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10. UPLC-Q/TOF-MS based metabonomics revealed protective effect of Terminalia chebula extract on ischemic stroke rats.


12. Licorice root extract and magnesium isoglycyrrhizinate protect against triptolide-induced hepatotoxicity via up-regulation of the Nrf2 pathway.

Sheng Jiang San, a traditional multi-herb formulation, exerts anti-influenza effects in vitro and in vivo via neuraminidase inhibition and immune regulation.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5941478/
By Zhang T, Xiao M, Wong CK, Mok KC, Zhao X, Ti H, et al.,

Abstract

BACKGROUND:
Sheng Jiang San (SJS), a multi-herb formulation, is used in treating high fever, thirsty and anxiety in ancient China and it is sometimes used to treat seasonal influenza nowadays. However, there is no evidence-based investigation and mechanism research to support the anti-influenza efficacy of SJS. This study aims at evaluating the anti-influenza effect of SJS and investigating its possible mechanism.

METHODS:
The inhibitory effect of SJS against different influenza virus strains on MDCK cells was examined. Influenza virus infected BALB/c mice were employed to evaluate the efficacy as in vivo model. Mice challenged with A/PR/8/34 (H1N1) were orally administrated 1 g/kg/day of SJS for seven days and monitored for 14 days. The survival rate, body weight changes, lung index, lung viral load, histopathologic changes and immune regulation of the mice were measured. The underlying anti-influenza virus mechanism of SJS was studied by a series of biological assays to determine if hemagglutinin, ribonucleoprotein complex or neuraminidase were targets of SJS.

RESULTS:
Results showed SJS exerted a broad-spectrum of inhibitory effects on multiple influenza strains in a dose-dependent manner. IC\textsubscript{50} of SJS against A/WSN/33 (H1N1) was lower than 35 μg/ml. SJS also protected 50% of mice from A/PR/8/34 (H1N1) infection. The lung index and the lung viral load of SJS treated mice were significantly decreased compared with untreated mice. Meanwhile, SJS targeted on neuraminidase of influenza virus as SJS at 2 mg/ml inhibited 80% of neuraminidase enzymatic activity. SJS also significantly down-regulated TNF-α and up-regulated IL-2 of influenza virus induced mice.

CONCLUSIONS:
Thus, SJS is a useful formulation for treating influenza virus infection.
Isolation of novel biflavonoids from Cardiocrinum giganteum seeds and characterization of their antitussive activities.

By Shou JW, Zhang RR, Wu HY, Xia X, Nie H, Jiang RW, Shaw PC.

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:
Seeds of Cardiocrinum giganteum var. yunnanense (Leichtlin ex Elwes) Stearn (Liliaceae), also known as Doulingzi, have been used as a folk substitute for conventional antitussive herb "Madouling" (Aristolochia species) to treat chronic bronchitis and pertussis. The active antitussive phytochemicals in C. giganteum seeds are not known.

AIM OF THE STUDY:
The present work aims at isolating the active phytochemicals in C. giganteum seeds and confirming their antitussive effects.

MATERIALS AND METHODS:
Active chemicals were isolated from C. giganteum seeds ethanol extract and identified their structures. Antitussive effects were evaluated with the cough frequency of guinea pigs exposed to citric acid. Electrical stimulation of the superior laryngeal nerve in guinea pigs was performed to differentiate the acting site of potential antitussives.

RESULTS:
Two racemic biflavonoids (CGY-1 and CGY-2) were isolated from C. giganteum seeds. CGY-1 was identified as (S)-2″R,3″R- and (R)-2″S,3″S-dihydro-3″-hydroxyamentoflavone-7-methyl ether, which are new compounds and firstly isolated from C. giganteum seeds. Racemic CGY-2 was identified as (S)-2″R,3″R- and (R)-2″S,3″S-dihydro-3″-hydroxyamentoflavone. Both CGY-1 and CGY-2 could significantly inhibit coughs induced by inhalation of citric acid. Further, they acted on the peripheral reflex pathway to inhibit cough after electrical stimulation of the superior laryngeal nerve in guinea pigs.

CONCLUSIONS:
These chemicals isolated from C. giganteum seeds showed good antitussive effects. The data provide scientific evidence to support the traditional use of C. giganteum seeds as an antitussive herbal medicine.
Effect of Rhubarb on Gastrointestinal Dysfunction in Critically Ill Patients: A Retrospective Study Based on Propensity Score Matching.


By Zhang X, Wang L, Chen DC.

Abstract

BACKGROUND:
Gastrointestinal dysfunction plays a critical role in the prognosis of critically ill patients. Previous studies showed rhubarb, a traditional Chinese herb, can protect the intestinal barrier function, prevent intestinal bacterial translocation, and promote gastrointestinal peristalsis, but the clinical studies are less. The aim of this study was to evaluate the effects of rhubarb on gastrointestinal dysfunction in critically ill patients.

METHODS:
From June 2015 to May 2017, a total of 368 critically ill patients with Grade I-III acute gastrointestinal injury (AGI) were enrolled in this study. Patients were divided into two groups according to the exposure factors (whether the patients received rhubarb treatment): the rhubarb group and the usual treatment group. Clinical data were collected within the first 24 h of the Intensive Care Unit (ICU) admission and 7 days after treatment. Survival data on day 28 after ICU admission and the durations of ICU and total hospitalization were also collected. Propensity score matching (PSM) was conducted to reduce confounding bias between the groups. The logistic regression was conducted to screen the influence factors.

RESULTS:
The eligible patients were divided into rhubarb group (n = 219, 59.5%) and usual treatment group (n = 149, 40.5%). Before PSM, the remission rate of feeding intolerance in rhubarb group and usual treatment group were 59.8% and 39.6%, respectively. After PSM, the remission rate of feeding intolerance in rhubarb group and usual treatment group was 77.9% and 30.9%, respectively. The remission rates of feeding intolerance in rhubarb group were significantly higher than those in the usual treatment group (all P < 0.05).

Compared with the usual treatment group, the rhubarb group had a higher rate of AGI improvement, lower level of C-reactive protein, shorter stay in ICU before and after PSM (P < 0.05). There was no significant difference in 28-day mortality between rhubarb and usual treatment groups before and after
PSM (48 vs. 33, P = 0.959; and 16 vs. 21, P = 0.335). The logistic regression analysis showed that the single factor, whether receiving rhubarb therapy, affected the proportion of patients whose enteral nutrition needs ≥83.7 kJ·kg⁻¹·d⁻¹ after 7 days of treatment (odds ratio: 7.908, 95% confidence interval: 3.661-17.083, P < 0.001). No serious adverse effects were found in two groups.

CONCLUSIONS:
The rhubarb might significantly improve feeding tolerance and relieve gastrointestinal dysfunction in critically ill patients, without serious adverse reactions. It provided proof for the treatment of gastrointestinal dysfunction with rhubarb during clinical practice.

Comparison of the chemical profiles and inflammatory mediator-inhibitory effects of three Siegesbeckia herbs used as Herba Siegesbeckiae (Xixiancao).


By Guo H, Zhang Y, Cheng BC, Lau MY, Fu XQ, Li T, et al.,

Abstract

BACKGROUND:
Herba Siegesbeckiae (HS, Xixiancao in Chinese) is a commonly used traditional Chinese medicinal herb for soothing joints. In ancient material medical books, HS is recorded to be the aerial part of Siegesbeckia pubescens Makino (SP) which is also the only origin of HS in the 1963 edition of the Chinese Pharmacopeia (ChP). The aerial parts of Siegesbeckia orientalis L. (SO) and Siegesbeckia glabrescens Makino (SG) have been included as two additional origins for HS in each edition of ChP since 1977. However, chemical and pharmacological comparisons among these three species have not been conducted.

METHODS:
An HPLC with diode array detector (HPLC-DAD) method combined with similarity analysis, hierarchical cluster analysis (HCA) and principal component analysis (PCA) was developed for comparing the fingerprint chromatograms of the three species. The inhibitory effects of the three species on NO production and IL-6 secretion in LPS-stimulated RAW264.7 macrophages were compared.

RESULTS:
Fingerprint chromatograms of the three species showed different profiles, but
had 13 common peaks. Results from HCA and PCA of the common peaks demonstrated that all 14 herbal samples of the three species tended to be grouped and separated species dependently. The extents of inhibition on NO production and IL-6 secretion of the three species were different, with SG being the most and SP the least potent. 

**CONCLUSIONS:**
Both chemical profiles and inflammatory mediator-inhibitory effects of the three species were different. These findings provide a chemical and pharmacological basis for determining whether the three species can all serve as the origins of HS.

**Effects of shenling baizhu powder herbal formula on intestinal microbiota in high-fat diet-induced NAFLD rats.**


**Abstract**

**BACKGROUND:**
Worldwide, non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease closely associated with obesity, diabetes and other metabolic diseases. Shenling Baizhu powder (SLBZP), a formulation of a variety of natural medicinal plants, has hepatoprotective properties and clinical efficacy in treating non-infectious intestinal disease. SLBZP has improved NAFLD symptoms; however, its mechanism of action is unknown.

**METHODS:**
We established an NAFLD model in rats given a high-fat diet (HFD), administered different interventions and measured serum biochemical indices and inflammatory factors. Liver tissues were stained with hematoxylin and eosin (HE) and oil red O, and colon tissues were analyzed by immunohistochemistry. The expression profiles of liver TLR4 pathway related protein was confirmed by western blotting. Changes in intestinal microbiota composition were analyzed using a 16S rDNA sequencing technique.

**RESULTS:**
Of note, SLBZP effectively reduced body weight in HFD-fed rats (p < 0.05). Serum biochemical analysis indicated that SLBZP decreased the serum level of total cholesterol (TC) and improved liver function. Additionally, SLBZP
decreased the serum level of endotoxin, tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β) (p < 0.05), and decreased the expression of TLR4 pathway related protein. Pathological examination showed that SLBZP alleviates hepatic steatosis and repairs colon mucosa. Microbiome analysis revealed that SLBZP improved the abundance of intestinal microbiota. In taxonomy-based analysis, compared with control rats, SLBZP-treated rats showed obvious changes in intestinal microbiota composition. Moreover, SLBZP increased the relative abundance of short-chain fatty acid (SCFA)-producing bacteria, including Bifidobacterium and Anaerostipes.

**CONCLUSION:**
Taken together, these results suggest that the effects of SLBZP against NAFLD may be related to the increased abundance of beneficial gut microbiota and decreased levels of LPS in the portal vein.

**Anti-Inflammatory Effects of p-Coumaric Acid, a Natural Compound of *Oldenlandia diffusa*, on Arthritis Model Rats.**

https://www.hindawi.com/journals/ecam/2018/5198594/


**Abstract**

**OBJECTIVES:**
In China, *Oldenlandia diffusa* (OD) is a natural herb that is widely used and has been proven to be effective in the treatment of rheumatoid arthritis (RA). This study aimed to preliminarily reveal the mechanism by which OD exerts its beneficial effect.

**METHODS:**
Ultra-performance liquid chromatography photodiode array was applied to identify the absorbable compounds in the plasma of collagen-induced arthritis (CIA) model rats. After 2 weeks, an OD decoction or the identified absorbable compound was administered to CIA rats. Morphology, X-ray images of the joints, pathological images, arthritis index, and cytokine (TNF-α and IL-6) levels were evaluated.

**RESULTS:**
p-Coumaric acid (p-CA) was identified as the absorbed compound in plasma. After administration of p-CA solution or the OD decoction, symptoms in the treated rats were alleviated as compared to the untreated model rats, and inflammatory cell infiltration was suppressed. The arthritis index and
The serum levels of TNF-α and IL-6 were decreased as compared to the control group.

**CONCLUSIONS:**
OD may exert its anti-inflammatory effect on RA via its active ingredient, p-CA. This information sheds light on the mechanism by which OD exerts its anti-inflammatory effort in RA and forms the basis for further development of therapeutic agents for RA.

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**Protective role and mechanism of snakegourd peel against myocardial infarction in rats.**


By Yang G, Min D, Yan J, Yang M, Lin G.

**Abstract**

**BACKGROUND:**
Injection of snakegourd peel (SP), an herb used in traditional Chinese medicine, is used to treat coronary artery disease and stable angina in China. However, its therapeutic role and mechanism of action for the treatment of myocardial infarction (MI) is not fully understood.

**PURPOSE:**
The present study was designed to investigate the effect of SP on MI-induced cardiac injury and elucidate its underlying molecular mechanisms.

**METHODS:**
To create an in vivo model of MI, we ligated the left coronary artery of Wistar rats. For our in vitro model of MI, we treated primary neonatal rat ventricular myocytes with hypoxia. Myocardial infarct size was measured by triphenyltetrazolium chloride (TTC) staining. Intracellular calcium concentration (Ca²⁺) was measured by confocal microscopy, and cardiomyocyte apoptosis was assessed by TUNEL assay. Western blot was applied to determine protein levels.

**RESULTS:**
Three days post-MI, SP significantly improved MI-induced impairment of cardiac function, as indicated by increased left ventricular systolic pressure (LVSP), maximum rate of left ventricular pressure rise and fall (± dp/dt max), and decreased left ventricular end-diastolic pressure (LVEDP). In addition, SP treatment markedly reduced the infarct size and serum lactate dehydrogenase (LDH) activity; inhibited cardiomyocyte apoptosis and
Caspase-3 activation both in vivo and in vitro; and decreased intracellular calcium overload, Cav1.2, phosphorylated JNK (p-JNK), and p38 MAPK (p-p38 MAPK) levels in ischemic myocardium.

**CONCLUSION:**
SP alleviated cardiac ischemic injury and inhibited cardiomyocyte apoptosis by attenuating intracellular calcium overload, suppressing Caspase-3 activation, and downregulating protein expression of p-JNK and p-p38MAPK. These results suggest that SP may serve as a potential novel therapeutic drug for MI.

Quality control of the traditional Chinese medicine Ruyi jinhuang powder based on high-throughput sequencing and real-time PCR.
https://www.nature.com/articles/s41598-018-26520-3
By Li Q, Sun Y, Guo H, Sang F, Ma H, Peng H, et al.,

Abstract
Traditional Chinese medicine (TCM) has been practiced for thousands of years, although concerns about the efficacy, legality, and safety of TCM continue to be raised. Chromatographic studies have detected the presence of heavy metals and plant toxins within some TCM preparations. However, chromatography is not able to identify all of the compounds of TCM, particularly those items that are not clearly labeled on the packaging. The present study aimed to establish a supplemental method that better assesses the ingredient components of TCM preparations. We established an effective approach to screen the biological and toxic composition of TCM based on high-throughput sequencing (HTS), as well as fast detection and validation of the toxic species by real-time PCR, based on ITS2 DNA barcoding. Ruyi jinhuang powder (RHP), a classical herbal prescription containing the toxic herb Arisaematis rhizoma, was chosen to test the method. This method could determine whether the Arisaematis Rhizoma had been replaced by Pinellia pedatisecta in the RHP. The results were validated by real-time PCR. 90% compositions of RHP were identified by ITS2 DNA barcoding, suggesting that more DNA barcoding markers are needed for TCM identification. The strategy of high-throughput sequencing has the potential for comprehensive ingredient profiling.
for TCM preparations. Real-time PCR provides a expeditious method for monitoring the safety and legality of TCM preparations.

The Critical Role of PTEN/PI3K/AKT Signaling Pathway in Shikonin-Induced Apoptosis and Proliferation Inhibition of Chronic Myeloid Leukemia.


Cell Physiol Biochem. 2018 May 24;47(3):981-993  

Abstract

BACKGROUND/AIMS:
Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm. Tyrosine kinase inhibitors (TKIs) are commonly used to treat CML; however, drug resistance of CML cells to TKIs has limited their clinical application. Shikonin, a traditional Chinese herb, has long been used to treat leukemia in China, but the roles and related molecular mechanisms of shikonin treatment in CML remain unclear. Here, we aimed to evaluate the effects of shikonin on the proliferation, apoptosis, and migration of K562 cells, a CML cell line.

METHODS:
Firstly, K562 cell proliferation and apoptosis were tested by CCK8 assay and flow cytometry with Annexin V-FITC/PI staining. Cell migration was measured by Transwell migration assay. In addition, western blot was performed to determine the proteins (PI3K, Bax, Bcl-2, cleaved caspase-3, PTEN, p-AKT, AKT, CXCR4, SDF-1, CD44) involved in the mechanism of action of shikonin. Finally, neutrophils from peripheral blood of CML patients were obtained, and cell proliferation and apoptosis were tested by CCK8 assay and flow cytometry.

RESULTS:
Shikonin reduced the proliferation of K562 cells in a time- and dose-dependent manner and promoted the apoptosis of K562 cells. Moreover, shikonin increased the PTEN level and inactivated the PI3K/AKT signaling pathway, subsequently upregulating BAX in K562 cells. In addition, shikonin could block K562 cell migration via the CXCR4/SDF-1 axis. Finally, shikonin significantly inhibited the proliferation and promoted the apoptosis of neutrophils from CML patients.

CONCLUSION:
These results demonstrated that shikonin inhibits CML proliferation and migration and induces apoptosis by the
PTEN/PI3K/AKT pathway, revealing the effects of shikonin therapy on CML.

**UPLC-Q/TOF-MS based metabonomics revealed protective effect of Terminalia chebula extract on ischemic stroke rats.**


By Liu W, Mu F, Liu T, Xu H, Chen J, Jia N, et al.,

**Abstract**

Terminalia chebula (TC), a kind of Combretaceae, is a widely used herb in India and East Asia to treat cerebrovascular diseases. However, the potential mechanism of the neuroprotective effects of TC at the metabonomics level is still not unclear. The present study focused on the effects of TC on metabonomics in stroke model. In our study, rats were divided randomly into Sham, Model, and TC groups. The TC group were intragastrically administered with TC for 7 days after middle cerebral artery occlusion (MCAO) operation. The Sham and the Model groups received vehicle for the same length of time. Subsequently, the neuroprotective effects of TC were examined by neurological defects evaluation, infarct volume assessment, and identification of biochemical indicators for antioxidant and anti-inflammatory activities. Further, metabonomics technology was employed to evaluate the endogenous metabolites profiling systematically. Consist to results of biochemical and histopathological assays, pattern recognition analysis showed a clear separation of the Model and the Sham group, indicating a recovery impact of TC on the MCAO rats. Moreover, 12 potential biomarkers were identified in MCAO Model group, involved in energy (lactic acid, succinic acid, and fumarate), amino acids (leucine, alanine, and phenylalanine) and glycerophospholipid [PC(16:0/20:4), PC(20:4/20:4), LysoPC (18:0) and LysoPC(16:0)] metabolism, and other types of metabolism (arachidonic acid and palmitoylcarnitine). Notably, we found that metabolite levels of TC group were partially reversed to normal. In conclusion, TC could ameliorate MCAO rats by intervening with energy metabolism (glycolysis and TCA cycle), amino acid metabolism, glycerophospholipid metabolism and other types of metabolism.
Matrine suppresses KRAS-driven pancreatic cancer growth by inhibiting autophagy-mediated energy metabolism.

By Cho YR, Lee JH, Kim JH, Lee SY, Yoo S, Jung MK, et al.,

Abstract
Matrine is a natural compound extracted from the herb Sophora flavescens Ait which is widely used in traditional Chinese medicine for treating various diseases. Recently, matrine was reported to have antitumor effects against a variety of cancers without any obvious side effects; however, the molecular mechanisms of its antiproliferative effects on cancer are unclear. Here, we report that matrine inhibits autophagy-mediated energy metabolism, which is necessary for pancreatic cancer growth. We found that matrine significantly reduces pancreatic cancer growth in vitro and in vivo by insufficiently maintaining mitochondrial metabolic function and energy level. We also found that either pyruvate or α-ketoglutarate supplementation markedly rescues pancreatic cancer cell growth following matrine treatment. Inhibition of mitochondrial energy production results from matrine-mediated autophagy inhibition by impairing the function of lysosomal protease. Matrine-mediated autophagy inhibition requires stat3 downregulation. Furthermore, we found that the antitumor effect of matrine on pancreatic cancer growth depends on the mutation of the KRAS oncogene. Together, our data suggest that matrine can suppress the growth of KRAS-mutant pancreatic cancer by inhibiting autophagy-mediated energy metabolism.

Licorice root extract and magnesium isoglycyrrhizinate protect against triptolide-induced hepatotoxicity via up-regulation of the Nrf2 pathway.

By Tan QY, Hu Q, Zhu SN, Jia LL, Xiao J, Su HZ, et al.,

Abstract
Triptolide, the predominant biologically active component of the Chinese herb Tripterygium wilfordii Hook f., possesses numerous pharmacological activities, including anti-inflammatory, anti-fertility, anti-neoplastic, and immunosuppressive effects. However, toxicity and severe adverse effects, particularly...
hepatotoxicity, limit the clinical application of triptolide. Licorice root extract contains various bioactive compounds and is potent hepatoprotective. Magnesium isoglycyrrhizinate, a magnesium salt of the 18α-glycyrrhizic acid stereoisomer of glycyrrhizic acid, is used clinically in China to treat chronic viral hepatitis and acute drug-induced liver injury. The aim of this study was to investigate the role of the factor erythroid 2-related factor 2 pathway in the protective effects of LE and MIG against triptolide-induced hepatotoxicity. Hepatotoxicity models were established in L-02 cells and rats using triptolide, and the protective effects of LE and MIG were investigated in vitro and in vivo, respectively. LE and MIG significantly protected against triptolide-induced cytotoxicity. Additionally, triptolide decreased the mRNA and protein levels of Nrf2 and down-regulated Nrf2 target genes, including UGT1A, BSEP, and MRP2, while pretreatment with LE and MIG reversed these effects. Finally, Nrf2-involved antioxidant responses were activated in the presence of LE and MIG.

Material basis research for Huangqi Jianzhong Tang against chronic atrophic gastritis rats through integration of urinary metabonomics and SystemsDock.
By Liu Y, Xu W, Wang G, Qin X.

Abstract
ETHNOPHARMACOLOGICAL RELEVANCE:
Huangqi Jianzhong Tang (HQJZ), a celebrated traditional Chinese medicine (TCM), is commonly used for treatment of chronic atrophic gastritis (CAG) in China.

AIM OF THE STUDY:
We aimed to screen out the material basis of HQJZ against CAG.

MATERIALS AND METHODS:
CAG rat model was constructed by alternant administrations of ammonia solution and sodium deoxycholate, and the hunger disorder method. Body weight, biochemical indexes and histopathological exam were used to evaluate the efficacy of HQJZ. 1H NMR-based metabonomics was employed to analyze the urine metabolic features of HQJZ deviated from CAG rats. SystemsDock analysis was utilized to explore the active compounds involved
into the efficacy of HQJZ against CAG based on the targeted metabolic biomarkers.

**RESULTS:**
The metabonomic results indicated that HQJZ could significantly improve 16 urinary perturbed metabolites in CAG rats, which were involved into the metabolism of energy and amino acids. And then 28 related proteins and genes were selected out to be the potential targets of HQJZ against CAG based on the six key metabolites closely correlating with biochemical indexes (α-ketoglutarate, valine, sarcosine, glycine, malonate and fumarate). 71 previous identified compounds were docked through systemsDock-aided molecular docking experiments. And the constructed herb-component-protein-metabolite interaction network (HCPMN) revealed the associations between the herbal formulae and CAG. At last, 51 compounds of them were screened as promising active constitutes for the inhibition of CAG, which could act on various targeted proteins.

**CONCLUSIONS:**
The results showed that the approach integrating of metabonomics and systemsDock is a powerful tool to obtain the material basis and regulatory mechanism of TCM formula.