identified using NMR spectroscopy (^{1}H and ^{13}C) by comparison with previously reported data. To the best of our knowledge, salidroside, 2-(4-Hydroxyphenyl)ethyl *β*-D-galactopyranoside, 2-(4-hydroxyphenyl)ethyl 3,4,5-trihydroxybenzoate, 3,3′,4,4′-tetrahydroxybiphenyl, (4-methoxyphenyl)acetic acid, daphnetin, 5,6,7-trimethoxycoumarin, 1,2-bis(2-methylheptyl) 1,2-benzenedicarboxylate, 1,4-benzenedicarboxylic acid, periplocoside N and 3,4-dimethoxycinnamyl alcohol were reported from this plant for the first time. Chemotaxonomic significance was discussed.

Keywords: ***Acer tegmentosum*** **Maxim; Chemical constituents; Chemotaxonomy**

References:

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[2] Cho E K, Jung K I, Choi Y J. Anti-diabetic, alcohol metabolizing enzyme, and hepatoprotective activity of Acer tegmentosum Maxim stem extracts. Journal of the Korean Society of Food Science and Nutrition, 2015, 44(12): 1-2.

Effect of ethanolic extract from *Oplopanaxs elatus* adventitious roots on a-glucosidase inhibition

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Abstract:

Oplopanax elatus Nakai is a perennial shrub of the genus *Oplopanax* in the family Araliaceae, mainly distributed in the Changbai Mountain area of Jilin Province. It is rich in various active substances and has long been used in traditional medicine for treating a variety of diseases. However, the development and production of its products have been severely limited due to the scarcity of plant materials. To address this limitation, the culture of adventitious roots of *O. elatus* has been considered an effective method for raw material production and has been proven to possess various pharmacological activities, such as antibacterial, anticancer, and anti-inflammatory effects. However, many potential roles of this plant remain to be explored. Inhibiting α-glucosidase activity is an effective strategy for controlling blood glucose, and natural products that serve as α-glucosidase inhibitors have attracted significant attention due to their safety and low toxicity. However, whether the adventitious roots of *O. elatus* possess this effect has not been reported.

In this study, the ethanolic extract of *O. elatus* adventitious roots was used to investigate its inhibitory activity against α-glucosidase, and the kinetics of the enzyme inhibition was further analyzed to elucidate the mechanism. The results showed that the ethanolic extract significantly inhibited α-glucosidase activity in a concentration-dependent manner, with a half-maximal inhibitory concentration of 0.37 mg/mL. The enzyme inhibition kinetic study revealed that the inhibition by the extract was reversible and classified as a mixed type of non-competitive and anti-competitive inhibition. Furthermore, analysis of the fluorescence quenching effect of the extract indicated that its binding to α-glucosidase is a dynamic process that does not involve the formation or breakage of covalent bonds, suggesting that the binding is reversible and that the extract's binding affinity to the enzyme is relatively weak. This study suggests that the adventitious roots of *O. elatus* have potential as α-glucosidase inhibitors, indicating a promising future for their application in the development and production of blood glucose-lowering products.

Key words: *Oplopanax elatus* adventitious root; hypoglycemia; α-glucosidase inhibition; enzyme inhibition kinetics; fluorescence quenching

Betulinic acid mediates STAT3 signaling pathway in regulating hepatic fibrosis

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Abstract:

To survey the effect of betulinic acid (BA) against hepatic fibrosis via signal transducer and activator of transcription 3 (STAT3) signaling pathway. Raw264.7 cells were incubated with Lipopolysaccharides (LPS, 1 mg · L^{-1}) for 12 h, and the supernatant was collected. Hepatic stellate cells (HSCs) were pretreated with betulinic acid (25 μmol · L^{-1}) for 2 h, and then incubated with the supernatant for 0-6 h. HSCs were pretreated with betulinic acid (0-25 μmol · L^{-1}) for 2 h, followed with the above supernatants for next 1 h. The effects of betulinic acid on extracellular matrix, inflammatory factors and related signaling pathways were analysed. C57BL/6 male mice were pretreated with BA for 4 d, and then injected with 10% CCl_4, intraperitoneally. The mice were euthanized for 24 h. The serum and liver were collected. When Raw264.7 cells were stimulated by LPS, the content of IL-6 in the supernatant of Raw264.7 cells were improved over time and arrived at the highest level at 12 h. HSCs were activated by the supernatant from Raw264.7 stimulated by LPS for 12 h. Betulinic acid significantly decreased the protein expression of α-SMA and collagen-I protein, and decreased the ratio of TIMP-1 and MMP-13 in a time-and dose-dependent manner. Betulinic acid significantly improved the expression of STAT3 phosphorylation, de- creased the expressions of TLR4 and CD14, and regulated the AMPK and LKB1 phosphorylation in a time-and dose-dependent manner. Betulinic acid may mediate STAT3 phosphorylation to regulate TLR4 and AMPK/LKB1 signaling in activated HSCs, which further ameliorates hepatic fibrosis.

Key words: betulinic acid; hepatic fibrosis; STAT3; TLR4; inflammatory factors

The effect of osthol on skeletal muscle inflammation

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Abstract:

Objective: To explore the positive effects of snake bed extract on skeletal muscle and its positive effects on restoring health in cases of muscle inflammation. In the early stages, it was preliminarily determined through literature review that osthol has a positive effect on inhibiting muscle inflammation. Subsequently, protein expression levels were analyzed through multiple protein immunoblotting experiments.

Skeletal muscles play an important role in maintaining posture and physical activity. As a source of glucose and amino acids, it can maintain energy production in all other organs when needed. Skeletal muscle atrophy is accompanied by a gradual decrease in muscle mass and strength. This is a complex and lengthy process caused by various factors such as sepsis, cancer, chronic diseases, metabolic syndrome, and muscle atrophy. Muscle atrophy and loss of function can further lead to a significant decline in quality of life, increased medical costs, and even higher mortality rates.

Studies have shown that inflammation plays an important role in the process of atrophy.Skeletal muscle atrophy caused by inflammation is a major clinical feature of heterogeneous diseases. Cnidium monnieric (L.) Cuss, an annual herbaceous plant in the Umbelliferae family, is the source of snake bed extract. Nowadays, it has been proven that it has the effects of lowering blood pressure, antibacterial, and enhancing male potency. Clinically, it is used to treat peripheral neuropathy, yellow water sores, male infertility, and female genital warts. Based on preliminary experimental data, it is determined that osthol has a positive effect on the treatment of inflammatory skeletal muscle atrophy. Subsequent experiments will investigate the positive effect of osthol on protein synthesis and its collective pathway of action.

Experimental method: Study the effect of osthol on skeletal muscle atrophy in C2C12 myotubes treated with inflammation. Western blot and qPCR were used to analyze protein expression and mRNA levels, respectively. Afterwards, further analysis was conducted by establishing a mouse model, observing changes in mouse body weight, normal exercise, grip strength, and finally dissecting and observing the different shapes of gastrocnemius and soleus muscles in different experimental groups of mice to determine the changes in mass, volume, and muscle strength of snake bed extract treatment for inflammatory skeletal muscle atrophy. Conduct comprehensive experimental verification from both *in vivo* and *in vitro* perspectives to ensure the accuracy of the results.

Advances in ginsenosides and pd-1/pd-l1 inhibitors in tumour therapy

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Abstract:

Tumours are the most lethal disease globally and have become a great burden to human public health and safety. In recent years, programmed death receptor 1 (PD-1) and its ligand (programmed death 1,PD-1) and its ligand (programmed death ligand 1 (PD-L1) inhibitors have attracted much attention in recent years, but resistance to tumour cells and the tumour microenvironment (TME) have been observed during treatment.However, during treatment, drug resistance to tumour cells and changes in the tumour microenvironment (TME) have resulted in an overall tumour remission rate of only about 20%. With the national emphasis on Chinese herbal medicine, ginsenoside treatment of tumours has become the focus of researchers. It affects tumour proliferation, apoptosis, invasion, angiogenesis, multidrug resistance and other aspects of tumour through the regulation of signalling pathways as well as TME, thus controlling tumour progression. It has been found that ginsenosides and PD-1/PD-L1 inhibitors can inhibit tumour evolution through immunotherapy. In this paper, the therapeutic potential of ginsenosides for tumour treatment is described, with a view to providing a reference for the clinical application of combined PD-1/PD-L1 inhibitors and subsequent research and development.

Keywords: Ginsenosides； Pd-1 inhibitors； Pd-l1 inhibitors

Study on mechanism of Acacetin in improving paracetamen-induced liver injury through caspase3/GSDMD signaling pathway

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Abstract:

Background: Acacetin (ACA) is a flavonoid active ingredient extracted from Acacia farnesiana (Linn.) Willd. It has been proven to have antioxidant, anti-inflammatory, antibacterial, anti-osteoporosis, anti-tumor, immunomodulatory, protective effects on the heart and nervous system. The purpose of this study was to study the mechanism of ACA in improving liver injury induced by Acetaminophen (APAP), and to provide theoretical basis for the development of new drugs to prevent or treat drug-induced liver injury (DILI) by ACA in the future.

Methods： Thirty-six 6-week-old male C57BL/6J mice were randomly divided into 6 groups: normal group (CON), ACA Alone group (ACA: ACA 20 mg/kg), APAP model group (AP: 350 mg/kg APAP), ACA High dose group (ACH: APAP 350 mg/kg + ACA 20 mg/kg), ACA Low dose group (ACL: APAP 350 mg/kg + ACA 10 mg/kg) and N-acetylcysteine (NAC) positive drug control group (AN: APAP 350 mg/kg +NAC 200 mg/kg). After fasting for 12 h, given each group mice corresponding dose of drugs by gavage. Two hours later, 300 mg/kg of APAP were injected to establish a pattern of liver damage in mice. 24 hours later, the mice were sacrificed, blood and liver tissue were drawn for follow-up testing.

Results: Immunofluorescence staining showed that ACA reduced the expression of IL-1β, GSDMD and GSDMDC1 in mouse liver in a dose-dependent manner. Compared with AP group, ACA down-regulated the protein expression levels of Bax, Cytochrome C and Caspase3, and up-regulated the protein expression levels of Bcl2 and PARP in a dose-dependent manner. ACA down-regulated the protein expression levels of GSDMD, Beclin1 and TXNIP, and up-regulated the protein expression levels of GSDMDC1 and Trx.

Conclusions: ACA may improve hepatocyte apoptosis and scorch death in APAP-induced DILI mice liver through caspase3/GSDMD signaling pathway.

Key words: acetaminophen; Drug-induced liver injury; pyrodeath

Study on the mechanism of maslinic acid improving non-alcoholic fatty liver disease via AMPK signaling pathway

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Abstract:

Objective: In this study, combined with both internal and external experiments, Non-alcoholic fatty liver disease (NAFLD) model of C57BL/6 mice induced by Tyloxapol (TY) and L02 normal human liver cells induced by Free fatty acid (FFA). To study the mechanism of Maslinic acid (MA) improving NAFLD through AMPK/ACC signaling pathway, which provided theoretical support for the treatment or prevention of NAFLD related diseases.

Results: In vivo experiments, MA significantly reduced TG, TC and LDL-C levels and increased HDL-C levels in TY induced hyperlipidemia mice in a dose-dependent manner. Western-Blot showed that MA significantly up-regulated the expression levels of lipid metabolist related proteins (p-AMPK, p-ACC, ATGL and p-HSL).

In vitro experiments, MTT results showed that MA was not cytotoxic to L02 cells and FFA induced L02 cells at 0-20 μM. The oil red O staining results of the cell slides showed that the accumulation of adipose droplet in the cells induced by FFA decreased significantly in a concentration-dependent manner after different concentrations of MA treatment. MA also significantly reduced the TG and TC contents in L02 cells induced by FFA in a concentration-dependent manner.

Conclusion: Maslinic acid may improve NAFLD in the liver of TY mice through AMPK/ACC signaling pathways.

Keywords: Maslinic acid; Tyloxapol; non-alcoholic fatty liver disease

表儿茶素没食子酸酯（EGCG）通过诱导铁死亡抑制三阴性乳腺癌细胞增殖的机制研究

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(延边大学肿瘤研究中心)

摘要:

三阴性乳腺癌（Triple-Negative Breast Cancer, TNBC）由于缺乏雌激素受体（ER）、孕激素受体（PR）和人类表皮生长因子受体2（HER2）表达，临床上对其治疗较为困难，具有高度侵袭性和易复发性。表儿茶素没食子酸酯（Epigallocatechin-3-gallate, EGCG）作为绿茶中的主要活性成分，因其广泛的抗癌活性受到关注。本研究旨在探讨EGCG诱导三阴性乳腺癌细胞铁死亡（ferroptosis）的分子机制及其潜在应用价值。我们使用三阴性乳腺癌细胞系Hs-578T和MDA-MB-231进行研究，采用EGCG处理后，观察细胞存活率、活性氧（ROS）水平及变化。结果显示，EGCG处理组的细胞存活率显著降低，ROS水平显著上升。使用铁死亡抑制剂Ferrostatin-1 (Fer-1)处理后，EGCG诱导的细胞死亡率显著降低，进一步通过Western blot研究表明，EGCG处理后，三阴性乳腺癌细胞内GPX4（一种关键的铁死亡调控蛋白）的表达水平显著下降,表明EGCG可能通过诱导铁死亡发挥其抗癌作用。此外，体外实验还发现，EGCG处理显著抑制三阴性乳腺癌细胞的侵袭和迁移能力，并通过破坏线粒体膜电位促使细胞发生能量代谢紊乱，进一步支持其通过多重途径发挥抗癌作用。

综上所述，本研究揭示了EGCG诱导三阴性乳腺癌细胞铁死亡的具体机制，并提出EGCG有可能作为一种新型的辅助治疗药物，为三阴性乳腺癌的临床治疗提供了新的思路和实践依据。

关键词: TNBC, EGCG, ferroptosis

Analysis of Effective Components of Bear Bile Powder by UPLC-Q-Orbitrap-HRMS and Network Pharmacology Analysis of its Effect on Alcoholic Liver Injury

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Abstract:

In order to explore the material basis of bear bile powder and the possible mechanism of action on alcoholic liver injury based on UPLC-Q-Orbitrap-HRMS and network pharmacology. The black bear bile obtained by non-invasive painless drainage technique was freeze-dried to obtain golden powdery bear bile powder. After pretreatment, UPLC-Q-Orbitrap-HRMS technology was used to obtain the ion fragment information of bear bile powder, and the fragment information was compared by Compound, Pubchem, Massbank and HMDB (Human Metabolome Database) databases to clarify the material basis of bear bile powder. The potential mechanism of its treatment of alcoholic liver injury was predicted, and the related pathways regulated by its biological targets were elucidated, through network pharmacology combined with molecular docking analysis. A total of 333 compounds were identified, including 14 bile acid active substances. Network pharmacology studies and molecular docking results show that ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid and choline can reduce alcohol-induced liver injury by regulating the NF-κB pathway to affect IL-6 and TNF-α. In this study, the pharmacoactive substances of bear bile powder were identified by UPLC-Q-Orbitrap-HRMS technology, and the potential mechanism of alcohol-induced liver injury was predicted by network pharmacology. The results provide a theoretical basis for the modernization research of bear bile powder.

Keywords: Bear bile powder; UPLC-Q-Orbitrap-HRMS; Network pharmacology; Molecular docking; Alcoholic liver injury

Preparation of thyme antioxidant emulsion

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Abstract:

An antioxidant moisturizing emulsion was prepared by using Baili perfume extract as raw material. The antioxidant capacity of Baili perfume extract was determined by DPPH free radical scavenging rate test. The optimal ratio of emulsion matrix was determined by orthogonal experiment. A comprehensive evaluation of thyme emulsion was carried out, including safety evaluation, long-term stability test, pH determination and cold and heat resistance analysis, to check the physical and chemical properties and sensory quality of the emulsion. Use a digital skin moisture tester to measure skin moisture content.

Key words: Thyme; Emulsion; Anti-oxidation; moisturize

A preliminary study on the development of natural medicine industry in Changbai Mountain

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Abstract:

[Objective] The purpose of this paper is to explore the development of natural medicine economy in Changbai Mountain area and to promote the development of Jilin medical and health industry.

[Contents] At present, the production of natural medicine in China is still in a state of scattered and blind small production. The general situation of the existing dozens of processing enterprises is: the process is backward, the analysis and testing of products are also backward, the variety of products is single, the production is targeted for sale, and the lack of foreign economic information.

[Results] Taking the development of natural medicine economy as the starting point, the development of Changbai Mountain economic Zone has not only prepared strong financial conditions for the development of forests, minerals, water conservancy and other resources in Changbai Mountain area, but also cultivated a group of new entrepreneurs, which can be said to be the fundamental conditions for further comprehensive development.

[Conclusion] This measure will become the breakthrough of comprehensive reform, but also to promote the province's economy into a virtuous cycle of an important link. We are convinced that such a scenario is not only feasible but also realistic. There is a need for further testing and demonstration.

Keywords: Changbai Mountain natural medicine; Pharmaceutical and health industry; Economic development

A preliminary study on the anti-toxoplasma gomdii potency of Angelica dahurica(Fisch.ex Hoffm.) and the preparation of its submicron emulsion

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Abstract:

Objective: Toxoplasmosis is an infection caused by Toxoplasma gondii (T.gondii). which has a worldwide distribution and its long-term parasitic and zoonotic nature makes it a serious, worldwide public health problem. Studies have shown that *Angelica dahurica (Fisch. ex Hoffm*.) *Angelica dahurica (Fisch. ex Hoffm*. (*A. dahurica*) has antiparasitic activity, but its active ingredient is unclear, so this experiment investigated the chemical composition of n-butanol extract of *A. dahurica* and performed quality analysis of its chemical composition with a view to finding the active ingredient. In order to improve bioavailability, it was prepared in dosage form and the anti-T.gondii effect of *A.dahurica* was further investigated. Based on a network pharmacology and molecular docking approach, the targets and pathways of action of the compounds for the treatment of toxoplasmosis were explored.**Results:**1. In vitro screening of the active site showed that the n-butanol layer extract had good anti-T.gondii activity.21 compounds were isolated from the n-butanol layer of *A. dahurica*. Its appearance was uniformly distributed as a milky white homogeneous liquid,which does not delaminate after standing, and has good fluidity. It is a stable emulsion system with good properties. In vitro experiments showed that the activity of the submicron emulsion was improved compared with that of the n-butanol extract.**Conclusion**: In this study, 21 compounds were isolated from the n-butanol layer of *A. dahurica,* which laid the foundation for further research on the chemical composition of *A. dahurica*. The results of content determination showed that five coumarin compounds were relatively high in n-butanol, which was hypothesized to be the key component in the treatment of T.gondii. The present study increases our understanding of the chemical composition of *A. dahurica* and provides a reliable theoretical basis for the development and utilization of *A. dahurica*.

Keywords: *A. dahurica*; chemical constituents; HPLC; submicron emulsion; anti-toxoplasma gondii

JTE-013 inhibits the S1PR2 mediated IGF-1/ATF2 pathway and affects the progression of pulmonary fibrosis

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Abstract:

Objective: To investigate the effect of JTE-013 inhibition on the S1PR2 mediated IGF-1/ATF2 pathway on the progression of pulmonary fibrosis.

Methods: Thirty clean grade male C57 mice were randomly divided into three groups: physiological saline control group (Control), bleomycin model group (BLM), and bleomycin+JTE-013 treatment group (BLM+JTE-013). The mice were euthanized on the 7th and 28th day after tracheal intubation with bleomycin. HE and Masson staining methods were used to observe the pathological changes in mouse lung tissue; ELISA method was used to detect the levels of IL-4 and IFN - γ in bronchoalveolar lavage fluid (BALF) of mice; Immunohistochemical methods were used to detect changes in the expression levels of pathway proteins IGF-1, ATF2, and pulmonary fibrosis related factors alpha SMA and Collagen-I; The expression levels of pathway proteins IGF-1 and ATF2 were detected by immunofluorescence assay; Western Blot method was used to detect the expression levels of pathway proteins IGF-1 and ATF2, as well as fibrosis related factors α - SMA and Collagen-I in lung tissue.

Results: JTE-013 can reduce BLM induced pulmonary fibrosis in mice; Reduce the levels of inflammatory factors IL-4 and IFN - γ in BALF; Inhibit the IGF-1/ATF2 pathway in pulmonary fibrosis, reduce the expression of IGF-1 and ATF2, and decrease the co expression of ATF2 and α - SMA in lung tissue; Reduce the expression of α - SMA and Collagen-I in lung tissue.

Conclusions: JTE-013 reduces the expression of pulmonary fibrosis markers and ECM deposition by inhibiting the IGF-1/ATF2 pathway, thereby alleviating BLM induced pulmonary fibrosis in mice.

Keywords: JTE-013; IGF-1； ATF2； pulmonary fibrosis

Effect of different glycosyl receptor structures on Endo-CC N180H enzymatic transglycosylation reaction

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Abstract:

In eukaryotic organisms, *N*-glycans playing crucial roles in biological processes such as cell adhesion and disease research. Endo-CC N180H, a mutant from the Endo-Gase family, can targets the bond between two *N*-GlcNAc residues in the *N*-glycan core, enabling transglycosylation with a glycosyl receptor containing *N*-GlcNAc for glycan or glycopeptide labelling. However, the effects of *N*-GlcNAc receptors with different structures on transglycosylation remain unreported.

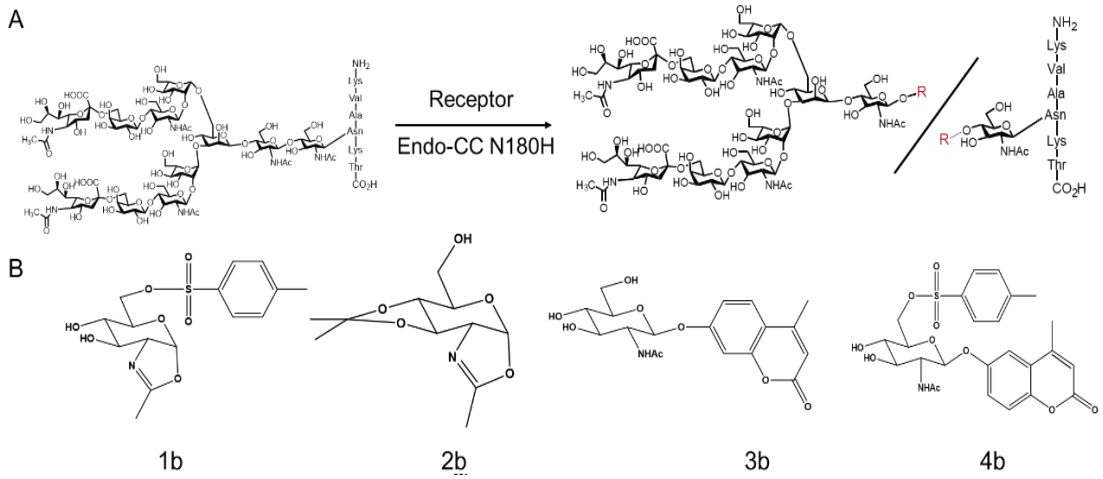

Fig.1 Edno-CC N180H transglycosylation reaction structural formula(A) and Glycosylation receptor (B)

As shown in Fig.1, the two *N*-GlcNAc residues in the N-glycan core are primarily linked by the condensation of the hydroxyl groups at positions 1 and 4. To investigate the transglycosylation reaction at the glycopeptide terminus, we synthesized a receptor with an oxazolidine structure, using *N*-GlcNAc as the lead compound and modifying the o-dihydroxyl group and the hydroxyl group at position 6 to obtain compounds 1b and 2b. These compounds were reacted with SGPs in the presence of Endo-CC N180H, and the resulting glycosylation products were analyzed using LC-MS. Unfortunately, neither receptor yielded glycopeptide end products. Therefore, we conclude that successful transglycosylation necessitates the introduction of oxazoline derivatives and the retention of the sixth hydroxyl group along with the adjacent dihydroxy structures.

Furthermore, this study validated the effects of the first and sixth hydroxyl groups on the transglycosylation reaction using receptors 3b and 4b. The results indicated that receptor 3b successfully underwent a transglycosylation reaction with SGP, while receptor 4b did not yield any transglycosylation products. Therefore, to facilitate the transglycosylation reaction

at the terminal sugar chain, it is essential to retain both the adjacent dihydroxy structure on the *N*-GlcNAc receptor and the sixth hydroxyl group.

Keywords: *N*-Glycan, Endo-CC N180H, Transfructosylation, Glycosyl receptor

Optimization of flash-ultrasonic extraction process for total anthraquinones from bioreactor-cultured *Damnacanthus major* cells

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Abstract:

To efficiently extract of total anthraquinones from bioreactor-cultured *D. major* cells, in this study, flash extraction was combined with ultrasonic extraction method was used and the extraction process was optimized using a single-factor experiment, Plackett-Burman analysis, and response surface methodology (RSM). The single-factor experiments identified the following optimal parameters: liquid-to-solid ratio of 50/1 mL/g, flash extraction time of 60 s, ethanol concentration of 90%, ultrasonic extraction time of 1 h, ultrasonic temperature of 40°C, and ultrasonic power of 50 W. Plackett-Burman analysis revealed that ethanol concentration, flash extraction time, and ultrasonic temperature significantly influenced anthraquinone yield. Subsequently, a Box-Behnken RSM experiment was conducted using these three key factors, yielding optimal extraction conditions: ethanol concentration of 86%, flash extraction time of 43 s, and ultrasonic temperature of 37°C, with a total anthraquinone yield of 14.83%. This study provides valuable data for optimizing the extraction of anthraquinones from *D. major*.

Keywords: *Damnacanthus major*; flash-ultrasonic extraction; total anthraquinone

Enhanced production of Lessertia frutescens adventitious roots in bioreactor and their potential for α-glucosidase inhibition

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Abstract:

To explore an alternative method for the production of *Lessertia frutescens* raw materials, this study was the first to culture *L. frutescens* adventitious roots (ARs) in an air-lift bioreactor (5 L) and investigate the factors (i.e., sucrose concentration, inoculation density, air volume, and harvest time) affecting AR biomass and accumulation of bioactive compounds (triterpenoid saponins and polysaccharides). Additionally, for future application of these cultured ARs, the inhibitory effect of the *L. frutescens* ethanolic extract (LFEE) from the cultured ARs on α-glucosidase and its underlying mechanisms were investigated to clarify its potential for blood glucose regulation. The results indicated that a sucrose concentration of 40 g/L, an inoculum density of 5 g/L, an air volume of 300 mL/min, and a harvest time of 50 days were optimal for maximizing AR biomass and the production of triterpenoid saponins and polysaccharides in the bioreactor. Under these conditions, approximately 550 mg/L triterpenoid saponins and 530 mg/L polysaccharides were produced. The blood glucose regulation experiments showed that LFEE significantly inhibited α-glucosidase activity, with approximately 0.5 mg/mL of the half-maximal inhibitory concentration, and was classified as a reversible inhibitor. LFEE exerted non-competitive inhibition on α-glucosidase through inhibitory kinetic studies and exhibited significant fluorescence quenching effect on α-glucosidase, indicating a strong binding affinity to the enzyme-substrate complex. These results suggest that AR bioreactor culture is a viable method for the production of *L. frutescens* raw material with potential applications in blood glucose management due to its α-glucosidase inhibitory effects.

Keywords: Adventitious roots; bioreactor culture; inoculation density; air volume; hypoglycemic effect; enzyme inhibition kinetics

基于UPLC-Q-Orbitrap HRMS和网络药理学的板栗叶抗菌药效物质基础及作用机制研究

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摘要：

板栗叶(*Castanea mollissima* Leaf)为壳斗科(Fagaceae)、栗属(*Castanea*)植物板栗(*C. mollissima*)的叶子，为药食同源植物，具有清肺止咳、解毒消肿功效，现如今被用来治疗百日咳、肺结核、咽喉肿痛、消毒等疾病。研究表明，板栗叶还具有抗菌活性，但其物质基础及作用机制尚未阐明。本研究采用超高效液相色谱-四极杆-静电场轨道阱高分辨质谱技术（UPLC-Q-Orbitrap HRMS)对板栗叶化学成分进行全面分析和表征，结合网络药理学进一步阐明板栗叶的抗菌作用机制。

通过 UPLC-Q-Orbitrap HRMS 技术从板栗叶醇提物中共鉴定出 72 种化合物。其中包括黄酮类 12 种、苯丙素类 11 种、糖苷类 3 种、生物碱 3 种、酚类 3 种、萜类 2 种、蒽醌 1 种、有机酸 15 种、其他类 22 种。网络药理学研究表明，板栗叶可能通过槲皮素、莽草酸、L-焦谷氨酸、异佛尔酮等活性成分作用于 ESR1(雌激素受体α)、PTGS2(前列腺素内过氧化物合成酶 2)、MAPK3(丝裂原活化蛋白激酶 3)、MMP9(基质金属蛋白酶 9)、EGFR(表皮生长因子受体)等关键抗菌作用靶点，来调节 HIF-1（缺氧诱导因子-1）、Metabolic pathways（代谢途径）等信号通路，从而发挥抗菌作用。

本研究在明确了板栗叶的化学成分基础上，通过网络药理学构建了“活性成分-靶点-通路”网络，阐释了板栗叶的抗菌作用机制，为今后板栗叶的抗菌研究提供理论依据，同时也为其临床应用奠定基础。

关键词：板栗叶; UPLC-Q-Orbitrap HRMS；网络药理学；抗菌活性

Chemical constituents of n-butyl alcohol extract from the leaves of *Ulmus pumila* L.

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Abstract:

Chemical constituents of *n*-butyl alcohol extract from the leaves of *Ulmus pumila* L. were investigated in this study. Seven compounds were isolated from 75% ethanol extract of *U. pumila* including eriodictyol 7-*O*-*β*-D-glucopyranoside (**1**), (7*R*,8*S*)-dihydrodehy-drodiconiferyl alcohol 9-*O*-*β*-D-glucopyranoside (**2**), kaempferol 7-*O*-*β*-D-glucopyranoside (**3**), kaempferol 3-*O*-*β*-D-glucopyranoside (**4**), quercetin-3-*O*-*β*-D-(6″-*n*-butyl) glucuronide (**5**), (*R*)-naringenin 7-*O*-*β*-D glucopyrano side (**6**), and dibutyl phthalate (**7**). Among them, compound **5** was reported from genus *Ulmus* for the first time, while compound **2** was isolated from the Ulmaceae family for the first time. Our phytochemical study of the leaves of *U. pumila* has not only enriched the understanding of the chemical composition of *U. pumila*, but also provided a scientific basis for its further research, development and utilization.

Keyword: *Ulmus pumila* L.; Chemical constituents; Structural identification

Protective role of Siberian onions against toxin induced liver dysfunction: an insight into health promoting effects

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Abstract:

Siberian onions (SOs) are delicious wild vegetables. Their taste is most unique, not only like scallions but also like leeks or garlic. They also have a traditional medicinal value for anti-inflammation, anti-oxidation, and anti-pyretic analgesia, particularly facilitating hepatoprotective effects. The current study investigates the potential mechanism of SOs against toxin-induced liver dysfunction. BALB/c mice were administrated with SO or silymarin by oral gavage for one week, followed by injecting carbon tetrachloride (CCl_4) to induce hepatic fibrosis. The effect of SO against hepatic fibrosis was evaluated by examining the liver tissue for serum transaminase, oxidative stress, extracellular matrix, histological alterations, cytokine levels, and apoptosis. In vitro, HSC-T6 cells were cultured with the supernatant from raw 264.7 cells stimulated with lipopolysaccharides, followed by SO extracts or Niclosamide (Signal Transducer and Activator of Transcription 3 (STAT3) inhibitor) at indicated time periods and doses. SO decreased serum transaminase levels and oxidative stress, and regulated the balance of ECM in CCl_4-induced mice, including α-SMA, collagen-I and TIMP-1. SO reduced the release of inflammatory factors and regulated apoptosis-associated proteins, which is related to the inhibition of STAT3 phosphorylation. Moreover, SO reduced the positive expressions of α-SMA and NLRP3 by inhibiting STAT3 phosphorylation in activated HSCs. SO could show health-promoting effects for liver dysfunction by alleviating hepatic fibrogenesis, apoptosis and inflammation in the development of hepatic fibrosis potential depending on the STAT3 signaling pathway.

Keywords: Siberian onions; STAT3; Hepatic fibrosis; Apoptosis; Inflammation

Chemical constituents from the branches and leaves of *Amorpha fruticosa* L.

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Abstract:

Amorpha fruticosa L. is a kind of tufted deciduous shrub belongings to the genus *Amorpha* of the family Leguminosae. It originated in North America and is primarily distributed in the southeastern and central United States, as well as the Atlantic coast [1]. At present, *A. fruticosa* is mainly cultivated in the northeast, North China, Northwest and the Yangtze River, Huaihe River basin and Sichuan basin in China. In recent years, the chemical composition and pharmacological activity of *A. fruticosa* have been studied intensively. The research has found that it contains a variety of active ingredients, including flavonoids, phenylpropanoids, steroids, volatile oils and so on. Among these, the content of flavonoid compounds is particularly abundant, and they exhibit pharmacological activities such as anti-tumor, anti-oxidation, anti-inflammatory, hepatoprotective and hypoglycemia effects [2]. In order to make rational use of and sufficiently exhibit the medicinal value of natural pharmaceutical resources, the chemical compositions in the branches and leaves of *A. fruticosa* were studied.

The chemical composition of CH_2Cl_2 fraction from *A. fruticosa* was separated and purified using various column chromatography methods, and the structure of the isolated compounds was identified by NMR, MS and other analytical techniques, combined with optical rotation and NMR data analysis in literature. Forty-three compounds were isolated from it, including twenty-four flavonoids (**1-24**), which were categorized into eight isoflavones (**1-8**), five flavonoids and dihydroflavonoids (**9-13**), four rotenones (**14-17**), three pterocarpans (**18-20**), three chalcons (**21-23**) and one flavonoid **24**. Additionally, there were ten phenylpropanoids (**25-34**), four phenolics (**35-38**), three terpenoids (**39-41**), and two chromones (**42-43**). Compounds **2**, **23**, **27**－**33**, **41** were isolated from the family Leguminosae for the first time, compounds **3**, **4**, **6**, **12**, **18**－**21**, **24**－**26**, **35**, **36**, **39**, **40**, **42**, **43** were isolated from the genus *Amorpha* for the first time. To sum up, this finding significantly enriches the variety of chemical components present in *A. fruticosa*, which provided a theoretical basis for the development and utilization of it.

Keywords: *Amorpha fruticosa* L.; Leguminosae; CH_2Cl_2 fraction; chemical constituents

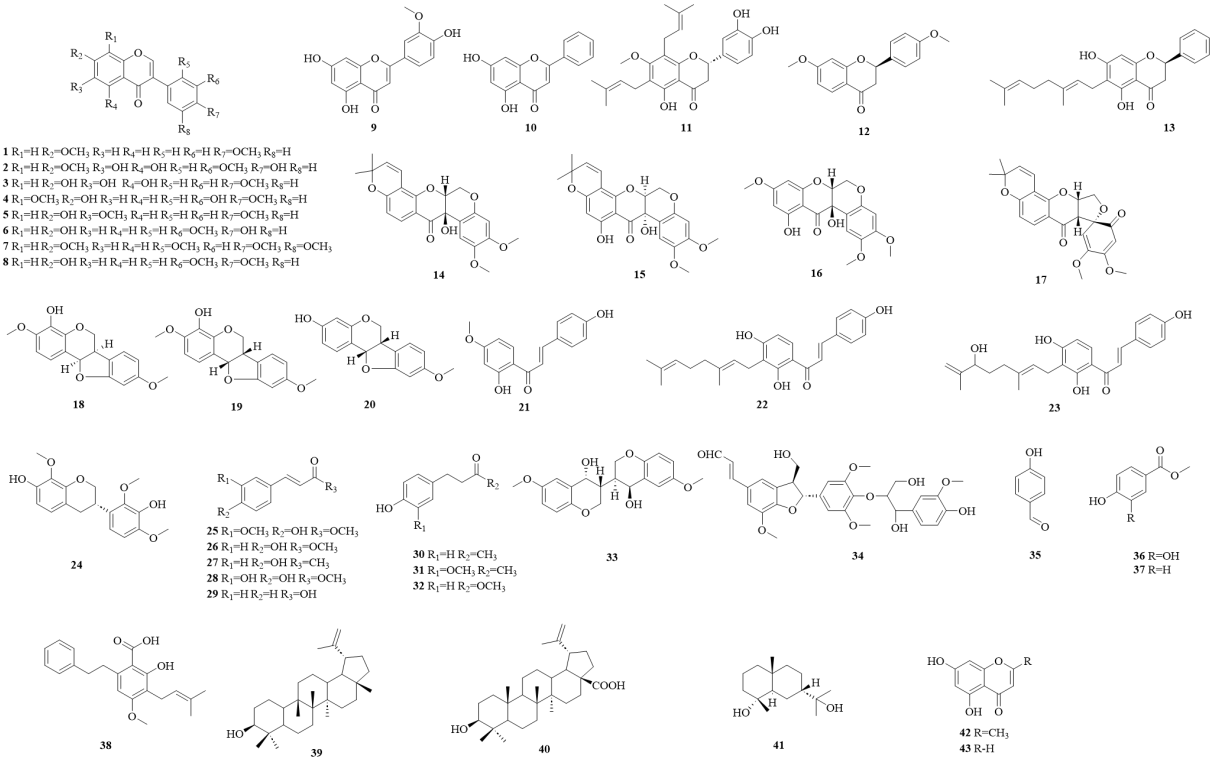

Figure 1. Structures of compounds **1**–**43**

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The protective mechanism of tanshinone IIA against neuronal injury induced by Toxoplasma gondii infection was studied based on microglia cells

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Abstract:

Toxoplasma gondii (*T. gondii*) is a neurotropic obligate intracellular parasite that can activate microglia and promote neuronal apoptosis, leading to central nervous system diseases. Tanshinone IIA (Tan IIA) is A fat-soluble component of *salvia miltiorrhiza* Bge, which has anti-inflammatory, anti-apoptosis, anti-tumor, neuroprotective and other pharmacological effects. Studies have shown that it can inhibit the growth of *T. gondii*. However, the protective effect of Tan IIA on neuronal damage induced by *T. gondii* infection remains unclear. In this study, a mouse model of acute *T. gondii* infection, a mouse microglial cell line (BV2 cell) activation model, and a co-culture system of BV2 cells/primary neurons in fetal rat cerebral cortex were established using *T. gondii* RH strain to investigate whether Tan IIA can reduce the neuronal damage caused by *T. gondii* infection by inhibiting the activation of microglia cells and its mechanism. The results showed that Tan IIA showed an effective anti-*toxoplasma* effect, which could significantly inhibit the proliferation of *T. gondii* in the brain tissue and BV2 cells of mice. At the same time, Tan IIA could improve the neurological symptoms of *T. gondii*-infected mice and inhibit neuronal apoptosis. Further studies showed that Tan IIA down-regulated the expression of *T.g*.HSP70/TLR4/NF-κB and NLRP3 inflammasome-signaling pathway related proteins in mouse brain tissue and BV2 cells, and reduced the secretion of inflammatory cytokines. In addition, the results of the microglial/primary cortical neuron co-culture system also demonstrated that *T. gondii*-induced microglial activation caused neuronal apoptosis, but Tan IIA reduced this effect.In summary, Tan IIA inhibits microglia activation and reduces the release of inflammatory factors through *T.g*.HSP70/TLR4/NF-KB and NLRP3 inflammatome signaling pathways, and has protective effects on neuronal injury induced by *T. gondii* infection. This study provides a theoretical basis for Tan IIA to treat central nervous system diseases caused by *T. gondii* infection.

Keywords: *Toxoplasma gondii*; Tanshinone IIA; microglia; Neuron; *T.g*.HSP70/TLR4/NF-κB/NLRP3

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Study of proteins' electrophoretic migration behavior based on the multi-compartment electrophoresis separation system

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Abstract:

The laboratory's multi-compartment electrophoresis separation system (MCESS) has achieved targeted drug screening in multi-flavour traditional Chinese medicines and accurate determination of the binding constants of proteins and drug molecules. In order to solve the problems of high protein consumption and cumbersome parameter optimization process during the application of the technology that pharmaceutical experts are concerned about, this study combined the unique chamber configuration of MCESS and the related electric field theory and established a protein electrophoretic migration model applicable to MCESS by taking the electrophoretic migration process of human serum albumin (HSA) (pH 8.0) as an example. Under the guidance of this model, the migration of proteins such as HSA (pH 7.0), HSA (pH 6.0) and α-Glucosidase (α-Glu) (pH 4.0) could reach more than 89.11%, and RSD ranged from 0.24% to 8.79%, which greatly simplified the process of experimental optimization with short time, low consumption, low cost, and provided a solid foundation for the subsequent development of drug screening and affinity determination.

Keywords: MCESS, HSA, proteins' electrophoretic migration behavior

Acknowledgement

This study was supported by Jilin Provincial Department of Science and Technology, China (No. YDZJ202301ZYTS301).

Synthesis of Oridonin derivatives and their Anti-tumor activity

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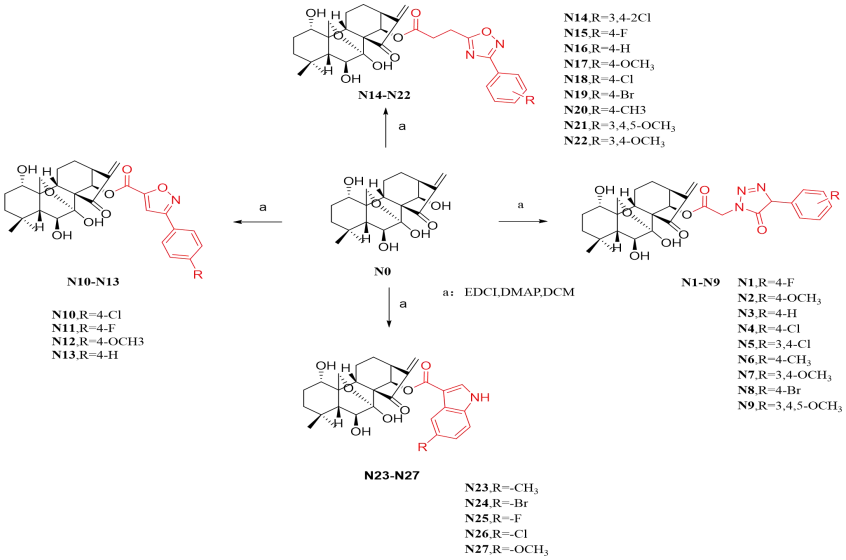
Abstract

Cancer is a disease in which the body cells lose their normal regulatory mechanism and grow out of control, which is one of the main causes of death and poses a serious threat to human health . The survey found that cancer diagnosis rates have been increasing in recent years, and by 2030, there are expected to be 21 million cancer patients worldwide . Most of the natural products have good pharmacological activity and low toxicity. A large number of literatures have also reported the antitumor activity of natural products . The main components of oridonin are natural organic compounds of kaempferol type tetracyclic diterpenes. A large number of studies have shown that oridonin has strong anti-tumor activity and has been used in the clinical treatment of esophageal cancer and liver cancer for many years.A large number of experiments have shown that oridonin has a significant inhibitory effect on more than 20 cancer cell lines such as human esophageal cancer, liver cancer, leukemia, nasopharyngeal cancer, colon cancer, kidney cancer, breast cancer and human melanoma. In recent years, some studies have shown that some potential anti-tumor cell proliferation compounds can be obtained by modifying and optimizing the C-14 hydroxyl group. In order to overcome its shortcomings, we will continue to modify and optimize its C-14 hydroxyl group, hoping to obtain derivatives with high anti-tumor activity and promote its clinical application as soon as possible. Therefore, we synthesized 30 derivatives of oridonin and tested their anti-tumor activity.Most of these compounds have strong antitumor activity.In particular, compound N27 has excellent inhibitory activity against three types of colon cancer cells and the best choice in these compounds for further studies.



Keywords: Oridonin derivatives, Structural modification, anti-tumor activity.

A tri-stage preclinical research on anti-Toxoplasma gondii candidates from Daphne koreana Nakai-based Traditional Chinese Medicine

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Abstract:

Toxoplasma gondii (*T. gondii*), the protozoan that causes toxoplasmosis, is a global public health concern, necessitating the exploration of safer and more potent alternatives to current treatments for *T. gondii* infection. Submicron emulsions, which are renowned for their ability to enhance drug solubility, hold promise as modern drug delivery systems for enhancing drug safety and effectiveness. *Daphne koreana* Nakai (*D. koreana*), an herbal plant that grows in the Changbai Mountain area of China, is used to make traditional Chinese medicines (TCMs) with diverse biological activities, including anti-parasitic activity with unknown effects on *T. gondii*. In this study, we isolated and identified 28 *D. koreana* compounds then evaluated their toxicity via MTT assays and screened them for biological activity and druggability using network pharmacology and molecular docking analyses. Notably, daphnetin (DAP) emerged as a promising compound with superior pharmacological properties and druggability. Rigorous *in vitro* prescription screening, quality assessments, and *in vivo* pharmacological evaluations in a murine model of *T. gondii* infection demonstrated superior efficacy of DAP against *T. gondii*. This comprehensive study provides valuable insights into the discovery, druggability assessment, and pharmacological evaluation of DAP, paving the way for the clinical development of natural drugs derived from TCMs.

Keywords: *Daphne koreana* Nakai, daphnetin, anti-*Toxoplasma gondii* activity, Traditional Chinese Medicine

Acknowledgments： This work was supported by the National Natural Science Foundation of China [grant number 81860666].

Effects of Euphorbia fischeriana cell extract on alleviating ulcerative colitis of DSS-induced mice via inhibiting inflammation and modulating gut microbiota

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Abstract:

Euphorbia fischeriana Steud is a perennial medicinal plant primarily native to northeastern China. Cell culture provides an alternative method for producing its raw material. To effectively utilize these cultured cells, it is crucial to clarify their bioactive properties. In this study, the ethanolic extract of *E. fischeriana* cell cultures (EFE) was evaluated for its effects on alleviating ulcerative colitis (UC) using a dextran sulfate sodium (DSS)-induced UC mouse model. The results showed that food and water intake, as well as body weight in DSS-induced UC mice, did not significantly decrease after EFE treatment, and a reduction was observed in the disease activity index, splenomegaly, intestinal shortening (small intestine and colon), and pathological damage. Additionally, 16S rDNA analysis revealed that EFE increased gut microbiota diversity and balanced the microbial structure by modulating the abundance of probiotics and pathogenic bacteria. ELISA assay results demonstrated that EFE reduced levels of pro-inflammatory factors, including tumor necrosis factor, interleukin-6, interleukin-1β, inducible nitric oxide synthase, and cyclooxygenase-2 in the colon, indicating its anti-inflammatory effect. These findings suggest that EFE has a beneficial impact on ameliorating UC by inhibiting inflammation and modulating the gut microbiota.

Keywords: *Euphorbia fischeriana*; Plant cell culture; Ulcerative colitis; Gut microbiota; Inflammation

Curcumol regulates psoriasis-like skin inflammation by IL-36/NLRP3 axis

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Abstract:

Background: Psoriasis is an immune-mediated disease that poses a significant problem for the treatment of psoriasis due to its complex pathogenesis. Curcumol is a sesquiterpenoid isolated from *Curcuma phaeocaulis* Valeton, exhibiting several biological activities including anti-inflammatory and immunomodulatory. Investigation on the IL-36/NLRP3 axis provided new ideas for the treatment of psoriasis-like skin inflammation.

Purpose: This study investigated the mechanisms by which curcumol modulated the ligand-mediated inflammatory response to TLRs and intervenes in imiquimod-induced psoriasis-like skin inflammation via the IL-36/NLRP3 axis.

Methods: The mice model of psoriasis-like skin inflammation and an *ex vitro* model were established applying imiquimod. Poly(I:C) and LPS were utilized to establish the *in vitro* model. The effect of curcumol on psoriasis-like skin inflammation was assessed by immunohistochemistry, H&E, immunofluorescence, western blot, and real-time quantitative PCR.

Results: Curcumol inhibited the expression of IL-36α and IL-36γ in NIH3T3 cells and IL-36γ in HaCaT cells stimulated by Poly(I:C) combined with LPS. Curcumol relieved psoriasis-like skin inflammation by blocking IL-36 signalling and inhibiting the expression of NLRP3 inflammasome. Curcumol inhibited the recruitment of macrophages and neutrophils in psoriatic skin-injured tissues and inhibited tissue damage produced during the inflammatory disease process.

Conclusion: Curcumol improved psoriasis-like skin inflammation by regulating the IL-36/NLRP3 axis, offered novel insights for psoriasis treatment.

Keywords: Psoriasis; Curcumol; IL-36; NLRP3; Imiquimod

Mechanism of neuronal damage induced by endothelin-1 activated microglia by tanshinone IIA sodium sulfonate

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Abstract:

Endothelin-1 (ET-1) is one of the most potent vasoconstrictors discovered to date and is considered a pro-inflammatory mediator in various diseases. Sodium tanshinone IIA sulfonate (STS) is a water-soluble compound produced by the sulfonation of tanshinone IIA. It has various pharmacological activities, including neuroprotection, anti-inflammation, and antioxidant, and has been widely recognized clinically for its therapeutic effects in ischemic stroke, but its specific mechanism of action is not clear. In this study, we analyzed the effect of STS on the TLR4/NF-κB/NLRP3 inflammasome signaling pathway in microglia using the ET-1 induced microglia activation model to further elucidate the potential molecular mechanism of STS on ET-1 induced microglia inflammation. The experimental results showed that STS was able to reduce the expression of Iba-1 and inhibit ET-1 induced microglia activation, meanwhile, it inhibited the TLR4/NF-κB/NLRP3 inflammasome signaling pathway and reduced the expression and secretion of high-mobility histone B1, tumor necrosis factor-α and inducible nitric oxide synthase. In conclusion, STS has a protective effect against neuronal injury induced by ET-1 induced microglial cell activation, and its possible mechanism is to inhibit the overproduction of neuroinflammation by interfering with the activation of the TLR4/NF-κB/NLRP3 inflammasome signaling pathway in microglia.

Keywords: Tanshinone IIA sodium sulfonate; Endothelin-1; Microglia; Neuronal damage; TLR4/NF-κB/NLRP3

Acknowlegment:

This work was supported by the Jilin Provincial Science and Technology Department (YDZJ202201ZYTS294), the National Natural Science Foundation of China (81960375), Yanbian University Doctoral Research Fund Project (ydbq202218).

Exploring the protective mechanism of Panax ginseng total saponin on glomerular thylakoid cells under high glucose based on miR-1231

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Abstract:

Diabetic nephropathy (DN) is one of the most serious complications of diabetes mellitus and is the main cause of end-stage renal disease (ESRD), which is characterised by thickening of glomerular basement membranes and dilatation of glomerular thylakoid membranes. Glomerular plasma cells are very important effector and target cells in diabetic nephropathy, and the persistent high glucose environment can induce their abnormal proliferation and inflammation.MicroRNA (miRNA) is a short-stranded non-coding RNA (non-coding RNA, ncRNA) with a length of about 18-22 nucleotides, which plays a role in a variety of physiological processes, such as cell differentiation, apoptosis, and lipid metabolism. In cell differentiation, cell apoptosis, lipid metabolism and other physiological processes, ncRNA plays a role. Panax notoginsenosises (PNS), the main active ingredient of Panax ginseng (Panax quinquefolius), can effectively ameliorate renal injury in diabetic nephropathy through various pathways such as anti-inflammatory and anti-oxidative stress. In the previous experiments, microRNA microarray analysis predicted that Panax notoginsenosides could up-regulate the expression of miR-1231 in HMCs under high glucose, but whether Panax notoginsenosides could achieve the protective effect on HMCs under high glucose by regulating miR-1231 is not clear to us, so we need to further experiments to explore the mechanism of action.

Keywords:Diabetic nephropathy; glomerular mesangial cells; miR-1231; inflammation; Panax ginseng total saponin;

Detection of Chiral Thiol Compounds in Sake Based on a Novel Mass Spectrometry Probe Labelling and Monitoring of Urinary Metabolic Dynamics After Alcohol Consumption

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Abstract:

Sake contains a variety of nutrients that are beneficial to the human body, such as amino acids, vitamins and minerals. To date, several research have revealed the detection of amino acids and other nutrients in sake. Few studies have dedicated the study of chiral thiols compounds. In view of this, a new UHPLC-HRMS method for the simultaneous detection and chiral splitting of five DL-thiol compounds (DL-GSH, γ-L-Glu-L-Cys, DL-Cys, DL-Hcy and DL-Nac) in sake was developed based on a novel chiral mass spectrometry probe (R)-(5-(3-isothiocyanatopyrrolidin-1-yl)-5-oxo-pentyl)-triphenylphosphormium (NCS-OTPP) labelling .

Firstly, we evaluated the chiral splitting efficacy of the novel chiral mass spectrometry probe NCS-OTPP using four DL-thiol compounds standards completely separated within 25 min, separations (Rs) ranging from 1.52-1.74, range of 2.50-500 μM with a good linear relationship ($R^2 \geq 0.9992$), and the detection limits were 2.5-14.4 fmol. Then, we estimated the differences of DL- thiol compounds in seven kinds of sake from different manufacturers. The contents of DL- thiol compounds in were different. This suggests that the content of DL-thiol compounds can be used as an indicator for the identification of sake ingredients. Finally, in order to investigate the metabolism of the three DL-thiol compounds in the human body after drinking sake, we dynamically monitored the metabolic changes of the three DL-thiol compounds in the urine of human beings after drinking sake and constructed a fitting curve. It was found that the content of DL-thiol compounds in the body showed a tendency of increasing and then decreasing after drinking sake, and the content of DL-thiol compounds in the body reached a peak in 15 min, and was almost metabolized completely in 60 min, which was nearly similar to that of drinking water. This method was successfully applied to analyze the content of DL-thiol compounds in wine and monitor the dynamic changes of in vivo metabolism after drinking, which provides a new strategy for the detection of chiral thiol compounds in wine and in vivo metabolism study.

Keywords: chiral thiol compounds; sake; NCS-OTPP; urine; UHPLC-HRMS

Synthesis and evaluation of 5,7-dihydroxy-4*H*-chromen-4-one derivatives and the antitumor activity

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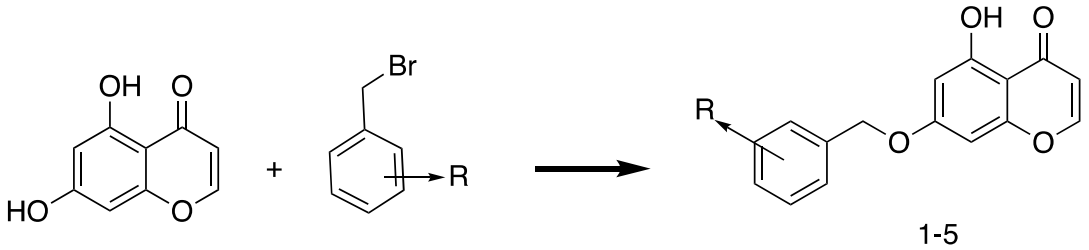
Abstract:

In recent years, cancer has always been a major serious disease plaguing mankind. With the continuous progress of medical technology, various new anti-cancer drugs continue to emerge. The anti-cancer drugs play a role through different mechanisms and inhibit the proliferation of cancer cells. However, existing anti-cancer drugs all have the characteristic of large side effects. While attacking cancer cells, they also harm normal cells and cause varying degrees of harm to patients. Therefore, developing an anti-cancer drug with high efficiency and low toxicity has become the primary problem in the process of fighting cancer. 5,7-Dihydroxy-4*H*-chromen-4-one is a natural product contained in many plants such as peanut shells. [1] Studies have shown that it is toxic to cancer cells and has no inhibitory effect on normal cells. In this study, five derivatives of 5,7-dihydroxy-4*H*-chromen-4-one were synthesized, and their antitumor activities were preliminarily studied. The lead compound 5,7-dihydroxy-4*H*-chromen-4-one itself is non-toxic to PC-12 and SW620.[2] However, after introducing a halogen iodine at the C-3 position (compound **2**), the anti-SW620 cancer cell proliferation activity (IC_{50}) is 34.9±15.1 μmol/L. After introducing a nitro group at the C-3 position (compound **5**), the anti-PC12 cancer cell proliferation activity (IC_{50}) reaches 19.0±1.3 μmol/L. When introduction of a -OCF_3 group at the C-3 position (compound **4**), the compound significantly enhanced the anti-cancer inhibitory activity against both SW620 and PC12 cancer cells. The five synthesized derivatives of 5,7-dihydroxy-4*H*-chromen-4-one are all non-toxic to normal human liver cell L-02.

Keywords: antitumor activity; 5,7-dihydroxy-4*H*-chromen-4-one; high efficiency; low toxicity



Scheme 1. Synthetic routes of target compounds.

Table 1. The IC_{50} values of derivatives on cancer cell and normal cell lines (μmol/L)

Compound	R	L-02	SW620	PC12
1	2-F	ND	ND	52.5±14.1
2	3-I	ND	34.9±15.1	ND
3	4-Cl	ND	ND	ND
4	3-OCF_3	ND	43.5±14.9	27.3±7.0
5	3-NO_2	ND	ND	19.0±1.3
5,7-dihydroxy-4*H*-chromen-4-one		ND	ND	ND

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[2] Mahnashi MH, Alshahrani MA, Nahari MH, et al. In-Vitro, In-Vivo, Molecular Docking and ADMET Studies of 2-Substituted 3,7-Dihydroxy-4*H*-chromen-4-one for Oxidative Stress, Inflammation and Alzheimer's Disease. J. Metabolites. 2022, 12 (11): 1055.

Progress on chemical composition and pharmacological effects of Acer tegmentosum Maxim

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Abstract:

Acer tegmentosum Maxim is a plant of the Acer genus in the Sapindaceae family， which is mainly produced in Changbai Mountain area of Jilin Province. The chemical components of *Acer tegmentosum* Maxim are diverse, mainly including flavonoids, phenols, and other compounds. Its pharmacological effects are extensive, with hepatoprotective, anti-inflammatory, and antioxidant effects.At present, there is relatively little research on the chemical components and pharmacological effects of *Acer tegmentosum* Maxim both domestically and internationally. Therefore, this article summarizes the relevant research progress on the chemical components and pharmacological effects of *Acer tegmentosum* Maxim, in order to provide reference for the subsequent research and development of *Acer tegmentosum* Maxim.

Keywords: *Acer tegmentosum* Maxim； chemical composition； pharmacological effect

References:

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Design and synthesis of piperazine amide compounds and research on HIF-1 targets and anticancer activity

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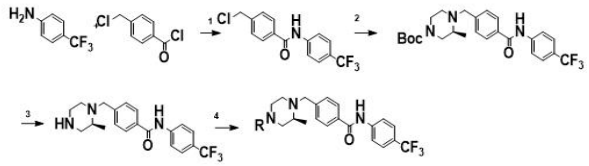
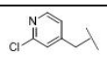
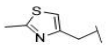
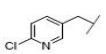
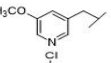
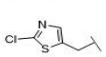
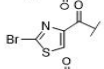
Abstract:

It is widely believed that cancer cells in hypoxic areas will resist existing chemotherapy and radiation therapy. Hypoxia itself can have various adverse effects on both normal and cancer cells, such as reduced energy production and induction of cell apoptosis. However, cancer cells can adapt to a low oxygen environment by activating the hypoxia inducible factor (HIF) pathway. At present, small molecule drugs are receiving increasing attention in the field of anti-cancer, and HIF-1, as a cancer target, is also receiving more and more attention in the research of anti-cancer drugs. This study synthesized a series of compounds containing piperazine amide structures using a total synthesis method and evaluated their HIF-1 target inhibition and anticancer activity. Among them, compounds 26, 27, and 28 have good inhibitory and anticancer activities against HIF-1, and further structural modification and pharmacological activity research are needed for these compounds.



1. THF, TEA
2. DMF, TEA
3, DCM, H_2O, F_3CCOOH
4. DMF, TEA/K_2CO_3

NO.	R	NO.	R	NO.	R	NO.	R
S1		S8		S15		S22	
S2		S9		S16		S23	
S3		S10		S17		S24	
S4		S11		S18		S25	
S5		S12		S19		S26	
S6		S13		S20		S27	
S7		S14		S21		S28	

Keywords: Small molecule drugs, piperazine amide, HIF-1 inhibitors, anti-cancer

基于网络药理学探讨玉竹改善糖尿病肾病的功能成分和潜在靶点

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摘要：

目的：基于网络药理学技术，对玉竹化学成分进行筛选，为发现玉竹防治糖尿病肾病（diabetic kidney disease，DKD）的功能成分和潜在靶点。

方法：根据OB值≥30%和DL值≥0.18，从TCMSP数据库中筛选活性成分。运用Pharmapper、Swiss Target和GeneCards、OMIM数据库，分别收集玉竹和DKD相关靶点。通过Venny 2.1.0获取交集靶点，将交集靶点上传至STRING平台获得PPI蛋白互作网络图，利用Cytoscape 3.10.1 degree值筛选潜在核心靶点。利用David数据库对交集靶点进行BP、CC、MF和KEGG富集分析，根据*P*-value各自取前20个条目进行GO和KEGG富集分析。利用Cytoscape 3.10.1构建“玉竹-交集靶点-疾病-信号通路”网络可视化图，获取防治DKD关键信号通路和核心靶点。

结果：从TCMSP数据库中共获得有效成分8个。通过Pharmapper、Swiss Target数据库共获得有效成分靶点379个，GeneCards、OMIM数据库共筛选出DKD靶点2382个，Venny 2.1.0显示交集靶点为179个。ALB、TNF、AKT1、EGFR靶点degree值较高，分别为122、120、117、101，可能为核心靶点。David数据库中获得与疾病密切相关的生物学过程709条、细胞组分79条、分子功能142条、信号通路169条。GO和KEGG结果显示，交集靶点主要位于extracellular region、extracellular exosome、extracellular space等细胞组分中，与nuclear receptor activity、identical protein binding、enzyme binding等分子功能有关，主要参与phosphorylation、negative regulation of apoptotic process、signal transduction等生物学过程，且与Pathways in cancer、Prostate cancer、Proteoglycans in cancer等信号通路有关。

结论：玉竹防治DKD的核心靶点可能为ALB、TNF、AKT1、EGFR，并通过Pathways in cancer、Prostate cancer、Proteoglycans in cancer信号通路发挥作用。

关键词：玉竹；糖尿病肾病；网络药理学；功能成分；潜在靶点

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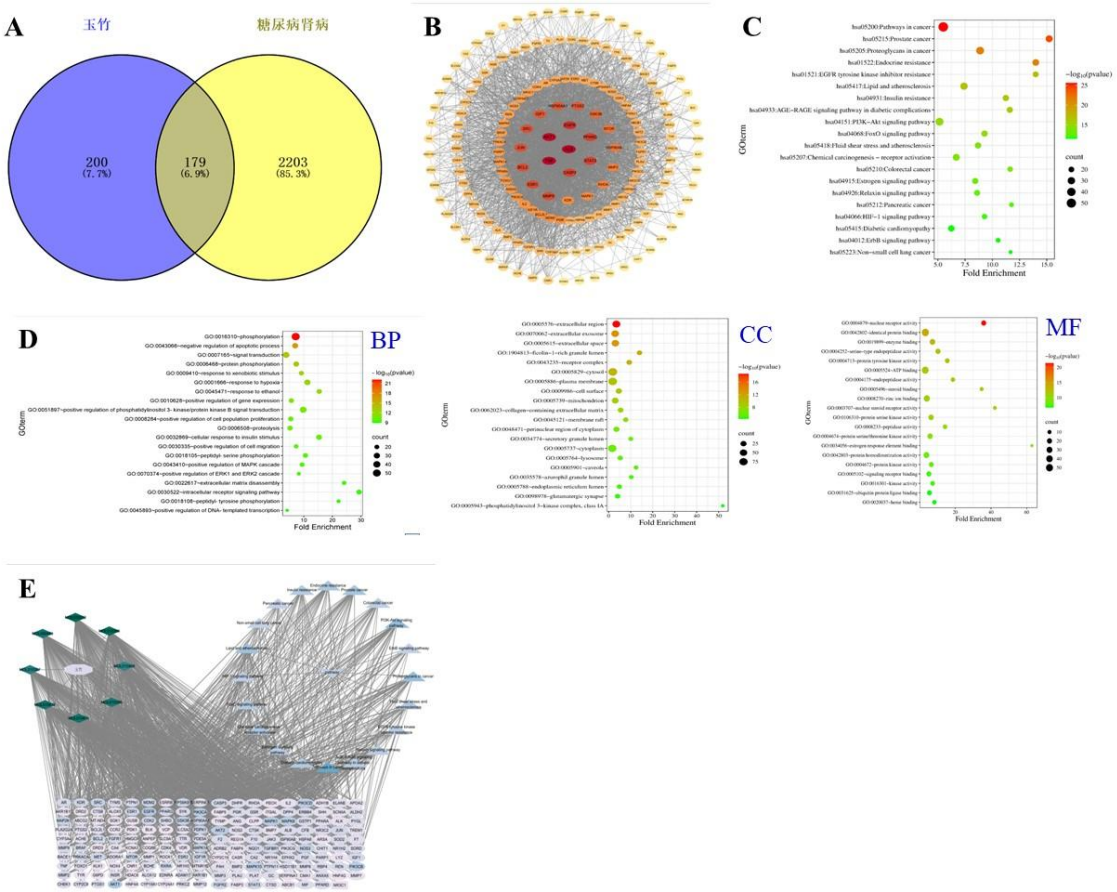

图1. A DKD、玉竹Venny交集基因图；B 交集靶点PPI可视化图；C KEGG富集气泡图；D BP、CC、MF富集气泡图；E “玉竹-交集靶点-疾病-信号通路”网络可视化图。

The eff ect of lipid metabolism regulator anthocyanins from Aronia melanocarpa on 3T3-L1 preadipocytes and C57BL/6 mice via activating AMPK signaling and gut microbiota

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Abstract:

This study investigated lipid metabolism regulation by anthocyanins from Aronia melanocarpa (AAM) in 3T3-L1 preadipocytes and high fat diet (HFD) mice. Ultra-performance liquid chromatography/ion mobility quadrupole time-of-flight mass spectrometry analysis identified the constituents of AAM, which decreased lipid content and inflammation in 3T3-L1 cells without cytotoxicity. Meanwhile, taking normal diet and orlistat mice as references, AAM supplementation improved blood lipid levels and adipocyte degeneration, promoted beneficial gut microbial growth, and maintained lipid metabolism in HFD mice.Furthermore, AAM activated the AMP-activated protein kinase (AMPK) signaling pathway, accompanied by the regulation of adipogenic transcription factors and their target genes in vitro and in vivo. Collectively,our data demonstrated that AAM exhibits anti-adipogenic activities that were partially mediated by the AMPK pathway and gut microbiota regulation. This study provides new insight into the regulation of lipid metabolism by AAM and suggests that AAM has potential therapeutic effects on hyperlipidemia.

Keywords: Aronia melanocarpa; Anthocyanins; Lipid metabolism; Gut microbiota

Properties of Tactile-stimulation Evoked Ca^{2+} Transients in Cerebellar Cortical PC and MLI in mice

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Abstract

The cerebellum is an important structure for motor balance and coordination. In this study, we used *in vivo* laser two-photon Ca^{2+} imaging technology, electrophysiological and pharmacological methods to study the Ca^{2+} transient characteristics of mouse cerebellar Purkinje cell (PC) and MLIs caused by facial hair blowing stimulation, and to explore the relationship between Ca^{2+} imaging and electrical signals of PC. **Results:** Air-puff stimulation obviously evoked Ca^{2+} transients on PC dendrites, which significantly increased in comparing with pre-stimuli. Air-puff stimulation also evoked Ca^{2+} transients on PC somas, but not so obvious as dendrites. Setting PC soma as the datum mark, 35um as a unit, we marked four locations (same areas of ROIs) on PC dendrites to observe the Ca^{2+} transients by different distances, showing that the variation of Ca^{2+} transients on somas is the least, the middle of dendrites is the biggest. Blocking $GABA_A$ receptors by Gabazine we find that the Ca^{2+} transients on dendrites are decreased. Combining with the electrophysiology results, the air-puff stimulation –evoked IPSC on PC dendrites are conversed into EPSC by blocking $GABA_A$ receptors, meanwhile the Ca^{2+} transients decreased slightly. Nevertheless the incident that the evoked IPSC transform into evoked action potential is not particularly relevant to the variation of Ca^{2+} transients on PC somas. Air-puff stimulation evoked Ca^{2+} transients on the somas and dendrites of MLIs, which is weaker than that of PCs. **Conclusion:** Tactile stimulation increases PC and MLI Ca^{2+} transients through PF-PC/PF-MLI synapses; Blocking MLI inhibitory afferent attenuates PC Ca^{2+} transients induced by tactile stimulation.

Key words: Two-photon imaging; Ca^{2+} transients; Purkinje cell (PC); Molecule layer interneuron (MLI); Air-puff.

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Enantioselective Synthesis of spiro[indoline-3,4- pyrrolo [3,4-b]pyridines] via Organocatalysed Three-Component Cascade Reaction

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Abstract:

Asymmetric synthesis of spiro[indoline-3,4-pyrrolo [3,4-b]pyridines] derivatives was first developed through organocatalytic cascade Knoevenagel/Michael/cyclization reaction using a quinidine -derived squaramide. Under the optimized conditions, the three-component reaction of isatins, cyanoacetates, and 3-aminomaleimides yield the desired heterocycle-fused spirooxindoles in good yields (79 – 91%) with up to 99% enantiomer excess (ee). Notably, this reaction enabled a broad substrate scope under mild conditions, and provided a convenient method for enantioselective construction of diverse spirooxindoles combined with dihydropyridine and maleimide skeleton, which brought great potential to build new bioactive chemical entities.

Keywords: organocatalysis; enantioselective; Knoevenagel/Michael/cyclization; spiro[indoline-3,4- pyrrolo [3,4-b]pyridines]; 3-arylaminomaleimides

Platycodin D targeting ZNF70 down-regulation STAT3 signaling pathway to inhibit the progression of hepatocellular carcinoma

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Abstract:

Platycodin D is a triterpenoid saponin monomer which extracted from the roots of traditional Chinese medicine *Platycodon grandiflorus (Jacq.) A. DC*. which is the main active compound that exerts the pharmacological activity. Platycodon grandiflorus is a traditional herb used as both medicine and food, which has a long history of use, including the preparation of Platycodon grandiflorus savory dishes and as the main medicine for cough suppressant. Its clinical application for the treatment of cough, phlegm, sore throat, lung and respiratory disorders has been used in China for thousands of years. Platycodin D has been reported to have various pharmacological effects such as anti-inflammatory, hypoglycemic, anti-tumor, and immune regulation. However, the molecular mechanism of its anti-tumor effect has not been clearly illustrated. In this work, we have explored the effectiveness of platycodin D in the treatment of hepatocellular carcinoma and determined the underlying mechanism of its anti-tumor activity. Zinc finger protein 70 (ZNF70) is a member of the zinc finger protein family and is closely related to cancer development. Abnormal activation of STAT3 can promote the development of liver cancer and is widely involved in the malignant proliferation of tumor cells. We first found that platycodin D inhibited TNF-α-induced the protein and mRNA expression of ZNF70. Platycodin D suppressived TNF-α-induced the activation of STAT3, and it also inhibited the activation pathway of STAT3 through JAK2 and Src but not through JAK1. It is noteworthy that platycodin D prohibited the activation of STAT3 signaling pathway by down-regulating ZNF70. Platycodin D inhibited STAT3 signal transduction pathway by down-regulating ZNF70, and inhibits tumor cell proliferation and angiogenesis. *In vivo*, the antitumor activity of platycodin D through down-regulating ZNF70 was proved in DEN/CCl_4 induced animal model of hepatocellular carcinoma, and the secretion of hepatocellular carcinoma markers was effectively reduced, which confirmed the results of *in vitro* observations. In conclusion, we first reported that platycodin D inhibited the activation of STAT3 signaling pathway by targeting down-regulation of ZNF70 expression and exerted anti-tumor effects. In summary, these results highlight the anti-tumor efficacy of platycodin D and provide new ideas and basis for the development of new anti-tumor drugs with platycodin D as the lead compound.

Keywords: Platycodin D; ZNF70; STAT3; Hepatocellular Carcinoma; Anti-tumor activity;

Schisandrin B inhibits malignant progression of breast cancer through the Wnt/β-catenin signaling pathway

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Abstract:

Objective To investigate the effect of Schisandrin B on the Wnt/β-catenin signaling pathway in breast cancer cells and its potential application in breast cancer therapy. **Methods** MTT assay was used to detect the proliferative changes of breast cancer cells with different concentrations of Schisandrin B. Its effect on cell migration and invasion ability was detected by cellular scarring and Transwell assays. The expression changes of β-catenin and related proteins were detected by Western blot technique. **Results** Schisandrin B significantly inhibited the proliferation, migration and invasion ability of breast cancer cell lines. And it inhibited the activation of Wnt/β-catenin signaling pathway by decreasing the expression of β-catenin protein, thus inhibiting the malignant progression of breast cancer cells. **Conclusion** Schisandrin B effectively inhibits the malignant phenotype of breast cancer cells by inhibiting the Wnt/β-catenin signaling pathway, which provides a new strategy and potential drug for the treatment of breast cancer.

Keywords: Schisandrin B; breast cancer; Wnt/β-catenin signaling pathway; malignant progression

Ligustilide Modulates Oxidative Stress-induced Mitophagy and Protects C2C12 Myoblasts

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Abstract:

Background and Objective：

Ligustilide, the principal active component of the volatile oil of Angelica sinensis, a traditional Chinese medicinal herb of the Umbelliferae family, is widely regarded as the most effective bioactive constituent of Angelica sinensis. Existing studies have indicated that ligustilide plays a significant role in preventing TNF-α-induced apoptosis and autophagy of C2C12 cells; however, its function in skeletal muscle oxidative stress remains unclear. The aim of this research is to explore the protective effect of ligustilide on oxidative damage in mouse skeletal muscle cells C2C12 and the underlying molecular mechanism.

Methods:

This study uses hydrogen peroxide (H_2O_2) oxidative stress as a classical model to simulate oxidative damage. After pretreatment of C2C12 skeletal muscle cells with Ligustilide, the cells were treated with hydrogen peroxide to simulate oxidative damage. The appropriate concentration and duration of hydrogen peroxide treatment, as well as the suitable concentration of Ligustilide, were determined by assessing cell viability. The impact of Ligustilide on the oxidative stress levels in the cells was analyzed by measuring reactive oxygen species (ROS). The influence of Ligustilide on cell apoptosis was assessed using the Annexin V/PI double staining method. Western blotting was employed to evaluate the effects of Ligustilide on antioxidant substances, and the antioxidant Vitamin C (Vc) was added to explore the regulatory mechanisms by which Ligustilide protects against oxidative damage.

Confocal microscopy was utilized to examine the effects of Ligustilide on autophagic flux and the impact on mitochondrial autophagy, as well as the colocalization of mitochondria and lysosomes in response to oxidative damage. The addition of the autophagy inhibitor chloroquine (CQ) further validated the effect of Ligustilide on mitochondrial autophagy alterations. The influence of Ligustilide on mitochondrial DNA (mtDNA) was assessed through mitochondrial DNA copy number measurement. Additionally, Western blotting and real-time quantitative polymerase chain reaction (qPCR) were conducted to investigate the molecular mechanisms underlying the effects of Ligustilide on mitochondrial autophagy and apoptosis.

Results:

Cell viability assays demonstrated that Ligustilide at concentrations ranging from 1 to 30μg/mL showed no toxicity to skeletal muscle cells, with a significant increase in cell viability observed at a concentration of 10 μg/mL. The inhibitory effect of hydrogen peroxide-induced oxidative damage on cell viability was found to be time- and dose-dependent, while pretreatment with Ligustilide significantly improved cell viability that was inhibited by hydrogen peroxide. Following treatment with hydrogen peroxide, levels of reactive oxygen species (ROS) in skeletal muscle cells were elevated. However, pretreatment with Ligustilide significantly suppressed ROS levels and markedly inhibited hydrogen peroxide-induced cell apoptosis. Moreover, Ligustilide was found to enhance the expression of antioxidant proteins Nrf2 and HO-1.After hydrogen peroxide treatment, there was an increase in the numbers of autophagosomes and autolysosomes; however, pretreatment with Ligustilide significantly reduced the quantity of both autophagosomes and autolysosomes, inhibiting hydrogen peroxide-induced mitochondrial autophagy and the colocalization of lysosomes with mitochondria. Following hydrogen peroxide treatment, the levels of LC3-II gradually increased, but pretreatment with Ligustilide had no significant effect on the conversion of LC3-I to LC3-II. Additionally, Ligustilide pretreatment suppressed the increase of Pink1 and Parkin induced by hydrogen peroxide. The addition of the autophagy inhibitor chloroquine significantly reversed the degradation of cytochrome c induced by hydrogen peroxide, while having no notable effect on the levels of cytochrome c in cells pretreated with Ligustilide. Furthermore, Ligustilide inhibited the degradation of mitochondrial DNA induced by hydrogen peroxide. After hydrogen peroxide treatment, the apoptosis-related Bax/Bcl-2 ratio increased; however, Ligustilide inhibited the transcription levels of Bax, significantly lowering the Bax/Bcl-2 ratio and inhibiting the transcription levels of apoptosis-related proteins.

Conclusion：

These results indicate that Ligustilide exhibits cytoprotective effects against oxidative damage in mouse skeletal muscle cells. Ligustilide alleviates hydrogen peroxide-induced growth inhibition, enhances the cells' antioxidant capacity, and increases the ability to scavenge reactive oxygen species induced by hydrogen peroxide. Additionally, Ligustilide inhibits the increase in autophagic flux induced by hydrogen peroxide and suppresses the expression of the apoptosis-related genes Bax/Bcl-2 caused by H2O2, thereby inhibiting mitochondrial autophagy and partially preventing the colocalization of lysosomes with mitochondria. Furthermore, Ligustilide inhibits hydrogen peroxide-induced apoptosis by reducing both transcription and protein levels of Bax, as well as the transcription levels of other apoptosis-related proteins.

These findings suggest that Ligustilide plays a regulatory role in the process of mitochondrial autophagy induced by oxidative stress, thereby inhibiting cell apoptosis. Given its antioxidant properties, Ligustilide may be considered for development as a therapeutic agent for diseases related to oxidative damage in skeletal muscle.

Keywords: Ligustilide; Skeletal muscle; Oxidative damage; autophagy

Diallyl disulfide, the bioactive component of Allium species, ameliorates pulmonary fibrosis by mediating the crosstalk of farnesoid X receptor and yes-associated protein 1 signaling pathway

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Abstract:

Environmental pollution, virus infection, allergens, and other factors may cause respiratory disease, which could be improved by dietary therapy. Allium species are common daily food seasoning and have high nutritional and medical value. Diallyl disulfide (DADS) is the major volatile oil compound of Allium species. The present study aims to explore the preventive effect and potential mechanism of DADS on pulmonary fibrosis. C57BL/6J mice were intratracheally injected with bleomycin (BLM) to establish pulmonary fibrosis and then administrated with DADS. Primary lung fibroblasts or A549 were stimulated with BLM, followed by DADS, farnesoid X receptor (FXR) agonist (GW4064), yes-associated protein 1 (YAP1) inhibitor (verteporfin), or silencing of FXR and YAP1. In BLM-stimulated mice, DADS significantly ameliorated histopathological changes and interleukin-1β levels in bronchoalveolar lavage fluid. DADS decreased fibrosis markers, HIF-1α, inflammatory cytokines, and epithelial-mesenchymal transition in pulmonary mice and activated fibroblasts. DADS significantly enhanced FXR expression and inhibited YAP1 activation, which functions as GW4064 and verteporfin. A deficiency of FXR or YAP1 could result in the increase of these two protein expressions, respectively. DADS ameliorated extracellular matrix deposition, hypoxia, epithelial-mesenchymal transition, and inflammation in FXR or YAP1 knockdown A549. Taken together, targeting the crosstalk of FXR and YAP1 might be the potential mechanism for DADS against pulmonary fibrosis. DADS can serve as a potential candidate or dietary nutraceutical supplement for the treatment of pulmonary fibrosis.

Keywords: Allium species; diallyl disulfide; farnesoid X receptor; pulmonary fibrosis; respiratory disease

Study on pharmacodynamic basis of Lespedeza davurica in treating chronic glomerulonephritis

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Abstract:

Chronic glomerulonephritis (CGN) is closely related to immune inflammatory injury. *Lespedeza davurica* is a plant of the genus *Leguminosae sp.* in the family of *Lespedeza*,and according to the "Salvation Materia Medica" and other canonical records, this plant has the efficacy of strengthening the tendons and benefiting the kidneys, clearing away heat and inducing diuresis, invigorating the spleen and dispelling dampness, which is of significant medicinal value. We comprehensively used column chromatography and preparative chromatography and other separation means to isolate and identify the active substances of the plant, evaluated the anti-inflammatory activity of the plant with the help of network pharmacology and molecular docking technology, and utilized the Lipopolysaccharide-induced RAW264.7 macrophage inflammation model to establish a new mode of identifying the active substances of traditional Chinese medicine, and explored the potential clinical application value of the natural active components of *Lespedeza davurica* in the treatment of chronic glomerulonephritis, in order to provide the best solution for the treatment of chronic glomerulonephritis and to improve the clinical efficacy of the plant. We also explored the potential clinical application value of the natural active ingredients isolated from *Lespedeza davurica* in the treatment of chronic glomerulonephritis, and provided a theoretical basis for the subsequent development of this plant. **Conclusion:** In this work, we verified the low toxicity and good anti-inflammatory activity of the ethyl acetate layer of *Lespedeza davurica* after in vitro experiments. Therefore, the isolation and purification of the ethyl acetate layer of *Lespedeza davurica* was carried out, and a total of 23 compounds were obtained, among which compounds 8-hydroxylinalool, eugenol-*O*-*β*-glucopyranoside and (-)-catechin were isolated from *Lespedeza davurica* for the first time. As verified by in vitro experiments, the compounds isolated from the ethyl acetate layer of *Lespedeza davurica* exhibited good cell viability and possessed some anti-inflammatory effects. The mechanism of action of *Lespedeza davurica* in the treatment of chronic glomerulonephritis was investigated by utilizing network pharmacology methods and molecular docking, which initially revealed the main active components, targets and signaling pathways of *Lespedeza davurica* in the treatment of chronic glomerulonephritis, and provided the basis for its in-depth study. Through the above experimental studies, it is hypothesized that flavonoids may be the main types of chemical components that play a major role in the treatment of

chronic glomerulonephritis in *Lespedeza davurica*, which provides a scientific basis for the clinical application and development of this plant.

Keywords: *Lespedeza davurica*; Chemical composition; Chronic glomerulonephritis; Network pharmacology; Anti-inflammatory

HOF-based catalytic platform combining sonodynamic therapy and biorthogonal activation of immunosuppression reversal for cancer therapy

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Abstract:

The hydrogen-bonded organic framework (HOF) nanodrug delivery system provides a platform for drugs to target tumor sites. However, chemotherapeutic drugs are distributed non-specifically in vivo and leakage of targeted agents, resulting in severe side effects and low treatment efficiency. Preliminary studies have proven that bioorthogonal reaction catalytic activation of prodrugs based on the HOF platform provides opportunities for precise drug delivery and intelligent drug release. The hypothesis is that sonosensitizers self-assemble into HOFs, and relying on sonodynamics, active targeting and bioorthogonal reactions to accurately activate the prodrug encapsulated in HOFs and intelligently release them. The model drug is the breast cancer chemotherapy drug doxorubicin (DOX) combined with metformin (MET), which degrades PD-L1 and reverses the immune evasion of triple-negative breast cancer. The sonosensitizer iron porphyrin constitutes a highly biocompatible HOF-based bioorthogonal precatalyst. In situ encapsulating prodrugs of DOX and MET into HOF-1, which is a sonosensitizer and anticancer prodrug carrier precatalyst. Finally, peptide ligands were modified on the surface of HOF-1 nanoparticles to target breast cancer cells. The active targeting and tumor microenvironment responsiveness of HOF-1 drug delivery system provide double insurance to ensure precise activation of prodrugs and spatiotemporally controlled release. The project provides a strategy to solve the failure and side effects of nano chemotherapeutic drugs.

Keywords: hydrogen-bonded organic frameworks; sonodynamic; bioorthogonal reaction; transition metal catalyst; activated prodrug; immunogenic cell death; immune evasion

2',4'-dihydroxychalcone induces ferroptosis through ERO1A/GPX4 regulatory axis in cholangiocarcinoma

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Abstract:

Cholangiocarcinoma (CCA) is a malignant tumor that is usually diagnosed at an advanced stage and has a poor prognosis. The exact regulatory mechanism by 2',4'-dihydroxychalcone(D2) inhibits CCA remains largely unexplored. In order to evaluate the therapeutic effect of D2 on the cholangiocarcinoma, we conducted in vivo and in vitro experiments. We provide evidence that D2 inhibits proliferation, migration and EMT processes of CCA. D2 can induce ferroptosis in CCA, and is involved in regulating GSH synthesis mainly through ERO1A. Subsequent experiments confirmed the interaction between ERO1A and GPX4, which ERO1A knockdown promoted ubiquitination of GPX4, leading to a decrease in GPX4 protein abundance in CCA. Furthermore, D2 was able to counteract the promotional effect of ERO1A on CCA biological function in vivo and in vitro. In summary, our study demonstrated that D2 induces ferroptosis of CCA cells through the ERO1A/GPX4 axis and inhibits the malignant progression of CCA. The results show that D2 can be used as a new adjuvant drug for clinical treatment of CCA.

Keywords: Cholangiocarcinoma; 2', 4 '-dihydroxychalcone; ERO1A； ferroptosis; GPX4;

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Salidroside targets P2X7R for the treatment of alcoholic hepatic steatosis

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Abstract:

Background: Purinergic receptor P2x7 (P2x7R) is a key modulator of liver inflammation and lipid metabolism. Salidroside (SDS) is one of the active components of the medicinal plant Rhodiola rosea, which has anticancer, antioxidant and hepatoprotective effects. The present study aimed to investigate the role of P2x7R in lipid accumulation and inflammatory response in alcoholic liver disease(ALD) by blocking P2X7R with A438079.

Methods: The mouse chronic-binge model was established by chronically feeding male C57BL/6 mice an ethanol-containing Lieber-DeCarli liquid diet. In vitro, AML12 cells were exposed to ethanol for 24 h. Study of the ameliorative effect on alcoholic liver disease after blocking P2X7R. We also investigated the anti-inflammatory effect of SDS and the underlying mechanism by murine peritoneal macrophages (MPM) were stimulated with LPS and ATP in vitro and a mouse model of binge drinking-induced liver injury in vivo.

Results: Histopathological staining showed that A438079 improved fat vacuole and lipid droplet accumulation in liver and hepatocytes and enhanced the sirtuin 1 (SIRT1) expression mediated by ethanol. A438079 prevents SREBP-1 regulation of fatty acid synthesis by blocking P2X7R. Additionally, A438079 inhibited the expression of P-AMPK and Caspase-3 and up-regulated the expression of PPARα in ethanol-stimulated AML-12 cells. In MPM, IL-1β was reduced after LPS/ATP stimulation in SDS-treated cells and supernatant. In conclusion, A438079 may alleviate liver injury by inhibiting the expression of P2X7R. And SDS may also achieve the improvement of hepatic inflammatory response through the P2X7R-NLRP3 axis.

Conclusion: P2X7 receptor; salidroside; inflammation; Lipid accumulation; Alcoholic liver disease;

Platycodin D inhibits PD-L1 expression and angiogenesis of human colon cancer cells

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Abstract:

In recent years, the incidence rate of colorectal cancer has increased sharply. According to the latest Annual Report of China Tumour Registry released by National Cancer Centre, the number of new cases of colorectal cancer in China is close to 400,000, and the number of deaths is about 200,000, and the deterioration of colorectal cancer can no longer be ignored. In recent years, the emergence of immunotherapy has greatly improved the situation.

Immunotherapy has been identified as an effective treatment for cancer. The main mechanism of cancer immunotherapy is to target recognition and destruction of cancer cells by utilising or activating immune system mechanisms by inducing or restoring the function of immune system effector cells as well as cytotoxic T cells. Programmed Cell Death Receptor-1 (PD-1) is a cell-surface receptor that serves as a T-cell checkpoint and regulates T-cell function. It has been shown that when PD-L1 is expressed in large quantities in tumour cells, it binds to the PD-1 receptor on the surface of T cells, inhibits the normal physiological function of T cells, blocks T cell activation and proliferation, and then generates immune escape, which promotes the growth and migration of tumours, leading to the development of malignant tumours.

Natural compounds have good anticancer potential. Platycodin D is a triterpenoid saponin isolated from *Platycodon grandiflorum* of the family Platycodonaceae, and numerous studies have confirmed that Platycodin D has good anti-inflammatory and anticancer activities. In this study, we first investigated whether Platycodin D could inhibit the proliferation of colon cancer cells HCT116, we found that Platycodin D significantly inhibited the proliferation of HCT116 cells when treated for 48 h, and we found that Platycodin D inhibited the protein expression of PD-L1 in colon cancer HCT116 cells in a concentration-dependent manner when treated for 12 h. The best effect was observed when the drug was treated for 12 h. At the same time, we found that Platycodin D could inhibit the colony formation, migration and angiogenesis of tumour cells, however, the inhibitory effect of Platycodin D on colon cancer requires further *in vivo* studies.

In conclusion, our results demonstrated that Platycodin D could inhibit the protein expression of PD-L1 in HCT116 cells, and inhibit the proliferation, migration and angiogenesis of HCT116 cells, which provides a new idea for the development of natural products to be applied to the treatment of colon cancer in the future.

Keywords: Platycodin D ; Colon Cancer ; PD-L1 ; Angiogenesis

Neferine-mediated NLRP3-related signaling pathway for the modulation of steatosis in alcoholic steatohepatitis

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Abstract:

NLRP3-related signaling pathway not only participates in pathologies of inflammatory diseases but also has a critical role against pathogenic infections. Modulation of NLRP3-related signaling pathway represents a promising therapeutic strategy for related inflammatory diseases, but the discovery of superior inhibitors for NLRP3-related signaling pathway remains an unmet demand. Neferine is an active alkaloid isolated from Nelumbinis Plumula, a traditional Chinese medicinal herb used for heat-clearing and detoxifying. Numerous studies suggest that Neferine, as a natural dibenzylisoquinoline compound, has anti-inflammatory, anti-fibrosis, anti-oxidation, cardiovascular and nervous system protection and other effects. Here, our data showed that the effects of Neferine on NLRP3-related signaling pathway in macrophage cellular models and a mouse model of NIAAA. We demonstrated Neferine not only prevented steatosis but also blocked the liver injury, macrophage and neutrophil infiltration and NLRP3 assembly. Collectively, our results demonstrate that Neferine inhibits NLRP3-related signaling pathway in macrophages by blocking macrophage and neutrophil infiltration and NLRP3 assembly, thus conferring protection against alcoholic steatohepatitis.

Keywords: Alcoholic steatohepatitis; Inflammatory response; Neferine

Extraction and isolation of ragweed root and determination of its anticancer activity

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Abstract:

Ragweed is an annual, widely distributed weed native to North America. It first invaded China in the 1930s and is now distributed in 17 provinces, including Beijing and Hebei. With the characteristics of wide adaptability, plasticity and competitiveness, it has a wide potential distribution area in China, and has caused great harm to our agricultural production, biodiversity and human health. Ragweed contains a variety of chemical components, mainly terpenoids, flavonoids, coumarins, etc., but little research has been done on the active substances of its roots, therefore, this experiment conducted a preliminary extraction of the active substances of ragweed roots and determined its antiproliferative activity against different cell lines, aiming to provide a reference for further in-depth research on the favorable value of ragweed deep this invasive species. Fourteen fractions were isolated by normal-phase silica gel column chromatography from the dichloromethane extract of the ethanolic extract of ragweed roots. Fr.P 3 showed good antiproliferative activity against human colon cancer cells SW620 cells, cervical cancer cells SiHa cells, and hepatocellular carcinoma cells BEL-7402 cells, which is to be further investigated in depth so as to isolate chemical constituents from ragweed root with good anticancer activity.

Keywords: Antitumor activity; Extraction and separation; Ragweed root

Methods:

(1) Drying and crushing of the collected roots of ragweed.

(2) Soaking in 80% ethanol and extracting with four organic solvents of different polarities.

(3) Separation of the dichloromethane extracted fraction.

(4) Pharmacological assay of the isolated constituents by MTT method to determine the antiproliferative activity of the crude extract against different cancer cells.

Table 1 The cell inhibitory rate (%) of extracts at 40 mg/L concentration

	Extraction condition	SW620	SiHa	Bel-7402
Fr.P 1	PE:EA=3:1	10.24	31.72	6.5
Fr.P 2	PE:EA=2:1	13.37	21.72	-13.96
Fr.P 3	PE:EA=1:1①	52.28	48.99	57.56
Fr.P 4	PE:EA=1:1②	14.42	32.41	7.14
Fr.P 5	PE:EA=1:1③	24.18	7.79	5.96
Fr.P 6	PE:EA=1:2	6.22	12.99	-10.37

DESIGN, SYNTHESIS AND ANTITUMOR ACTIVITY OF CDK4/PARP1 DUAL-TARGET INHIBITORS

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Abstract:

Research background: In the world, malignant tumors seriously affect people's health and life. At present, the main means of cancer treatment are surgery, radiotherapy, chemotherapy and targeted therapy, and targeted therapy is playing an increasingly important role in the treatment of malignant tumors. The malignant proliferation of tumor cells is controlled by a complex signal network, and the molecular mechanism of cell carcinogenesis has not been fully elucidated. Intervention of only one of these targets often fails to completely inhibit the proliferation of tumor cells due to the compensatory mechanism of the signal network, which is easy to produce drug resistance. Therefore, in recent years, it has been found that the effect of most single-target inhibitors in the treatment of malignant tumors is not significant, and long-term use is easy to cause insensitivity and drug resistance. There are two strategies to address this conundrum. The first is the combination of drugs, that is, the combination of multiple drugs for different targets, for example, the use of anti-VEGF monoclonal antibody immunomodulators combined with EGFR inhibitors (Erlotinib) for the treatment of non-small cell lung cancer is undergoing phase III clinical trials. However, although the combination of drugs has a high anti-tumor efficacy, there are also some problems, such as poor patient dependence, enhanced adverse reactions, difficult to predict pharmacokinetic characteristics, and drug interaction, which seriously affect the effectiveness of one or more drugs.The other is to design a multi-target tumor inhibitor by fusing two or more drugs or pharmacophore that act on different targets into the same molecule. It can simultaneously act on multiple molecular targets that control the proliferation, metabolism, apoptosis and metastasis of tumor cells, inhibit different cell pathways or compensatory mechanisms, and has a wide range of biological activities. It can overcome the resistance caused by the long-term use of single-target drugs and avoid drug interactions. Therefore, the

development of multi-target drugs has been considered as an effective way to discover new anticancer drugs and has a good development prospect.

CDKs is a key regulator of cell growth and division, and plays a key role in cell cycle regulation and transcriptional regulation. Ribociclib is a listed CDK4/6 inhibitor with IC50

values of 10 nM and 39 nM for CDK4/6, respectively. The docking data of Ribociclib and CDK4 (PDB:7SJ3) molecules show that, the 7H-pyrrolidine [2,3-d] pyrimidine structure binds to the catalytic site of CDK4 enzyme and has hydrogen bonding interaction with Val 96, which is the key pharmacophore of Ribociclib. The pyridine-3-piperazine structure is located in the solvent region of CDK4 enzyme and can be modified. PARP is a DNA repair enzyme that plays an important role in DNA damage repair. Olaparib is a marketed PARP inhibitor. The molecular docking data of Olaparib with PARP1 (PDB:5DS3) enzyme showed that the structure of phthalazinone was bound to the catalytic site of PARP1 enzyme, and it had hydrogen bonding interactions with Ser 904 and Gly 863. It has π - π interaction with Tyr 907 and Tyr 896, which is the key pharmacophophor of Olaparib, and the structure of cyclopropyl(piperazin-1-yl)methanone is in the solvent region of PARP1 kinase, which can be structurally modified. Furthermore, it has been shown that cell cycle progression determines PARP1 transcription via the growth factor/inhibitor-G1 /G0-CDK4/6-RBs axis, so dual target inhibition of CDK4 and PARP1 can synergically enhance anti-tumor activity and delay the development of drug resistance.

Research purpose: 1. Retain the key pharmacophore of Ribociclib and Olaparib in the active pockets of CDK4 and PARP1 respectively, and design and synthesize high-efficiency and low-toxicity dual-target inhibitors of CDK4 and PARP1 by replacing parts of the solvent region with different linkers. 2. To explore the effects of different Linker structures on the antitumor activity of target compounds.

Research methods: Based on the principle of computer-aided drug design and molecular fusion, three series of compounds were designed to synthesize target compounds through substitution reaction and condensation reaction, retaining the key pharmacophore of Ribociclib and Olaparib. ADP-GloTM method and ELISA method were used to detect the inhibitory effects of the target compounds on CDK4 and PARP1 enzyme activities at the molecular level. The inhibitory activities of the target compounds on SKOV-3, Hela, MDA- MB-231 and MCF-7 cell lines were determined by MTT method.

Experimental results: All the compounds were confirmed by 1H-NMR and 13C-NMR, and some compounds were confirmed by MS. In addition, the inhibitory activities of the target compounds against CDK4 and PARP1 enzymes at molecular level and SKOV-3 、Hela 、MDA-MB-231 and MCF-7 cell lines at cellular level were determined. The results

showed that some of the A series compounds had strong inhibitory effects on CDK4, PARP1 enzymes and four cell lines.The IC50 values of compound A14 against CDK4 and PARP1 were 4.3 ± 1.6 nM and 22.0 ± 8.5 nM, respectively. The activity of compound A14 against CDK4 was similar to that of Ribociclib, but its activity against PARP1 was slightly weaker than that of Olaparib. However, it had a strong inhibitory effect on SKOV-3 、Hela 、 MDA-MB-231 and MCF-7 cell lines, with IC50 values of 0.40 ±

0.02 、0.41 ± 0.01 、 0.51 ± 0.06 and 1.56 ± 0.16 μM, respectively. Its antitumor activity was significantly better than that of Ribociclib (IC50 SKOV-3 > 30 μM 、IC50 Hela = 12.74 ± 0.11 μM 、 IC50 MDA-MB-231 = 7.61 ± 4.08 μM 和 IC50 MCF-7 = 9.8 ± 1.09 μM) and Olaparib (IC50 > 30 μM).

Conclusion ： In this paper, we found an inhibitor A14 that is balanced and potent to CDK4 and PARP1, and is significantly superior to the listed drugs Ribociclib and Olaparib at the cellular level, which has the value of further research and development. This paper has a certain reference value for the design of CDK4 and PARP1 dual-target inhibitors.

Keywords: CDK4 and PARP1 dual target inhibitors; Linking groups; Structure-activity relationship

A New Method for the Analysis of Free DL-Amino Acids in Saliva of Diabetic Patients by Fluorescent Chiral Probe DBMA Targeting Amino Functional Groups

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Abstract:

Diabetes mellitus type 2 (T2DM) is a chronic progressive metabolic disorder with high prevalence, many complications and long course of disease. In recent years, metabolomics have found that there is a close relationship between amino acid levels in saliva and diabetes. Specific amino acids may be used as new biomarkers for the diagnosis of diabetes. Therefore, a new UPLC-FL method for 18 DL-amino acids was established and the chiral resolution efficiency was investigated based on new fluorescent chiral probe (R)-1-(7-(N,N-dimethylsulfamoyl)-benzo[c][1,2,5]oxadiazol-4-yl)-2-methylpyrrolidine-2-carboxylic acid (DBMA). The new method was used to detect the content of chiral amino acids and D/L ratio in saliva of diabetic patients and healthy volunteers.

In this study, Waters BEH C_{18} (2.1 × 100 mm, 1.7 μm) chromatographic column was used to detect and analyze chiral amino acids under the gradient elution of mobile phase 10 mM ammonium acetate-0.05% formic acid aqueous solution, 0.1% formic acid acetonitrile solution or 0.1% formic acid methanol solution. The 18 DL-amino acids labeled with DBMA can achieve good chiral resolution, and the resolution is between 1.51-4.40. The results of methodological investigation showed that the established analysis method was good. Finally, the new method was used to detect the difference of four amino acids (DL-Asp, DL-Thr, DL-Ile, DL-Lys) in saliva of 31 healthy volunteers and 19 diabetic patients. It was found that the average contents of D-Asp, DL-Thr, L-Ile and DL-Lys in saliva of diabetic patients were significantly higher than those of healthy volunteers ($p < 0.01$). The ratios of D/L-Asp, D/L-Thr and D/L-Lys were significantly different ($p < 0.01$). In this research, a novel fluorescent chiral probe DBMA for labeling amino functional groups was developed, which realized the effective separation of 18 DL-amino acids and applied to the screening of amino acid biomarkers in biological samples, providing a new chiral probe for the study of chiral metabolomics.

Keywords: DBMA; diabetes; saliva; DL-amino acid; fluorescent chiral probe

Analysis of Anti-depression Mechanism of Korean Medicine Qingxin Lianzi Decoction Based on Network Pharmacology

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Abstract:

To predict the major anti-depression active ingredients and related targets of Qingxin Lianzi Decoction (QXLZD) by network pharmacology, and to explore the anti-depression mechanism of QXLZD. The potential active ingredients and targets of twelve kinds of herbs in the decoction were predicted by TCMSP and screened by Swiss ADME. Make use of Cytoscape 3.7.2 software, human genome annotation database (Genecards) and Venny2.1.0 tool, the network diagram of components and targets of QXLZD was constructed, and the related targets of QXLZD anti-depression were obtained. String database and Cytoscape 3.7.2 software were used to determine the core anti-depression targets of QXLZD. DAVID database was used to analyze the signaling pathways and biological processes of anti-depression targets of QXLZD. A total of 132 active components with good oral absorption and drug-like properties were screened from QXLZD. There were 282 targets for these components, including 65 key anti-depression targets, mainly including ATK1, SRC, ESR1, TNF and other target genes. 185 anti-depression related signaling pathways were obtained, including neuroactive ligand-receptor interaction, pathways in cancer, metabolic pathways, etc. There were 649 related biological processes, including chemical synaptic transmission, dendrite biological processes, enzyme binding biological processes and so on. In this study, 132 anti-depression active components and 282 anti-depression targets were obtained, indicating QXLZD may play an anti-depression role through neuroactive ligand-receptor interaction and pathways in cancer.

Keywords:Qingxin Lianzi Decoction; Depression; Network Pharmacology

Mechanism of Maslinic acid Improving Non-alcoholic fatty liver disease by Tyloxapol through Nrf2 Signaling Pathway

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Abstract:

Objective: To study the mechanism of Maslinic acid (MA) improving Non-alcoholic fatty liver disease (NAFLD) through Nrf2 signaling pathway, which provided theoretical support for the treatment or prevention of NAFLD related diseases.

Results: In vivo experiments, the results of liver H&E, oil red O and Nile red staining showed that MA significantly improved the accumulation of lipid and inflammatory infiltration in mouse liver tissue induced by TY. Western-Blot showed that MA significantly down-regulated the expression levels of fatty acid synthesis related proteins (SREBP1c, FAS, SCD1 and Lipin1). Down-regulated Keap1 and Nrf2 protein expression levels in cytoplasm.

Conclusion: Maslinic acid may improve NAFLD in the liver of Tyloxapol mice through Nrf2 signaling pathways.

Keywords: Hyperlipidemia; Maslinic acid; Tyloxapol

Integrating Virtual Screening and In Vitro Validation to Analyze the Potential Therapeutic Effects of Platycodon grandiflorum Saponins in Sepsis

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Abstract:

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Platycodon grandiflorum (PG) is an edible and medicinal plant (EMP) widely used in Asia, known for its heat-clearing and detoxifying properties. However, the mechanisms by which PG treats sepsis remain to be elucidated. This study aims to predict and verify the biological mechanisms of PG in the treatment of sepsis. UPLC-Q-TOF-MS was employed to analyze the saponin components in Platycodon grandiflorum. A network pharmacology approach was used to construct a protein-protein interaction (PPI) network, followed by KEGG and GO analyses to build a "active component-target-pathway" network for the treatment of sepsis by Platycodon grandiflorum saponins (PGS). Molecular docking and dynamic simulation were used to analyze the binding of PGS active components with key targets. Through network pharmacology, it was found that proteins such as STAT3, JUN, and PRKCA were significantly associated with PGS treatment of sepsis. Lipopolysaccharide (LPS) was used to establish a cell model for in vitro experimental validation. Our findings suggest that PGS can partially reverse LPS-induced expression of STAT3 and NF-κBp65 proteins, inhibit M1 macrophage polarization, and improve the inflammatory environment. This study provides a foundation for understanding the potential mechanisms of PGS in the treatment of sepsis.

Keywords: Sepsis; Platycodon saponins; Network pharmacology; NF-κB; Macrophage polarization.

Erianin Alleviates Atopic dermatitis by Regulating Mitophagy and Mitochondrial Apoptosis

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Abstract

The purpose of our study was to demonstrate the effectiveness of Erianin on TNF-α-stimulated HaCaT cells and on DNCB-induced AD mice , respectively. Measurements were taken for skin thinkness and the weights of the spleen and lymphnodes were measured, the back skin and ear tissues were stained with toluidine blue and H&E, inflammatory factors were detected by flow cytometry and ELISA, and tissue and cell apoptosis were detected by TUNEL. Immunohistochemistry, Immunofluorescence and Western Blot were also used to detect the expression of relevant proteins. Reactive oxygen species (ROS), mitochondrial reactive oxygen species (mtROS) and JC-1 kit were used to detect ROS, mtROS and mitochondrial membrane potential (MMP). we showed that Erianin was able to significantly inhibit the ROS, mtROS and promote the production of MMP in TNF-α-stimulated HaCaT cells in vitro.In vivo , Erianin significantly improved the symptoms of DNCB-induced AD skin thickness, decrease lymphnode and spleen index, improve inflammatory cells and mast cell infiltration . Moreover, it was also able to enchanced the expression of B-cell lymphoma-2 (Bcl-2) and suppressed the expression levels of Bcl-2-associated X (Bax), Cleaved-Caspase3, PTEN induced putative kinase 1 (PINK1) and Parkin in vivo and vitro expression.Conclusively, Erianin has anti-inflammation and potential by reducing mitophagy and mitochondrial apoptosis .

Key words: Erianin; atopic dermatitis;mitophagy; mitochondrial apoptosis

Platycodin D Inhibits NLRP3 Inflammasome Activation via Zinc Finger Protein 91 to Ameliorate Acute Gout in Mice

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Abstract:

Background: Platycodin D (PLD), a pentacyclic triterpenoid saponin derived from the traditional Chinese medicinal herb Platycodon grandiflorum, is recognized as one of its principal bioactive components. PLD has demonstrated significant anti-inflammatory properties. Zinc finger protein 91 (ZFP91) is considered a potential pharmacological target in the treatment of inflammation, infections, and autoimmune disorders. However, the precise molecular mechanisms underlying the anti-inflammatory effects of PLD via modulation of ZFP91 remain unclear.

Objective: Previous studies have shown that PLD exhibits inhibitory effects on the activation of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome. The objective of this study is to elucidate the molecular mechanisms by which PLD inhibits ZFP91-mediated inflammatory responses during lipopolysaccharide (LPS)/ATP-induced pyroptosis in J774A.1 macrophages, and to explore its therapeutic potential in a mouse model of monosodium urate (MSU) crystal-induced acute gout.

Results: PLD significantly inhibited cellular pyroptosis, IL-1β secretion, and oxidative stress in macrophages in a dose-dependent manner. Furthermore, PLD markedly reduced ankle swelling and suppressed the secretion of IL-1β, IL-6, and TNF-α in the gout mouse model. Overall, PLD exhibited anti-inflammatory effects by targeting ZFP91, thereby inhibiting cell death and modulating the expression and assembly of NLRP3 inflammasome-associated proteins.

Conclusion: The results indicate that PLD inhibits NLRP3 inflammasome activation by targeting ZFP91, thereby mitigating LPS-induced macrophage pyroptosis and acute gout induced by monosodium urate (MSU) in mice. This study highlights PLD as a promising therapeutic candidate for the treatment of inflammatory diseases associated with NLRP3 inflammasome activation.

Keywords: Platycodin D; NLRP3; ZFP91; Acute Gout

Preparation of submicroemulsion of the active components of T. gondii. Ligusticum sinense Oliv.,L. sinense.and its anti-Toxoplasma gondii effects

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Abstract:

Object: The objective of this study was to investigate the anti-infective effects of the natural drug *Ligusticum sinense* Oliv., *L.sinense*（*L.sinense*）against *Toxoplasma gondii*（*T.gondii*） and to prepare sub-microemulsions of its active ingredients with the aim of improving the stability of the drug and enhancing its anti-*T.gondii* effect. **Methods:** The ten compounds were successfully isolated using a variety of methods, including extraction, separation, and mass spectrometry. The cytotoxicity and anti-*T.gondii* selectivity of the samples were determined using the MTT method, and potential targets for the treatment of Toxoplasmosis were identified through network pharmacology. **Result:** The main active components of *L.sinense* and their potential mechanisms of anti-*T.gondii* action were analysed using network pharmacology, and six small molecule drug active components and 31 core targets were identified. Of these, 18 were found to be common to *T.gondii*, indicating that *L. sinense* species contain active substances with anti-*T.gondii* properties. The principal pharmacological active ingredient, Z-ligustilide, was identified in *L.sinense* and selected as the primary drug. The optimal formulation was then determined through the use of a pseudo-ternary phase diagram, which involved the use of Tween 80, anhydrous ethanol, castor oil, Z-ligustilide, and deionized water in a ratio of 3:1:6:0.4:4. The resulting sub-microemulsions were obtained through high-speed shearing. **Conclusion:** In this paper, we present the preliminary findings of a network pharmacological investigation into the mechanism of action of *L. sinense* in the treatment of toxoplasmosis. In order to enhance the safety and stability of the main active ingredient, Z-ligustilide, it was prepared into a sub-microemulsion preparation. The anti-toxoplasmosis activity of Z-ligustilide and its sub-microemulsion was demonstrated through an MTT experiment. This study enhanced our comprehension of the chemical composition of *L.sinense* and furnished a dependable theoretical foundation for the advancement and application of *L.sinense* .

Keywords: *Ligusticum sinense Oliv.*; Content determination; Sub-microemulsion; Resistance to toxoplasma; Network pharmacology

Study on the protective effect of Rebamipide hollow adhesive microspheres on gastric mucosal injury

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Abstract:

Objective: Rebamipide is an active, bi-directional bioregulatory gastric mucosal protector, which is commonly used clinically for the treatment of gastric ulcer, acute gastritis, acute exacerbation of chronic gastritis and other digestive disorders [1], but it belongs to the low solubility and low osmolality of class IV drugs, which is absorbed into the bloodstream mainly in the stomach and the duodenum, with a narrow window of absorption, and it also has problems such as low oral bioavailability and a short half-life, which These problems have seriously affected its clinical application [2]. Floating adhesive synergistic intragastric retention drug delivery system can make the drug stay in the stomach for a longer period of time, increase the absorption of the drug in the upper part of the gastrointestinal tract, improve the bioavailability, enhance the efficacy of the drug, and realise the intragastric targeted drug delivery [3-6]. The purpose of this study is to develop hollow adhesive microspheres loaded with Rebamipide, which can improve the oral bioavailability of Rebamipide by prolonging the retention and absorption time of Rebamipide in gastric target organs, so that the drug can have a long-term therapeutic concentration in gastric ulcer lesions and promote the rapid healing of gastric ulcer.

Methods: In this experiment, Rebamipide was used as a model drug, and the hollow microspheres were prepared by emulsification solvent evaporation technology, and then the hollow adhesive microspheres were prepared by coating glyceryl monooleate by dipping glue method. The preparation process of microspheres was determined by single factor investigation of reaction temperature, stirring speed and curing time. Single factor investigation and Box-Behnken design were used to optimize the dosage, polymer mass ratio, organic solvent volume and polyvinyl alcohol concentration, so as to determine the optimal formulation of microspheres. Then, the hollow microspheres were coated with petroleum ether solutions of glycerol monooleate with different concentrations, and the concentration of the coating solution was screened by using the coating weight gain and in vitro adhesion as evaluation indexes. The quality of microspheres was evaluated by investigating the appearance, powder characteristics, drug release under different PH media, compatibility and stability of drugs and excipients. The gastric retention effect of Rebamipide hollow adhesive microspheres in vivo was investigated by the number of gastric retention microspheres and near infrared small animal in vivo imaging technology. The plasma drug concentration was determined by HPLC to evaluate the pharmacokinetic parameters of Rebamipide hollow

adhesive microspheres in rats. In the safety experiment, the safety in vivo was analysed by investigating the body weight, histopathology and biochemical indexes of rats. The rat model of gastric ulcer was established, and the serum, gastric biochemical indexes and histopathological analysis indexes were tested after treatment to evaluate the protective effect of gastric mucosa in vivo and the safety of treatment.

Results: The hollow adhesive microspheres of Rebamipide are milky white spheres with a round appearance, with an average diameter of 768.47 ± 2. 86 μm, an encapsulation efficiency of 82.88 ± 3. 29%, a drug loading of 10.35 ± 0. 45%, and a yield of 71.33 ± 2. 11%. The percentage of in vitro floating at 8 h was 84.32 ± 2. 21%, and the percentage of in vitro adhesion in rabbit gastric mucosa and rat gastric mucosa were 95.67 ± 4. 16% and 93.67 ± 4. 51%, respectively. Through powder evaluation, it is shown that the density of microspheres is less than that of gastric juice, and the fluidity and formability of microspheres are good. Through in vitro release experiments, it is proved that the dissolution rate of microspheres in the dissolution medium of artificial gastric juice conforms to Weibull equation, and it has certain sustained release characteristics. FT-IR and DSC results indicate that Rebamipide is well compatible with the excipients. In vivo intragastric retention results showed that Rebamipide hollow adhesive microspheres could prolong the retention time in the stomach. The results of pharmacokinetic studies indicate that the bioavailability of Rebamipide hollow adhesive microspheres is approximately 2.26 times greater than that of regular Rebamipide tablets, maintaining therapeutic concentrations for long periods of time. The results of safety experiments show that taking Rebamipide hollow microspheres will not cause obvious damage to stomach and major organs, indicating the safety of long-term use of microspheres. Pathological results showed that Rebamipide hollow adhesive microspheres had good preventive and therapeutic effects on gastric mucosal injury, and its treatment would not damage other organs.

Conclusion: The developed hollow adhesive microspheres of Rebamipide have obvious sustained-release effect, significantly prolong the residence time of the drug in the stomach, improve the relative bioavailability of Rebamipide, and maintain the therapeutic concentration in the lesion of gastric ulcer for a long time, thereby improving the therapeutic effect of gastric ulcer. Therefore, the hollow adhesive microspheres loaded with Rebamipide prepared in this study have a good application prospect in the treatment of gastric ulcer.

Keywords: Synergistic intragastric retention drug delivery system; Rebamipide; In vitro adhesion; Pharmacokinetics; Gastric mucosal injury

海参硫酸化多糖的抗肿瘤作用研究进展

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摘要：

海参是我国传统保健食品，具有极高的营养及药用价值。海参多糖是海参的重要活性成分之一，以硫酸化多糖为主，包括岩藻糖化硫酸软骨素和硫酸岩藻聚糖。岩藻糖化硫酸软骨素是由D-乙酰氨基半乳糖、D-葡萄糖醛酸和L-岩藻糖组成的分支杂多糖，其相对分子质量多在40000-50000；而硫酸岩藻聚糖是由L-岩藻糖构成的直链匀多糖，相对分子质量多在80000-100000。海参多糖具有免疫调节、抗肿瘤、抗凝血、抗炎、降血糖、降血脂、抗氧化等多种生物活性，而其抗肿瘤作用是近年来研究最多的。为了更全面地了解和梳理海参硫酸化多糖的抗肿瘤活性，本文综述了近年来国内外有关海参硫酸化多糖抗肿瘤活性的最新研究成果，同时针对海参硫酸化多糖抗肿瘤的前景以及存在的一些问题进行探讨。海参硫酸化多糖的具体抗肿瘤机制大致可以分为阻滞细胞周期和促进细胞凋亡、阻碍细胞核酸的合成、抑制细胞增殖及促进细胞分化、抑制新生血管、调节免疫活性等多个方面。大量研究表明，海参硫酸化多糖作为一种天然高分子化合物对不同的肿瘤（如乳腺癌、宫颈癌、胃癌、肺癌和肝癌等）都有一定的抑制作用。

然而海参硫酸化多糖抗肿瘤活性的构效关系研究仍处于初步阶段，这严重阻碍了海参硫酸化多糖的临床应用。进一步系统解析海参硫酸化多糖的精细结构，有助于明确海参硫酸化多糖的结构与其生物学活性关系，探索新的抗肿瘤机制，进而有针对性地开发相关的海洋功能性食品或药品。

关键词：海参；硫酸化多糖；抗肿瘤；构效关系

Optimization of ultrasound-assisted two-phase deep eutectic solvents extraction of bioactive extracts from *Radix Paeoniae* Alba and evaluation of the extracts against cerebral ischemic/ reperfusion injury

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Abstract:

To develop an environmentally sustainable and efficient extraction method for bioactive extracts from *Radix Paeoniae* Alba, two-phase deep eutectic solvents (TDES) with ultrasound-assisted extraction were utilized in this study. The TDES were developed with 28 deep eutectic solvents and aqueous solutions of the choline chloride + glycerol + betaine + benzyl alcohol were selected, considering their protective effects on PC12 cells. The optimal extraction conditions that had better protective effect were determined to be 50 ℃ for extraction temperature, 250 W for ultrasonic power, 20 min for extraction time, 40 mL/g for solvent to solid ratio, leading to the highest cell viability of PC12 cells. These results not only suggested that ultrasound-assisted TDES extraction is an effective method to enhance the neuroprotectivity of extraction from Radix Paeoniae Alba, but also established a foundation for further investigation into the potential medical value of Radix Paeoniae Alba.

Keywords: Deep eutectic solvent; Ultrasonic-assisted extraction; Radix Paeoniae Alba; Ischemic/ reperfusion injury

Synthesis of amide derivatives containing indazole and HPK1 inhibitory activity

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Abstract:

Hematopoietic progenitor cell kinase 1 (Hematopoietic progenitorkinase 1, HPK1), also known as MAP4K1, is one of the members of the MAP4K family and belongs to the category of mammalian STE20-like protein serine/threonine kinases. It is a negative regulator of immune responses mediated by T cells, B cells, and dendritic cells and is mainly expressed in hematopoietic lineage cells. In recent years, there has been increasing evidence that HPK1 is a promising target for cancer immunotherapy, and to date, no small-molecule inhibitor drugs of HPK1 have been approved for clinical use. In this study, a series of novel amide derivatives containing indazole structures were designed and synthesized, and their inhibitory activity against HPK1 kinase was evaluated. In the ADP-Glo kinase experiment, most of the differentiated organisms had strong inhibitory effects on HPK1 kinase. The IC_{50} of compounds **Y23**, **Y24**, **Y25**, **Y26**, and **Y27** inhibiting HPK1 kinase activity were 64.08 nM, 66.58 nM, 53.68 nM, 29.39 nM, and 42.54 nM, respectively. Because GLK and HPK1 have high sequence homology, they play opposite roles in immune cell signal transduction. Therefore, we further evaluated the inhibitory activity of compound **Y26** against GLK kinase. In the detection of ADP-Glo kinase, the selectivity of **Y26** to HPK1 was 1.8 times that of GLK, and further modifications will be made to improve the selectivity of the compound to GLK in the future. In summary, this study provides ideas for further designing and synthesizing safe and effective HPK1 inhibitors for cancer immunotherapy.

Keywords: HPK1，Kinase inhibitor，Tumor immunotherapy，Selectivity

Optimization of flash extraction process of Agrimonia Pilosa total flavonoids and antibacterial and anti-inflammatory activities of the extract

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Abstract:

To optimize a flash extraction process of *Agrimonia Pilos*a total flavonoids,the whole plants of *A.pilosa* were used as the experimental material to investigate the optimization conditions of flash extraction by controlling the extract time, liquid to material ratio,and solvent(methanol) concentration,using the total flavonoid content as the evaluation index. The results showed that the highest total flavonoid content reached 94.25 mg/g when the extraction time was 41.09 s, the extract liquid to material ratio was 40.19:1(mL:g),and the extraction solvent concentration was 4l.37%.Furthermore, the antibacterial and anti-inflammatory activities were investigated to use the extract of *A. pilosa* for the application in the production of products. The results of the antibacterial activity showed that the extract obviously inhibited the growth of six tested pathogenic bacteria, amomg which the highest antibacterial activity was observed against *Bacillus cereus*, with the minimum inhibitory concentration of 4 mg/mL. In the anti-inflammatory experiment,a lipopolysaccharide(LPS)-induced mouse monocyte-macrophage(Raw264.7) inflammation model was established,and the effects of the extract on levels of inflammatory mediators,i.e.,NO,iNOS,and COX-2,were investigated.The results showed that after treatment with the extract, the LPS-induced inflammatory mediators in Raw 264.7 cells decreased in a dose-dependent manner.The findings of this study provided theoretical basis for the further development and use of *A.Pilosa*.

Keywords: Total flavonoids of Agrimonia pilosa; flash extraction; bacteriostatic activity; inflammatory factors

β-caryophyllene, a phytochemical food additive, ameliorates alcoholic steatohepatitis via improving inflammation and lipid metabolism in mice

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Abstract:

Alcoholic steatohepatitis (ASH) represents the excessive lipid accumulation and inflammatory infiltration in the spectrum of Alcohol-associated liver disease (ALD). However, there is no FDA-approved drugs for the treatment of ALD. Our study demonstrated that β-caryophyllene (BCP), a natural dietary sesquiterpene, alleviated lipid accumulation and inflammatory response in ASH. BCP modulated sterol-regulatory element binding protein 1 (SREBP1) and Peroxisome proliferator-activated receptor α (PPARα) expression in AML12 cells and inhibited the expression of Toll-like receptor 4 (TLR4), Purinergic ligand-gated ion channel 7 receptor (P2X7R), Nucleotide-binding domain-(NOD-) like receptor protein 3 (NLRP3) inflammasome and production of inflammatory cytokines in mouse peritoneal macrophages (MPMs). In the mouse model of chronic-binge ethanol feeding, BCP reduced liver damage, on account of diminishing lipid accumulation, macrophages and neutrophils infiltration and subsequent releasement of inflammatory cytokines as well as neutrophil extracellular traps (NETs). Our study identified the therapeutic effect of BCP on lipid accumulation and inflammatory response in vivo and in vitro, provided new option for dietary supplementation or clinical drug candidates against ASH.

Keywords: Alcoholic steatohepatitis; β-caryophyllene; Lipid accumulation; Inflammation.

Exploring the treatment of allergic rhinitis with Mahuang Dingchuan Decoction based on network pharmacology

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Abstract:

Objectives: Allergic rhinitis is a common disease of the upper respiratory tract, which is a non-infectious inflammatory disease of the nasal mucosa with the release of mediators mainly mediated by IgE and the participation of various immunoreactive cells and cytokines after exposure to allergens in atopic individuals. It has been proved that Mahuang Dingchuan Decoction can treat allergic rhinitis, so this paper mainly used to explore the mechanism of action of Mahuang Dingchuan Decoction via other targets for the treatment of allergic rhinitis through network pharmacology. Methods: The TCMSP database was used to obtain the components and targets of Mahuang Dingchuan Decoction, the Gen eCards, OMIM, TTD, and DrugBank databases were used to obtain the allergic rhinitis targets, and the Metascape platform was used to conduct the pathway enrichment analysis, and the "Mahuang Dingchuan Decoction Components - Allergic Rhinitis Targets" network was constructed by Cytoscape 3.9.0 software. Cytoscape 3.9.0 was used to construct the "Mahuang Dingchuan Decoction Ingredients-Allergic Rhinitis Targets" network to determine whether the key targets could be combined with the important active ingredients in Mahuang Dingchuan Decoction to play a role. Results: A total of 814 targets corresponding to the active ingredients of Mahuang Dingchuan Decoction were obtained. A total of 1121 allergic rhinitis-related disease-causing targets were obtained, and 156 targets for the treatment of allergic rhinitis were identified in Mahuang Dingchuan Decoction. Among these 156 targets, 4 targets with strong interactions were identified by protein interaction network analysis. These 4 targets included IL6, PI3K, STAT3, and AKT.Conclusion:Based on the network pharmacology approach, this study investigated the mechanism of action of Mahuang Dingchuan Decoction in the treatment of allergic rhinitis by reducing the expression levels of IL6, PI3K, STAT3, and AKT in the nasal mucosa of the allergic rhinitis model mice to inhibit the inflammation and provide potential targets for the treatment of allergic rhinitis, and provided potential targets for the study of the treatment of allergic rhinitis. It provides a new direction for the study of the mechanism of treatment of allergic rhinitis by Mahuang Dingchuan Decoction.

Key words: allergic rhinitis, network pharmacology, Mahuang Dingchuan Decoction

The Molecular Mechanisms of Caulophyllum Robustum Maxim Extract Inhibition by Regulating FAK/PI3K Signaling Pathway in Gastric Cancer HGC-27 Cells

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Abstract:

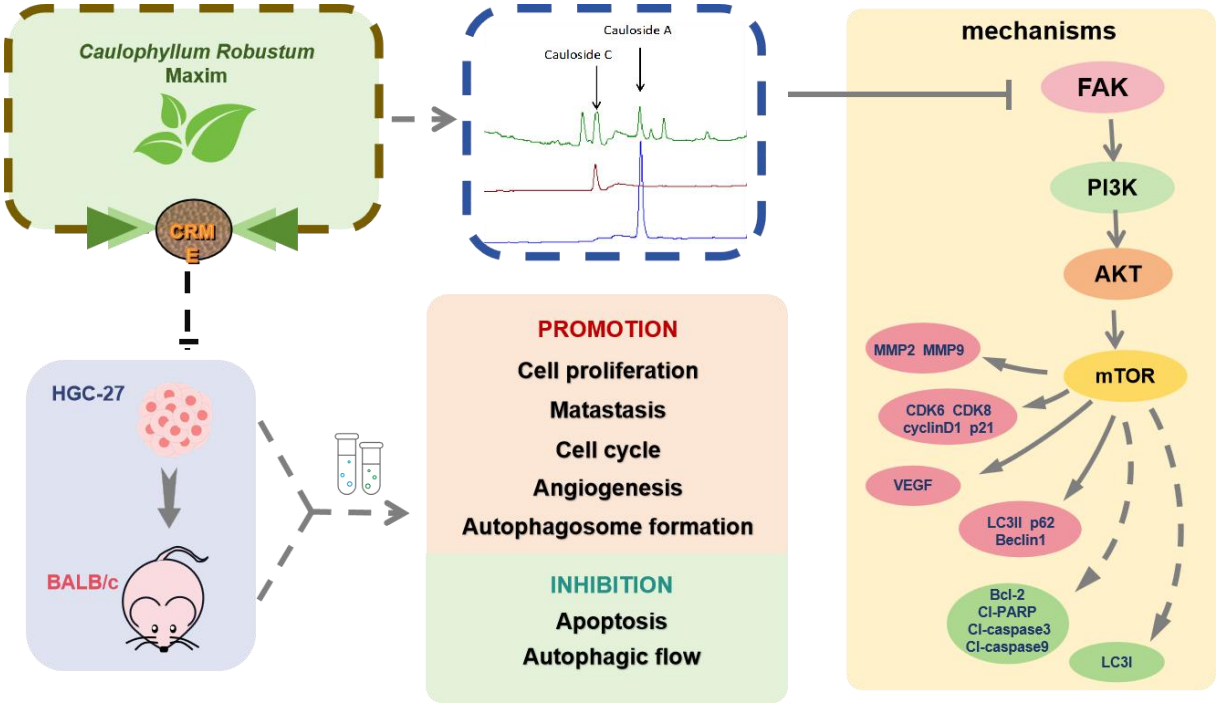
Ethnopharmacological relevance: *Caulophyllum Robustum* Maxim Extract (CRME), as recorded in traditional Chinese medicine, has the function of dispelling Feng, regulating Qi and dredging collaterals, promoting blood circulation and regulating menstruation, gingering up and relieving pain, clearing heat simultaneously detoxifying, lowering blood pressure and hemostasis. CRME is often used as Chinese materia medica preparation for rheumatoid arthritis, traumatic injury, irregular menstruation, abdominal pain, and hypertension treatment. Since gastric cancer (GC) existed as a health problem of human over the years, we are committed to the development of potential components of Chinese herbal medicine curing cancer, and we found CRME is expected to be one of the effective anti-tumor traditional Chinese medicine preparations.

Aims of the study: To investigate the molecular mechanisms of CRME anticancer effects and the potential links between CRME and FAK.

Results: CRME can significantly inhibit HGC-27 cells on proliferation, migration and angiogenic capacity. Xenograft model indicated CRME inhibited cell proliferation in vivo. Annexin V-FITC/PI double staining assay and PI single staining assay depicted that CRME induces cell apoptosis, and arrests cell cycle at G0/G1 phase. AO (acridine orange) staining assay showed that CRME promoted autophagosome formation and inhibited autophagic flow. HPLC indicated Cauloside A and Cauloside C are components of CRME. Western blot indicated that FAK/PI3K signaling pathway is critical in the inhibition of CRME on HGC-27 cells.

Conclusions: The anti-tumor components of CRME, Cauloside A and Cauloside C, inhibited tumor progression in HGC-27 cells. This inhibition is achieved by decreasing the phosphorylation levels of FAK, thereby modulating PI3K/AKT signaling pathway.

Keywords: gastric cancer; *Caulophyllum robustum* Maxim; angiogenesis; FAK; PI3K/AKT signaling pathway


Caulophyllum Robustum
Maxim
CRME
Cauloside A
Cauloside C
HGC-27
BALB/c
PROMOTION
Cell proliferation
Matastasis
Cell cycle
Angiogenesis
Autophagosome formation
INHIBITION
Apoptosis
Autophagic flow
mechanisms
FAK
PI3K
AKT
mTOR
MMP2 MMP9
CDK6 CDK8
cyclinD1 p21
VEGF
LC3II p62
Beclin1
Bcl-2
Cl-PARP
Cl-caspase3
Cl-caspase9
LC3I

Metabolomics Study of Intrahepatic Cholangiocarcinoma Based on Mass Spectrometry Technology

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Abstract:

Intrahepatic cholangiocarcinoma (ICC) is a malignant tumor originating from the epithelial cells of the bile ducts, with an increasing incidence rate. It ranks second among liver diseases, following hepatocellular carcinoma, characterized by high malignancy, and a median survival time of only 18-24 months, with a three-year survival rate that is low. The primary treatment method is surgical, with poor prognosis, difficulty in cure, and short postoperative survival time. According to the latest 2010 standards, ICC has been excluded from primary liver cancer and, together with perihilar cholangiocarcinoma (pCCA) and distal cholangiocarcinoma (dCCA), forms the category of cholangiocarcinoma. Currently, the pathogenesis of ICC is not well understood, and there is a lack of effective early diagnostic methods and treatment options. Spatial metabolomics, an emerging omics technology based on mass spectrometry imaging and metabolomics, detects the molecular structure, spatial distribution, and content changes of endogenous small molecules and exogenous drug metabolites in situ within biological systems, accurately reflecting the metabolic network changes of metabolites in the tissue as a whole or in micro-regions. It has been widely used in the search for disease biomarkers and the elucidation of disease pathogenesis and pharmacodynamic mechanisms. Mass spectrometry is a highly sensitive and high-resolution detection method that can be used to analyze small organic molecules and metabolic products in biological samples. Metabolomics studies the changes in metabolic products after organisms are stimulated or disturbed to reveal the metabolic processes and regulatory mechanisms of organisms. Combining mass spectrometry technology with metabolomics research can provide insights into the pathogenesis, diagnostic markers, and therapeutic targets of ICC, offering new perspectives and methods for the prevention, diagnosis, and treatment of ICC. Therefore, conducting metabolomics research on ICC has significant practical importance and clinical value. This study will use a combination of metabolomics and mass spectrometry imaging to identify spatial differences in metabolites in ICC and to explore the impact of related metabolic enzymes on intrahepatic cholangiocarcinoma through differential metabolic networks in different liver regions. This can provide a deeper understanding of the pathogenesis, diagnostic markers, and therapeutic targets of ICC, offering new insights and methods for the prevention, diagnosis, and treatment of ICC.

Keywords: Mass Spectrometry Imaging; Metabolomics; Intrahepatic Cholangiocarcinoma

Construction of a New Method for Dynamic Detection of Chiral Mercaptan Compounds in Human Urine Labeled with Different Oxidative Stress States Based on N^{13}CS-OTPP Mass Spectrometry Probe

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Abstract:

Monitoring the changes in the content of chiral mercaptan compounds in human body is crucial for the early diagnosis and pathogenesis of oxidative stress-related diseases. To solve this problem, we synthesized a new isotope mass spectrometry (MS) probe, denoted as (R)-(5-(3-isothiocyanyl (C) pyrrolidine - 1-yl) -5-oxo-amyl) Triphenylphosphine (N^{13}CS-OTPP). In addition, we developed a new ultra-high performance liquid chromatography-High resolution mass spectrometry (UHPLC-HRMS) relative quantitative method for monitoring chiral mercaptan compounds in human urine under different oxidative stress conditions.

First, to evaluate the chiral separation efficiency of N^{13}CS-OTPP, we used three types of thiol compound (DL-GSH, DL-Cys, and D/ L-Hcy) as templates, and observed degrees of separation (Rs) ranging from 1.82 to 1.89. In addition, D/L-Cys was used as the model compound to further verify the accuracy and feasibility of the relative quantitative method. $N^{12}C^{13}$/CS OTPP Cys showed a good linear relationship (R^2=0.9993-0.9994) at different molar ratios (D/L-Cys=10:1, 4:1, 2:1, 1:1, 1:2, 1:4, 1:10) and achieved a low detection limit of 2.5 fmol. Then, we monitored the dynamic changes in urine D/L-Cys and D/L-Hcy ratios in 12 healthy volunteers (6 men and 6 women) under various oxidative stress states to study trends in chiral mercaptan compounds in vivo based on fitted curves.

This study presents a new method for relatively quantitative monitoring of chiral thiol compounds in different oxidative stress states in human body, and also provides a new strategy for understanding the pathogenesis of related diseases caused by abnormal mercaptan metabolization.

Key words: Relative quantification; Chiral mercaptan compounds; Isotope labeling; N^{13}CS-OTPP; UHPLC-HRMS

Research on the Mechanism of Inhibiting Prostate Cancer by Ginsenoside RG3 Combined with Near-Infrared Photothermal Therapy

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Abstract:

The aim of this study was to investigate the inhibitory effect of ginsenoside RG3 combined with near-infrared light hyperthermia on prostate cancer evolution and its potential mechanism. Through in vitro experiments, we found that the combination of ginsenoside RG3 and near-infrared light could significantly inhibit the proliferation, migration, angiogenesis, epithelial-mesenchymal transition, and induce apoptosis of prostate cancer cells compared with the treatment group alone. This effect may be related to its inhibition of the activation of the Ras/Raf/MEK/ERK signaling pathway. Notably, under conditions of co-culture with THP-1 cells, the combination treatment group induced M1 polarization and reversed M2 polarization in macrophages. In the in vivo experiments, we divided the prostate cancer mouse model into a control group, a NIR photothermal therapy group, a ginsenoside RG3 group, and a combination therapy group. The results showed that tumor growth was significantly inhibited in the combined treatment group, and there was no significant change in the body weight of the mice. In conclusion, our results suggest that ginsenoside RG3 combined with near-infrared photothermal therapy may be an effective strategy for the treatment of prostate cancer, and has important clinical applications.

Keyword:Prostate Cancer;Ginsenoside RG3;NIR

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Chemical constituents from Acanthopanax sessiliflorus and their cytotoxic activities against human cancer cell lines

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Abstract:

Acanthopanax sessiliflorus (Rupr. et Maxim.) Seem. is a shrub mainly present in northeastern China, Japan and Korea, the root bark of which is considered as one of the sources of "wu-jia-pi" and widely used for dispelling rheumatism, reinforcing kidney, strengthening bones and promoting blood circulation based on the Chinese Chaoxian traditional folk medicine. Modern pharmacological studies have shown that *A. sessiliflorus* possessed various pharmacological actions such as anti-inflammatory analgesic activity, anti-tumor and immunostimulating activities, etc. Our previous study has shown that *A. sessiliflorus* exhibited both antithrombotic and antiplatelet activities *in vivo* on rats. In our search, 10 compounds were isolated from the EtOAc fration of the stem bark of *A. sessiliflorus*, including known compounds (**1**-**10**). Their structures were identified to be oleanolic acid (**1**), ursolic acid (**2**), betulinic acid (**3**), 3-oxo-22*α*-hydroxy-olean-12-en-28-oic acid (**4**), 22*α*-hydroxyoleanolic acid (**5**), 28-O-*β*-D-glucopyranosyl pomolic acid (**6**), (-)-hinokinin (**7**), (+)-sesamin (**8**), quercetin (**9**), naringin (**10**). The seven compounds **3**–**7**, and **10** were isolated from *A. sessiliflorus* for the first time. The cytotoxic activities of the isolated compounds 1-4 were evaluated by determining their inhibitory effects on cultured human nonsmall cell lung cancer (NCI-H460), human hepatoblastoma (Hep G2) and human gastric carcinoma (MKN-28) cell lines using the MTT bioassay(**Table 1**). Compound **1**-**10** exhibited significant cytotoxicity towards NCI-H460, Hep G2 and MKN-28 cell lines with IC_{50} values ranging from 12.65 to 97.07 μM.

Keywords: *Acanthopanax sessiliflorus*, cytotoxic activities, Chinese Chaoxian traditional folk medicine

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Application of Human Sweat DL- Lactic Acid Dry Paper Method (DSSP) in Early Warning of Diabetes Mellitus

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Abstract:

Sweat has the advantages of non-invasive sampling and low risk of infection, which a new and potential biological sample for disease diagnosis. However, the analysis of DL-lactic acid (DL-LA) in sweat and its relationship with diabetes have not been reported. In order to realize the trace analysis of DL-LA in sweat, a new mass spectrometry probe N-[1-OXO-5-(triphenylphosphonium) Pentyl]-(S)-3-aminopyrrolidine (OTPA) was developed. Based on the probe combined with dry spot sampling technology, a new quantitative method of ultra-high performance liquid chromatography-mass spectrometry was established, it was used for quantitative analysis of DL-LA in sweat of healthy volunteers and diabetic patients.

In order to evaluate the chiral separation efficiency of OTPA, the chiral resolution efficiency was investigated by DL-LA standard. The resolution (Rs) is 1.78, the derivatives can be completely separated on C_{18} column. The linear relationship between D-LA and L-LA is good in the range of 0.002-1 mM and 0.16-80 mM ($R^2 \geq 0.9996$). The precision range is 0.11-10.18%, and the minimum detection limit (S/N=3) is 20.83 fmol. In addition, the content of DL-LA in sweat of 22 healthy volunteers and 18 diabetic patients was monitored and the proportion difference among different configurations was analyzed. The correlation ($r=0.7744$, $p < 0.0001$) between the D/L ratio of lactic acid in human sweat and fasting blood glucose (FPG) in healthy volunteers and diabetic patients was verified.

In this study, a new UHPLC-MS/MS method for chiral resolution and detection of DL-LA in human sweat based on OTPA pre-column derivatization was introduced. It provides a new strategy for early warning, screening and low-invasive monitoring of diabetes and related complications.

Key words: Lactic acid enantiomer; Sweat dry paper method; Pre-column derivatization; OTPA; UHPLC-MS/MS

MECHANISM OF ACACETIN AMELIORATING LIVER INJURY BY ACETAMINOPHEN

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Abstract:

Acacetin, As a natural product component in medicinal herbs,it extract has the characteristics of low cytotoxicity, wide pharmacological activity, and convenient source. The purpose of this study was to investigate the mechanism of ACA on liver injury induced by Acetaminophen (APAP), to provide a theoretical basis for the development of new drugs for the prevention or treatment of drug-induced liver injury (DILI) by using ACAIn the future, which provided theoretical support for the treatment or prevention of AILI and related hyperlipidemia diseases People are increasingly paying attention to finding effective active ingredients for treating diseases from natural products.

Method: Thirty-six 6-week-old male C57BL/6J mice were randomly divided into 6 groups: normal group (CON), ACA Alone group (ACA: ACA 20 mg/kg),APAP model group (AP: 350 mg/kg APAP), ACA High dose group (ACH: APAP 350 mg/kg + ACA 20 mg/kg), ACA Low dose group (ACL: APAP 350 mg/kg + ACA 10 mg/kg) and N-acetylcysteine (NAC) positive drug control group (AN: APAP 350 mg/kg+NAC 200 mg/kg). After fasting for 12 h, given each group mice corresponding dose of drugs by gavage. Two hours later, 300 mg/kg of APAP were injected to establish a pattern of liver damage in mice. 24 hours later, the mice were sacrificed, blood and liver tissue were drawn for follow-up testing. Using corresponding kits tested the levels of Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) in blood and levels of Malondialdehyde (MDA), Superoxide dismutase (SOD) and Glutathione (GSH) in liver tissue ,H&E staining observe the histopathological changes in the liver tissue. Western blot tested oxidative stress-related proteins (Keap1, Nrf2, HO-1,NQO1).

Results: Compared with CON group, the levels of ALT, AST in blood and MDA in liver tissue were increased, the levels of SOD and GSH in liver decreased in AP group. ACA Dose-dependently reversed the biochemical parameters in blood and liver tissue of mice. The results of H&E staining showed that ACA Dose-dependently reduced inflammatory cell infiltration in the liver of mice .Western blot results showed that ACA Activated Nrf2 nuclear translocation, down-regulated Keap1 and Nrf2 protein expression in the cytoplasm, and up-regulated HO-1,NQO1 and Nrf2 protein expression in the nucleus.

Conclusion: ACA May alleviated the oxidative stress of liver cells in APAP-induced DILI mice through Nrf2 signaling pathways.

Keywords: Acacetin, Acetaminophen, DILI, Oxidative stress

黑果腺肋花楸果实水层化学成分及生物活性研究

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摘要:

黑果腺肋花楸（*Aronia melanocarpa* (Michx.) Elliott.）为蔷薇科涩石楠属一种小型灌木，也被称为不老莓。黑果腺肋花楸广泛种植于我国华北和东北地区，具有抗菌、抗氧化、抗炎、降血压、保肝等多种药理活性。为了更好地发现无毒副作用且活性强的单体化合物，本研究对于黑果腺肋花楸果实醇提取物的水层进行分离纯化和结构鉴定，并对分离得到的单体化合物进行抗菌、抗氧化活性测试。

本研究采用甲醇对黑果腺肋花楸果实进行提取，依次用石油醚和乙酸乙酯对其进行萃取。以黑果腺肋花楸果实水层作为实验对象，利用大孔吸附树脂柱色谱、正（反）相硅胶柱色谱、羟丙基葡聚糖柱凝胶柱色谱以及中压制备液相色谱仪等多种分离手段进行分离纯化，运用核磁共振波谱技术对分离得到的单体化合物进行结构鉴定。从黑果腺肋花楸果实水层中共分离鉴定27个单体化合物，包括1个新化合物：Methyl-3-hydroxy-(*β*-D-glucopyranosyloxy)-hexanoic acid（**1**）；6个黄酮类化合物：异槲皮苷（**2**）、金丝桃苷（**3**）、Quercetin-3-*O*-[*α*-L-arabinopyranosyl-(1'''→6'')-*β*-D-glucopyranoside]（**4**）、rutin（**5**）、Isorhamnetin-3-*O*-*β*-D-xylopyranosyl-(1→6)-*β*-D-glucopyranoside（**6**）、Quercetin-3-*O*-*β*- D-glucopyranoside(3'→3''')quercetin-3-*O*-*β*-D-galactopyranoside（**7**）；3个酚酸类化合物：原儿茶酸（**8**）、原儿茶酸甲酯（**9**）、苹果酸-1-甲酯（**10**）；3个单糖类化合物：*α*-D-呋喃果糖（**11**）、甲基-*β*-D-吡喃葡萄糖苷（**12**）、甲基-*β*-D-吡喃阿拉伯糖苷（**13**）；3个双糖类化合物：蔗糖（**14**）、麦芽糖（**15**）、1-*O*-*β*-D-呋喃果糖-*α*-D-阿洛酮糖苷（**16**）；10个糖苷类化合物：香草酸 4-*O*-*β*-D-吡喃葡萄糖苷（**17**）、(R)-4-*O*-*β*-D-吡喃葡萄糖基-4-羟基-2-戊酮（**18**）、长寿花糖苷（**19**）、4,6-二羟基-2-*O*-*β*-D-吡喃葡萄糖基苯丙酮（**20**）、methyl (3S,5S)-5-hydroxy-3-(*β*-D-glucopy ranosyloxy) hexanoate（**21**）、苯甲酸 1-*O*-*β*-D-吡喃葡萄糖苷（**22**）、parasorboside（**23**）、Benzyl 6-*O*-*α*-L-arabinofuranosyl-*β*-D-glucoside（**24**）、二氢菜豆酸 4'-*O*-*β*-D-吡喃葡萄糖苷（**25**）、顺式香豆酸-4-*O*-*β*-D-吡喃葡萄糖苷（**26**）和1个其他类化合物：jaboticabin（**27**）。其中化合物**7**、**18**、**21**首次从蔷薇科分离，化合物**13**、**16**、**23**、**26**首次从涩石楠属分离，化合物**19**首次从黑果腺肋花楸果实中分离得到。

对27个化合物进行体外生物活性测试。抗菌活性结果显示，化合物**1**、**3-4**、**6**、**8-9**、**16-19**具有一定的抗菌活性，其中化合物**8**、**9**对大肠杆菌 *Escherichia coil* KCTC（1924）的MIC_{50}达到64 μg/mL和256 μg/mL，化合物**1**、**3-4**、**6**、**8-9**、**16-19**对金黄色葡萄球菌 *Staphylococcus aureus* RN（4220）的MIC_{50}为128~256 μg/mL。

抗氧化活性结果显示，化合物**2**、**7-9**、**27**的DPPH自由基清除率与阳性对照药抗坏血酸相近；化合物**4-5**、**7**、**27**的ABTS自由基清除率与阳性对照药抗坏血酸相近，说明化合物**7**、**27**具有良好的抗氧化活性。

本研究对黑果腺肋花楸果实水层中筛选了抗菌和抗氧化活性成分，该结果为黑果腺肋花楸的开发和利用提供了理论依据，为开发具有良好生物活性的单体化合物提供了基础依据。

关键词：黑果腺肋花楸果实；化学成分；抗菌活性；抗氧化活性

Nelumbinis Plumula preparation and efficacy evaluation of nanoemulsions

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Abstract:

Objective: Using Nelumbinis Plumula extract as the main ingredient, an emulsion was prepared and its efficacy was evaluated. Methods: The pseudo-ternary phase diagram was used to screen the surfactant, co-surfactant and oil phase in the matrix to obtain the optimal addition amount. The antioxidant activity of the extract was determined by DPPH free radical scavenging rate. The particle size and appearance of nanoemulsions were determined by potential particle size analyzer and Hitachi transmission electron microscope. The stability and efficacy of Nelumbinis Plumula nanoemulsion were evaluated. Results: Tween-80:CO-40 (1:2 by mass) was screened as surfactant, PEG-400 was used as a co-surfactant, and ethylhexyl palmitate was used as the oil phase to prepare lotus seed heart nanoemulsion. Conclusion: The particle size of *Nelumbinis Plumula* nanoemulsion reaches the standard of nanoemulsion. Good stability, high safety, in line with industry standards; It has strong antioxidant and moisturizing properties, and has good development and utilization value.

Keywords: Nelumbinis Plumula; nanomilk; pseudo ternary phase diagram; antioxidant; moisturizing

Synthesis and Antimicrobial Activity of 3-Alkylidene-2-Indolone Derivatives

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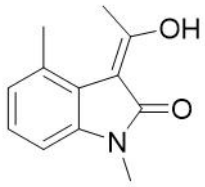
Abstract:

The issue of antimicrobial resistance has emerged as a universal challenge faced by countries worldwide. It is of utmost urgency to expedite the research and development process of novel antibacterial drugs and innovative strategies, and actively explore new therapeutic targets in order to effectively enhance the efficacy of antibiotics and minimize the potential risk of antimicrobial resistance. Through an in-depth exploration of the relevant literature, it has been discovered that compounds containing 3-alkyl-2-indolone have demonstrated extensive application potential in the domain of pharmacology, yet their antibacterial effects remain relatively scarce. Hence, a series of novel 3-alkyl-2-indolone derivatives were designed and synthesized in accordance with the bioelectronic isosteric principle and the principle of synthesis feasibility and economy. Subsequently, the antibacterial activity was evaluated systematically in vitro. The evaluation encompassed 7 representative strains, with Gatifloxacin and fluconazole being selected as positive controls to guarantee the accuracy and reliability of the experiment.

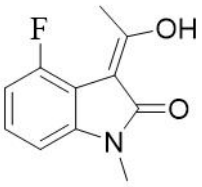
Among the compounds synthesized in this study, for Staphylococcus aureus 4220, compounds a, b, c, and d (MIC =4-16μg/mL) demonstrated moderate or high antibacterial activity. Among the compounds we synthesized, compound e (MIC = 0.5 μg/mL) exhibited antibacterial activity comparable to that of Gatifloxacin. For Staphylococcus aureus ATCC 6538, f and g (MIC =0.5μg/mL) manifested antimicrobial activity equivalent to that of gatifloxacin.

These results disclosed the structural features with remarkable antibacterial activity, and these discoveries undoubtedly offered a theoretical basis and inspiration for further research and optimization of the antibacterial properties of compounds.

Key words: 3-alkylidene-2-indolone; Synthesis; Antibiosis; Structure activity relationship

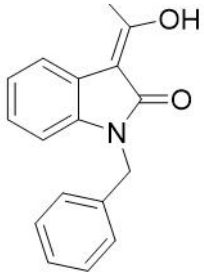


a



b

c



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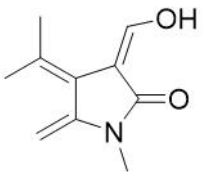
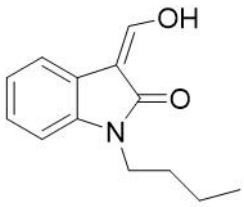


e



f

Mechanism of LY-0919 modulates spontaneous activity of cerebellar Purkinje cells and motor behavior in mice

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Abstract:

The cerebellum is an important motor center. YL-0919 is an active antidepressant with dual action of partial stimulation of 5-HT receptors and selective inhibition of 5-HT reuptake. The 5-HT nerve projection and receptor are widely distributed in the cerebellar cortex, involved in regulating PC activity and affecting motor behavior. In this study, under urethane anesthesia, *in vivo* electrophysiological recording techniques were used to study the pharmacological mechanism of YL-0919 on spontaneous discharge activity of PC in the vermis of mouse cerebellar cortex, and surface microinjection technique was used to study the effect of YL-0919 on motor behavior. Adult Kunming mice were selected and used urethane to anesthetize the mice for tracheal intubation. Cell-attached recording was used to record the discharge activity of Purkinje cells (PCs) in the cerebellar Vermis area of the mouse. The behavioral experiments included walking obstacle analysis and pole test. Mice were anesthetized with chloral hydrate and a microinjection cannula was placed in the cerebellar worm for drug administration. **Results:** YL-0919 inhibited the discharge frequency of SS in the mouse cerebellar Purkinje cells. The inhibitory effect of YL-0919 on SS amplitude was concentration-dependent, with an IC50 of 5.8 μM. Giving the 5-HT reuptake inhibitor FLX did not significantly affect PC firing activity and did not affect YL-0919-induced PC SS inhibition. In the presence of 5-HT2B or 5-HT7 receptor blockers, YL-0919 caused a decrease in the spontaneous SS discharge frequency of PC and an increase in CV without being affected. However, in the presence of a 5-HT1A receptor blocker, YL-0919 could not reduce the spontaneous SS discharge frequency of PC or cause a significant change in CV. In the gait analysis experiment, microinjection of YL on the surface of the cerebellum resulted in a significant increase in the total number of errors and duration of errors in the limbs of mice when walking on the sensor bar. Injection of a 5-HT1A receptor blocker and YL-0919 at the same time did not show a significant difference in the number of errors and duration of errors in the limbs compared to the control group. In the constant speed rod test, microinjection of YL-0919 on the surface of the cerebellum significantly reduced the latency of mice falling off the rod. Giving a 5-HT1A receptor blocker and YL-0919 at the same time did not significantly reduce the movement time of mice on the constant speed rod. The results of the

accelerated rod test showed that microinjection of YL-0919 on the surface of the cerebellum for five consecutive days significantly reduced the rotational speed and latency of mice falling off the rod. Giving a 5-HT1A receptor blocker and YL-0919 at the same time did not significantly change the rotational speed and latency of mice falling off the accelerated rod. **Conclusion:** The inhibitory effect of YL-0919 on PC firing activity is mediated by the 5-HT1A receptor and not due to the inhibition of endogenous 5-HT reuptake. Cerebellar surface application of YL-0919 on the surface of the cerebellum can affect mouse motor coordination and motor learning function via 5-HT1A receptor.

Keywords: cerebellar Purkinje cells; simple spike; YL-0919; motor behavior; *In vivo* electrophysiological recording

This work was supported by the National Natural Science Foundations of China (grant nos.32260195, 31660272), the Jilin Province Science and Technology Development Plan Project (YDZJ202201ZYTS588 and YDZJ202301ZYTS164) .

Study on the antitumour activity of COF-loaded Platycodonopsis saponinsD

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Abstract:

Covalent organic skeleton materials are composed of lightweight elements such as C, H, O, N, etc. which are connected by covalent bonds to make the covalent bond strength inside the whole space increase and the structure stable. The large surface area and high porosity are conducive to the loading of guest drugs, and compared with amorphous materials, covalent organic skeleton materials are highly crystalline with a clear crystal structure, which can be structurally modified for the loading of the drug structure.The structure of COFs does not contain metal elements, which also avoids some of the potential toxicity of the metal problem. This also avoids some of the potential metal toxicity problems, which makes them have a lot of room for development in the field of medicine. Cancer cells proliferate very quickly traditional chemotherapeutic drugs reach the whole body through the blood circulation, which not only kills the cancer cells normal cells are also subject to toxic effects. The elimination effect after long-term use and the resistance of cancer cells are also urgent problems. We chose Platycodonopsis saponin D extracted from Platycodon grandiflorum as a guest-loaded drug to conduct a series of pharmacological activity studies against hepatocellular carcinoma cells.

Keywords: COFs; diabetes; Platycodonopsis saponin; pharmacological activity;

Mechanism Through Which 5-HT Modulates Tactile Stimulation-Evoked Long-Term Plasticity at Cerebellar Cortical Molecular Layer Interneuron-Purkinje Cell Synapses in Mice *in Vivo*

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Abstract

The cerebellum is innervated by afferent 5-hydroxytryptamine (5-HT) neurons in the dorsal raphe nucleus and regulates neuronal activity, synaptic transmission, and synaptic plasticity in the cerebellar cortex through its receptors. In this study, the mechanism through which 5-HT affects tactile stimulation-evoked synaptic LTD of MLI-PC in the cerebellar cortex of urethane-anesthetized mice was investigated by in vivo cell-attached recordings, pharmacological methods, and molecular biology techniques. Adult mice (6-8 weeks old) were anesthetized with urethane (1.3 g/kg body weight) by intraperitoneal injection. Purkinje cells in the cerebellum were cell-attached recorded using an Axopatch-200B amplifier. Using air-puff stimulation train (10 ms, 1 Hz, 240 pulses) to induce MLI-PC long-term synaptic plasticity. **Results:** Tactile stimulation (1 Hz) evoked synaptic LTD of MLI-PC in the cerebellar cortex of mice. Perfusion of the cerebellar surface with 50 μM 5-HT significantly inhibited synaptic LTD of MLI-PC. Blockade of 5-HT1B and 5-HT2A receptors did not significantly modulate the 5-HT-induced inhibition of synaptic LTD of MLI-PC, whereas the inhibitory effect of 5-HT was abolished by a 5-HT7 receptor blocker. These results suggest that 5-HT inhibits the synaptic LTD of MLI-PC by activating the 5-HT7 receptor. Synaptic LTD of MLI-PC can be completely blocked by NMDA receptor blockers or CB1 receptor antagonists. Under such conditions, 5-HT can induce long-term potentiation (LTP) of MLI-PC synapses via sensory stimulation. Inhibition of protein kinase A can completely block synaptic LTD of MLI-PC. In the presence of protein kinase A inhibitors, 5-HT induces synaptic LTP of MLI-PC via sensory stimulation. However, LTP can be blocked by protein kinase C (PKC) inhibitors, suggesting that 5-HT induces synaptic LTP of MLI-PC by stimulating the PKC signaling pathway.The immunofluorescence reaction the 5-HT7 receptor in the cerebellar cortex was strong for PCs in the Crus II region.**Conclusion:**(1) The 5-HT7 receptor is present on PC bodies in Crus II of the mouse cerebellar cortex, and the inhibitory effect of 5-HT on tactile stimulation-evoked synaptic LTD of MLI-PC in the mouse cerebellar cortex is exerted through the 5-HT7 receptor. (2) Through the blockade of synaptic LTD in MLI-PC, 5-HT induces synaptic LTP of MLI-PC in the mouse cerebellar cortex by stimulating the 5-HT7 receptor and PKC signaling pathway. Therefore, the inhibitory effect of 5-HT on the synaptic LTD of MLI-PC may be exerted through PKC-dependent LTP.

Keywords: 5-hydroxytryptamine (5-HT); 5-HT receptor; Sensory stimulation; Molecular layer interneuron-Purkinje cell synaptic plasticity; Electrophysiological recording; Neuropharmacology

This work was supported by the National Natural Science Foundations of China(grant nos.32260195,31660272),the Jilin Province Science and Technology Development Plan Project(YDZJ202201ZYTS588 and YDZJ202301ZYTS164).

基于网络药理学探讨Ginsenoside Compound K“异病同治”糖尿病并发症的作用机制

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摘要：

目的：糖尿病肾病（diabetic kidney disease，DKD）、糖尿病视网膜病变（diabetic retinopathy，DR）和糖尿病周围神经病变（diabetic peripheral neuropathy，DPN）为糖尿病主要并发症，运用网络药理学预测Ginsenoside Compound K（CK）“异病同治”糖尿病并发症关键信号通路和核心靶点，为CK后续研发提供参考。

方法：运用PharmMapper、Swiss Target Prediction、Sea和GeneCards、OMIM、TTD数据库分别收集CK和DKD、DR、DPN相关靶点。通过Venny 2.1.0获取交集靶点，将交集靶点上传至STRING平台获得PPI蛋白互作网络图，利用Cytoscape 3.10.1 degree值筛选潜在核心靶点。利用DAVID数据库对交集靶点进行BP、CC、MF和KEGG分析，根据*P*-value各自取前20个条目进行GO和KEGG富集分析。利用Cytoscape 3.10.1构建“CK-交集靶点-疾病-信号通路”网络可视化图，获得“异病同治”糖尿病并发症关键信号通路和核心靶点。

结果：PharmMapper、Swiss Target Prediction、Sea数据库共获得CK作用靶点313个；GeneCards、OMIM、TTD数据库筛选DKD、DR、DPN疾病靶点，分别为2386个、3093个、4130个，最终Venny 2.1.0显示交集靶点为133个。ALB、STAT3、CASP3、MMP9靶点degree值较高，分别为94.0、78.0、76.0、75.0，很可能为核心靶点。DAVID数据库中获得与疾病密切相关的生物学过程555条、细胞组分70条、分子功能125条、信号通路154条。GO和KEGG富集分析结果显示，交集靶点主要位于extracellular region、extracellular space、cytosol等细胞组分中，与nuclear receptor activity、identical protein binding、endopeptidase activity等分子功能有关，主要参与response to hypoxia、positive regulation of phosphatidylinositol 3-kinase/protein kinase B signal transduction、negative regulation of apoptotic process等生物学过程，且与Pathways in cancer、Proteoglycans in cancer、Lipid and atherosclerosis等关键生物信号通路有关。“CK-交集靶点-疾病-信号通路”网络可视化图显示PI3K-AKt signaling pathway同样为关键信号通路之一。

结论：CK防治DKD、DR、DPN的核心靶点可能为ALB、STAT3、CASP3、MMP9，并通过Pathways in cancer、Proteoglycans in cancer、Lipid and atherosclerosis、PI3K-AKt signaling pathway关键信号通路发挥作用，具有“异病同治”糖尿病并发症的潜力。

关键词：异病同治；Ginsenoside compound K；网络药理学；糖尿病并发症

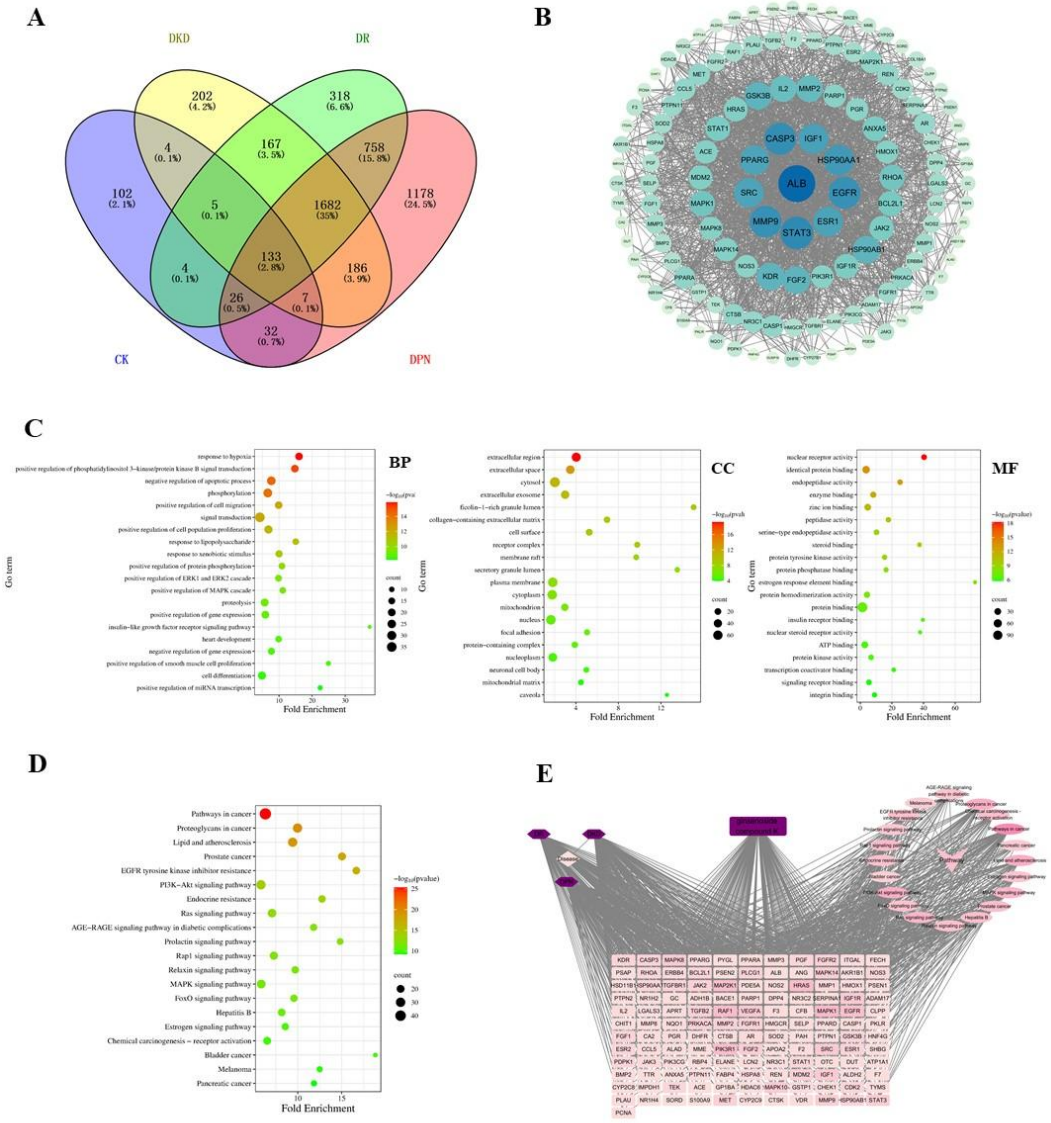

图1. A CK、DKD、DR、DPN靶点Venny图；B 交集靶点PPI可视化图；C GO富集气泡图；D KEGG富集气泡图；E “CK-交集靶点-疾病-信号通路”网络可视化图。

Casting NETs on psoriasis: The modulation of inflammatory feedback targeting IL-36/IL-36R axis

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Abstract:

NETosis happens when neutrophils are activated and neutrophil extracellular traps (NETs) are formed synchronously, which is a hallmark of psoriasis. However, the specific trigger that drives NET formation and the distinct contents and interaction with interleukin-36 receptor (IL-36R) of NETs remain to be further elucidated. This work identified NET formation driven by toll-like receptor (TLR) 3 ligand (especially polyinosinic-polycytidylic acid (Poly(I:C)) were enhanced by purinergic receptor P2X ligand-gated ion channel 7 receptor (P2X7R) ligands (especially adenosine 5'-triphosphate (ATP)). NET formation was accompanied by the secretion of inflammatory cytokines and characterized by IL-1β decoration. NET formation blockade decreased expressions of inflammatory cytokines and chemokines, which consequently improved inflammatory responses. Additionally, imiquimod (IMQ)-induced psoriasiform symptoms including neutrophilic infiltration tended to be time-sensitive. Mouse primary keratinocytes and mice deficient in *Il1rl2*, which encodes IL-36R, mitigated inflammatory responses and NET formation, thereby de-laying the pathophysiology of psoriasis. Together, the findings provided the therapeutic potential for IL-36 targeting NET inhibitors in psoriasis treatment.

Keywords: Psoriasis, IL-36R, Neutrophil extracellular traps, NETosis

Immunomodulatory effects of different molecular weight sporisorium reilianum polypeptides on LPS-induced RAW264.7 macrophages

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Abstract:

Although polysaccharides from S. reilianum have been shown to exert anti-inflammatory and anti-tumor effects,studies of other molecules are still scarce. This study was conducted to examine the immunomodulatory effects of different molecular weights of S. reilianum polypeptides (SRP) on lipopolysaccharide (LPS)-induced RAW264.7 macrophages. A neutral protease was used to prepare SRP, which was divided into different components based on their molecular weights (SRP1, SRP2, SRP3, and SRP4). Evaluation of the immunomodulatory effects of SRP on LPS-induced RAW264.7 macrophages showed that SRP enhanced cell viability and phagocytic activity, and effectively decreased the nitric oxide (NO) content. Furthermore, the SRP with the smallest molecular weight, SRP4 (500–1000 Da) exhibited the strongest effects compared to the other groups. Secretion of the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 was markedly decreased by SRP4 in a dose-dependent manner. Moreover, the mRNA expression levels of IL-1β, nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, and toll-like receptor (TLR)-9 in RAW264.7 macrophages were also significantly downregulated by SRP4. Taken together, SRP, particularly SRP4, showed good immunomodulatory effects, indicating its potential as an immune-enhancing agent.

Keywords: Sporisorium reilianum ;Polypeptide ;Lipopolysaccharide ;RAW264.7 macrophage ;Immunomodulation

Progress on chemical composition and pharmacological effects of Alnus

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Abstract:

In order to promote the further development and utilisation of *Alnus*, the article reviewed relevant papers at home and abroad in recent years, and summarised the chemical composition and pharmacological effects of *Alnus*. Alder plants contain terpenoids, flavonoids, diarylheptanoids, phenols, steroids and tannins, of which diarylheptanoids are the main components in *Alnus*. The pharmacological effects include anti-inflammatory, antioxidant, inhibition of HIV virus replication and related enzymes, inhibition of cancer cells and hepatoprotective effects. Currently, there is a lack of research on *Alnus* at home and abroad, but due to the fact that many of its chemical constituents have good pharmacological activities, *Alnus* have good research prospects.

Key words: *Alnus*; chemical composition; pharmacological effects; medicinal value

Synthesis and anti-colorectal cancer activity of celastrol-fused heterocyclic derivatives

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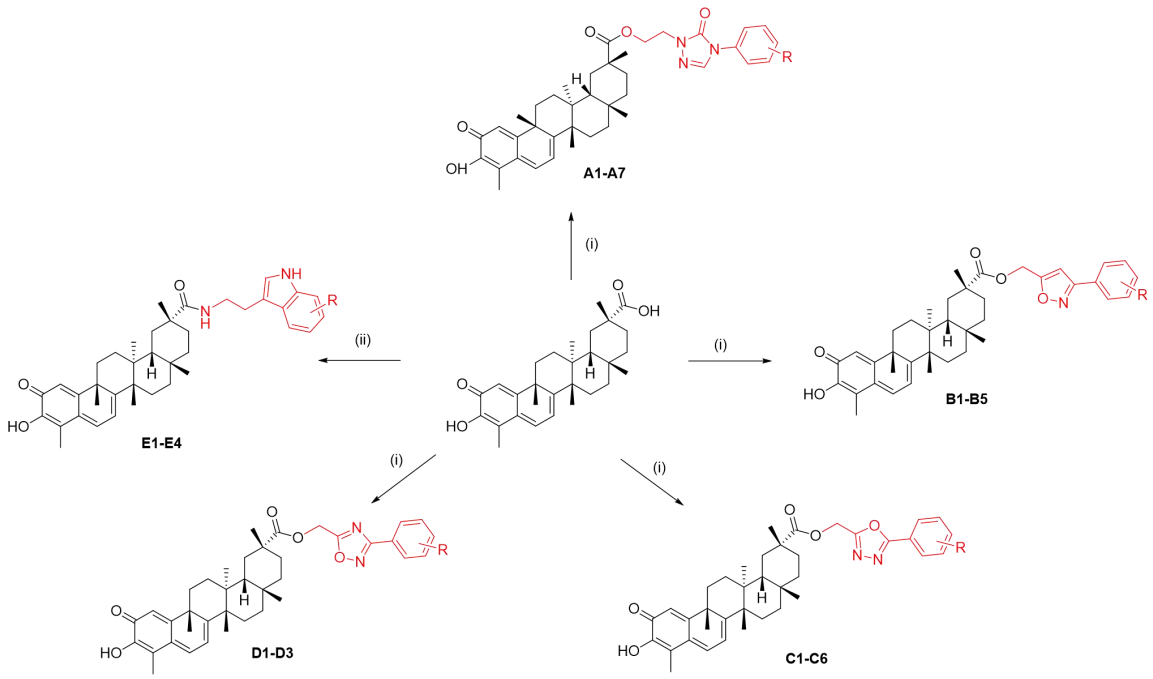
Abstract

Colorectal cancer, a prevalent yet preventable malignancy, stems from the malignant transformation of the large intestine or rectal mucosa, often progressing with the insidious growth and infiltration of tumors into adjacent tissues and organs. Encouragingly, the global promotion and implementation of colorectal cancer screening programs have contributed to a favorable decline in incidence and mortality rates among targeted populations. Nevertheless, a concerning trend has emerged over the past quarter-century: a rise in the proportion of young individuals (under 50) being diagnosed with this disease, necessitating the combined vigilance of society and the medical fraternity. Celastrol, a quinone methyl pentacyclic triterpenoid extracted from the root bark of the traditional Chinese medicinal plant *Tripterygium wilfordii*, has shone brightly in the realm of drug discovery due to its distinct structural features and extensive biological activities. Its remarkable antitumor capabilities, particularly its aptitude for inducing apoptosis in digestive tract tumor cells, have sparked fresh perspectives on colorectal cancer treatment. Scientific investigations have revealed that celastrol exerts potent toxicity against pancreatic and gastric cancer cells by meticulously modulating the expression of crucial signal genes like ATF3 and DDIT3 and suppressing Prdx2 activity, leading to ROS accumulation and subsequently triggering endoplasmic reticulum stress, mitochondrial dysfunction, and cell death. Furthermore, celastrol's inhibition of NOS activity and angiogenesis pathways effectively curtails the proliferation and migration of colorectal cancer cells.Leveraging these exceptional attributes of celastrol, our project innovatively embraced the principle of combinatorial drug design. By introducing 1,2,4-triazolone, isoxazole, oxadiazole, and indole derivatives at the C-20 position of celastrol, we successfully devised and synthesized 25 novel celastrol analogues. Notably, derivatives belonging to the A-C series demonstrated remarkable potency in suppressing HCT-116 colon cancer cells, with the C series outperforming the rest. In contrast, for SW-480 and SW-620 cell lines, E1 from series A and E, respectively, displayed the strongest inhibitory effects. Most significantly, when compared to celastrol itself, the highly active C5 and E1 derivatives exhibited notably reduced toxicity towards normal HCOEPIC cells, underscoring their enhanced therapeutic safety profile.

Keywords: Colorectal cancer ; Celastrol derivatives ; Antitumor capabilities.



A1, R=H
A2, R=4-OCH_3
A3, R=4-F
A4, R=4-Cl
A5, R=4-Br
A6, R=3,4-2Cl
A7, R=4-CH_3

B1, R=H
B2, R=4-Cl
B3, R=3,4-2Cl
B4, R=4-OCH_3
B5, R=3,4,5-3OCH_3

C1, R=H
C2, R=4-F
C3, R=4-Cl
C4, R=4-OCH_3
C5, R=3,4,5-3OCH_3
C6, R=4-NO_2

D1, R=H
D2, R=4-F
D3, R=4-Cl

E1, R=H
E2, R=2-CH_3
E3, R=5-OCH_3
E4, R=5-Cl

Design, Synthesis and Activity Evaluation of Novel CDK12 Inhibitors

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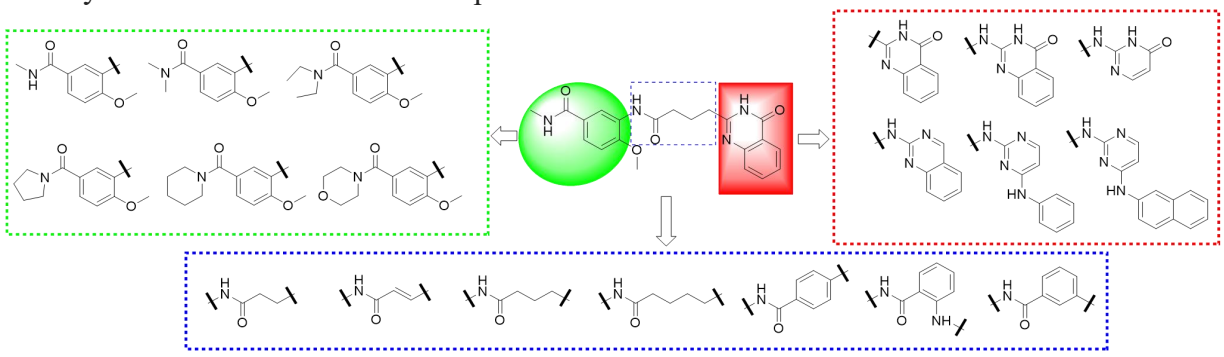
Abstract:

Cancer, known as the king of diseases, has now become the number one killer taking human lives, with over 1.5 million people dying from cancer in our country every year. Nowadays, the main clinical treatments for cancer include chemotherapy, radiotherapy, and surgical treatment, but the severe toxic side effects cause great torment to patients' physical and mental health. Therefore, it is necessary to develop more effective cancer treatment drugs and strategies. Cyclin-dependent kinase 12 (CDK12) belongs to the CDK family of serine/threonine kinases and, as a transcriptional CDK, is involved in regulating multiple stages such as gene transcription elongation, RNA splicing, transcription termination, and DNA damage repair.[1-2]Due to its direct regulatory effect on the DNA damage repair pathway, it is involved in the drug resistance process of various tumors and has been identified as a key anti-tumor target. [3]Based on the structure of the CDK12 kinase and by combining classical drug design with computer-aided drug design, target compounds were designed. From a library of 500,000 small molecules, 24 structurally novel small molecule CDK12 inhibitors with the highest scores were virtually screened. These 24 small molecules were synthesized using commercially available materials and their inhibitory activity against CDK12 was determined through enzyme activity experiments. The molecule with the best activity was selected as the lead compound.



Keywords: Cancer, CDK12, CDK12 inhibitors

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酒精摄入对非酒精性脂肪肝发病进程的影响及潜在机制研究进展

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摘要:

非酒精性脂肪性肝病（non-alcoholic fatty liver disease，NAFLD）如今作为全球最常见的肝病之一，其发病率也呈现出日益增长的趋势。单纯性脂肪肝、非酒精性脂肪性肝炎、还有可能进一步发展变成的肝硬化、肝衰竭和肝癌等一系列的肝脏疾病都可以统称为NAFLD。通过对影响NAFLD产生的众多因素进行研究，发现其主要病理机制为脂肪的过多合成，且难以被转运入血，从而引起了大量脂质蓄积。酒精对肝脏有直接损伤作用，会抑制肝脏脂肪的分解，最终形成酒精性脂肪肝。然而酒精对NAFLD发病是否具有协同作用仍存在争议，因此该文针对酒精摄入对NAFLD的影响及其潜在的作用机制进行综述。

关键字：非酒精性脂肪肝；酒精；发病机制；酒精摄入对脂肪肝的两面性；治疗

Accurate determination of binding constant of tyrosinase and kojic acid based on the multicompartment electrophoresis technique

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Abstract:

The binding strength of small molecules and proteins affects the absorption, distribution, metabolism, efficacy, and toxicity of drugs in vivo. In-vitro interactions have been studied by methods such as spectroscopic analysis, bio-layer interferometry, surface plasmon resonance *etc*. However, each of these methods has its own limitations, and a new technique is urgently needed to further study the interactions between small molecules and proteins. In this study, the binding constant (K_a) of kojic acid - tyrosinase was accurately determined at a low voltage (20 V) using the unique microchamber structure of multicompartment electrophoresis with tyrosinase and kojic acid as examples. The K_a was 7.4×10^3, which was in the same order of magnitude compared with that determined by fluorescence ($K_a = 9.55\times10^3$), which verified the accuracy of the multicompartment electrophoresis technique in the determination of the K_a. The interaction mechanism between kojic acid and tyrosinase was further characterized using UV-visible spectroscopy of Cu^{2+} titration, showing the unchanged maximum absorption wavelength of kojic acid, and suggesting that it does not chelate with copper ions in tyrosinase, but rather interacts with amino acid residues in the active center of tyrosinase. This study preliminary elucidates the interaction between kojic acid and tyrosinase in a multicompartment electrophoresis system and provides support for the accurate determination of binding constant by multicompartment electrophoresis.

Keywords: multicompartment electrophoresis technique, binding constant, tyrosinase, kojic acid

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NETs contribute to psoriasiform skin inflammation: A novel therapeutic approach targeting IL-36 cytokines by a small molecule tetrahydroxystilbene glucoside

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Abstract:

Background: Psoriasis, a chronic immune-mediated skin disease with pathological features such as aberrant differentiation of keratinocytes, dermal-epidermal inflammation, and angiogenesis. 2,3,5,4′-Tetrahydroxy stilbene 2-O-β-d-glucoside (2354Glu) is a natural small molecule polyhydrostilbenes isolated from *Polygonum multiglorum Thunb*. The regulation of IL-36 subfamily has led to new pharmacologic strategies to reverse psoriasiform dermatitis.

Purpose: Here we investigated the therapeutic potential of 2354Glu and elucidated the underlying mechanism in psoriasis.

Methods: The effects of 2354Glu on IL-36 signaling were assessed by psoriasiform *in vivo*, *in vitro* and *ex vivo* model. The *in vivo* mice model of psoriasis-like skin inflammation was established by applying imiquimod (IMQ), and the *in vitro* and e*x vitro* models were established by stimulating mouse primary keratinocyte, human keratinocytes cells (HaCaT) and *ex vivo* skin tissue isolated from the mice back with Polyinosine-polycytidylic acid (Poly(I:C)), IMQ, IL-36γ and Lipopolysaccharide (LPS) respectively. Moreover, NETs formation was inhibited by Cl-amidine to evaluate the effect of NETs in psoriatic mouse model. The effects of 2354Glu on skin inflammation were assessed by western blot, H&E, immunohistochemistry, immunofluorescence, enzyme-linked immunosorbent assay and real-time quantitative PCR.

Results: In Poly(I:C)-stimulated keratinocytes, the secretion of IL-36 was inhibited after treatment with 2354Glu, similar to the effects of TLR3, P2X7R and caspase-1 inhibitors. In aldara (imiquimod)-induced mice, 2354Glu (100 and 25 mg/kg) improved immune cell infiltration and hyperkeratosis in psoriasis by directly targeting IL-36 in keratinocytes through P2X7R-caspase-1. When treatment with 2354Glu (25 mg/kg) was insufficient to inhibit IL-36γ, NETs reduced pathological features and IL-36 signaling by interacting with keratinocytes to combat psoriasis like inflammation.

Conclusion: These results indicated that NETs had a beneficial effect on psoriasiform dermatitis. 2354Glu alleviates psoriasis by directly targeting IL-36/P2X7R axis and NET formation, providing a potential candidate for the treatment of psoriasis.

Keywords: Psoriasis, 2,3,5,4′-tetrahydroxy stilbene 2-O-B-D-glucoside, Net, IL-36, P2X7R

Signal Mining and Network Analysis of Avatinib Adverse Drug Events Based on FAERS Database

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Abstract:

Objective To mine the related adverse events of Avapritinib based on FAERS database, evaluate and analyze its post-marketing adverse drug reaction signals, explore its occurrence characteristics and relationship, and provide reference for clinical safety management. Methods The adverse events about avatinib collected in FAERS database were analyzed, and the risk signals were mined by Reporting Odds Ratio (ROR) and network signal method, and classified systematically by medical dictionary for drug regulatory activities (Meddra). Results A total of 20,428,426 reports were obtained, among which 5,996 cases were reported with Avatinib as the primary suspect, and 803 positive signals were obtained by screening. According to the System Organ Class, SOC), the top five reports are all kinds of examinations, systemic diseases and various reactions at the administration site, gastrointestinal diseases, infections and infectious infections, and skin and subcutaneous tissue diseases. Network signal diagram shows that hematocrit is decreased, hemoglobin is decreased, red blood cell count is decreased, gastrointestinal diseases are closely related to bone pain ADE, blood iron and red blood cells are decreased, skin lesions and red blood cell count are decreased, paresthesia and blood potassium are decreased, tryptase is increased and abdominal distension, abdominal distension and splenomegaly are closely related. Conclusion The detection of adverse event signals in FAERS database shows that in the clinical use of Avatinib, we should pay close attention to the occurrence of related adverse events, especially the decrease of hematocrit, hemoglobin and red blood cell count, gastrointestinal diseases and bone pain, and pay attention to the relationship between adverse events, and take timely intervention measures to ensure the safety of medication. The research results are helpful for clinicians and drug safety evaluation institutions to better understand the safety characteristics of avatinib and provide scientific basis for clinical medication.

Keywords: Avatinib, adverse events, FAERS, signal mining, network analysis.


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