英国中医药学会

The Association of Traditional Chinese Medicine and Acupuncture UK

TCM Research Updates

Issue No 19

1st July 2016

Contents

Anti-inflammatory and anti-allergic effects and underlying mechanisms of Huang-Lian-Jie-Du extract: Implication for atopic dermatitis treatment.

http://www.ncbi.nlm.nih.gov/pubmed/26976763.

J Ethnopharmacol. 2016 Jun 5;185:41-52.

By Chen Y

ETHNOPHARMACOLOGICAL RELEVANCE:

Huang-Lian-Jie-Du Decoction (HLJDD), a well-known Chinese herbal formula recorded in the Tang dynasty, is composed of Coptidis rhizoma (Huang-Lian), Scutellariae radix (Huang-Qin), Phellodendri Chinensis cortex (Huang-Bai) and Gardenia fructus (Zhi-Zi). It has clinical efficacy of purging fire for removing toxin and is commonly used for the treatment of disease including Alzheimer's disease, stroke and gastrointestinal disorders. HLJDD is also frequently applied for the treatment of various skin diseases, such as atopic dermatitis (AD) and various types of eczema. The aim of this study is to investigate the anti-inflammatory and anti-allergic actions of Huang-Lian-Jie-Du ethanolic extract (HLJDE) and to elucidate underlying molecular mechanisms of action using relevant in vitro experimental models.

MATERIALS AND METHODS:

The anti-inflammatory effects of HLJDE were investigated through evaluating the change of nitric oxide (NO) and the production of several cytokines and chemokines in lipopolysaccharide (LPS)-stimulated RAW264.7 cell line. Expression of mitogen-activated protein kinases (MAPKs), NF-κB p65 phosphorylation, inhibitor-κBα (IκBα) degradation were further investigated to elucidate its anti-inflammatory molecular mechanisms. Meanwhile, the anti-allergic activities of HLJDE was also evaluated using antigen-induced RBL-2H3 cell line. β-hexosaminidase and histamine release and selected cytokines and chemokines were measured to evaluate the anti-allergic activities of HLJDE. In addition, intracellular Ca(2+)level, MAPKs and Lyn phosphorylation were further investigated to reveal its anti-allergic molecular mechanisms.

RESULTS:

HLJDE could significantly suppress the secretion of NO, IL-1β, IL-4, MCP-1 and GM-CSF in RAW264.7 cells in a dose-dependent manner. In addition, HLJDE also markedly reduced the phosphorylation of MAPKs, and inhibited the transcriptional activity of NF-κB and IκBα degradation. Furthermore, HLJDE exerted marked anti-allergic activity through inhibiting the release of β-hexosaminidase and histamine. The release of cytokines and chemokines (IL-4, TNF-α, MCP-1) from activated RBL-2H3 cells were also attenuated by pretreatment with HLJDE. The inhibitory effects on intracellular Ca(2+)level, and reduced phosphorylation of

MAPKs and Lyn are believed to be the anti-allergic mechanisms.

CONCLUSIONS:

HLJDE exerted significant anti-inflammatory and anti-allergic effects through suppressing the production of allergic and inflammatory mediators via the NF-κB and MAPKs inactivation and IκBα degradation in the LPS-stimulated RAW24.7 cells, inactivation of MAPKs and Lyn pathway in antigen-induced RBL-2H3 cells. The present study provides in vitro experimental evidence to support the use of HLJDE for the clinical treatment of AD.

Guizhi Fuling Wan, a Traditional Chinese Herbal Formula, Sensitizes Cisplatin-Resistant Human Ovarian Cancer Cells through Inactivation of the PI3K/AKT/mTOR Pathway.

http://www.ncbi.nlm.nih.gov/pubmed/27293459

Evid Based Complement Alternat Med. 2016;2016:4651949. .

By Han L

Abstract

The aim of the study was to explore the possible mechanisms that Guizhi Fuling Wan (GFW) enhances the sensitivity of the SKOV3/DDP ovarian cancer cells and the resistant xenograft tumours to cisplatin. Rat medicated sera containing GFW were prepared by administering GFW to rats, and the primary bioactive constituents of the sera were gallic acid, paeonol, and paeoniflorin analysed by HPLC/QqQ MS. Cell counting kit-8 analysis was shown that coincubation of the sera with cisplatin/paclitaxel enhanced significantly the cytotoxic effect of cisplatin or paclitaxel in SKOV3/DDP cells. The presence of the rat medicated sera containing GFW resulted in an increase in rhodamine 123 accumulation by flow cytometric assays and a decrease in the protein levels of P-gp, phosphorylation of AKT at Ser473, and mTOR in a dose-dependent manner in SKOV3/DDP cells by western blot analysis, but the sera had no effect on the protein levels of PI3K p110α and total AKT. The low dose of GFW enhanced the anticancer efficacy of cisplatin and paclitaxel treatment in resistant SKOV3/DDP xenograft tumours. GFW could sensitize cisplatin-resistant SKOV3/DDP cells by inhibiting the protein level and function of P-gp, which may be medicated through inactivation of the PI3K/AKT/mTOR pathway.

Effects and mechanisms of Shaofu-Zhuyu decoction and its major bioactive component for Cold - Stagnation and Blood - Stasis primary dysmenorrhea rats.

http://www.ncbi.nlm.nih.gov/pubmed/27060631

J Ethnopharmacol. 2016 Jun 20;186:234-43.

By Huang X[1]

ETHNOPHARMACOLOGICAL RELEVANCE:

Traditional Chinese medicine (TCM) is used under the guidance of the theory of traditional Chinesemedical sciences in clinical application. The Chinese herbal formula, Shaofu Zhuyu decoction (SFZYD), is considered as an effective prescription for treating Cold - Stagnation and Blood - Stasis (CSBS) primary dysmenorrhea. The previous studies showed the SFZYD exhibited significant anti-inflammation and analgesic effect. In this present study the metabolomics of CSBS primary dysmenorrhea diseased rats and the cytokine transcription in PHA stimulated-PBMC were investigated to explore the effects and mechanisms.

AIM OF THE STUDY:

Explore a valuable insight into the effects and mechanisms of SFZYD on Cold - Stagnation and Blood - Stasis primary dysmenorrhea rats.

MATERIALS AND METHODS:

We established CSBS primary dysmenorrhea diseased rats according the clinical symptoms. A targeted tandem mass spectrometry (MS/MS)-based metabolomic platform was used to evaluate the metabolic profiling changes and the intervention effects by SFZYD. The PBMC cell was adopted to explore the mechanisms by analyzing the signaling pathway evaluated by expression of inflammatory cytokines, c-jun and c-fos and corresponding phosphorylation levels.

RESULTS:

Estradiol, oxytocin, progesterone, endothelin, β-endorphin and PGF2α were restored back to the normal level after the treatment of SFZYD. Total twenty-five metabolites (10 in plasma and 15 in urine), up-regulated or down-regulated, were identified. These identified biomarkers underpinning the metabolic pathway including pentose and glucuronate interconversions, steroid hormone biosynthesis, and glycerophospholipid metabolism are disturbed in model rats. Among these metabolites, twenty one potential biomarkers were regulated after SFZYD treated. The compound of paeoniflorin, a major bioactive compound in SFZYD, was proved to regulate the MAPK signaling pathway by inhibiting the expression of IL-1β, IL-2, IL-10, IL-12, TNFα, INFγ, c-jun and c-fos in PHA stimulated-PBMC.

CONCLUSION:

These findings indicated that SFZYD improved the metabolic profiling and biochemical indicators on CSBS primary dysmenorrhea rats. And the mechanisms were closely related with the regulation of the MAPK pathway by reduction in phosphorylated forms of the three MAPK (ERK1/2, p38 and JNK) and down regulation of c-jun and c-fos by paeoniflorin. The data could be provided the guidance for further research and new drug discovery.

Effects of the Chinese herbal formula "Zuojin Pill" on the pharmacokinetics of dextromethorphan in healthyChinese volunteers with CYP2D6*10 genotype.

http://www.ncbi.nlm.nih.gov/pubmed/27023460

Eur J Clin Pharmacol. 2016 Jun;72(6):689-95.
By Qiu F

OBJECTIVE:

Zuojin Pill has been shown to inhibit the cytochrome P450 (CYP) 2D6 isoenzyme in vitro. In Chinese individuals, CYP 2D6*10 is the most common allele with reduced enzyme activity. In this study, we investigated the pharmacokinetic interaction between Zuojin Pill and the sensitive CYP2D6 probe dextromethorphan in healthy Chinese volunteers with CYP2D6*10 genotype.

METHODS:

A pharmacokinetics interaction study was carried out in three groups with CYP2D6*1/*1 (n = 6), CYP2D6*1/*10 (n = 6), and CYP2D6*10/*10 (n = 6) genotypes. Each participant received a single oral dose of dextromethorphan (15 mg) followed by Zuojin Pill (3 g twice daily) for 7 days, and received 3 g Zuojin Pill with 15 mg dextromethorphan in the last day. Blood samples (0-24 h) and urine samples (0-12 h) were collected at baseline and after the administration of Zuojin Pill, and the

samples' concentration of dextromethorphan and its main metabolite dextrorphan was determined.

RESULTS:

Compared to baseline values, co-administration of Zuojin Pill (3 g twice daily) for 7 days increased the AUC0-24 of dextromethorphan [mean (90 % CI)] by 3.00-fold (2.49~3.61) and 1.71-fold (1.42~2.06), and decreased oral clearance(CL/F) by 0.27-fold (0.2-0.40) and 0.57-fold (0.48-0.67) in the participants with CYP2D6*1/*1 and CYP2D6*1/*10 genotypes, respectively. In contrast, no significant change was observed in these pharmacokinetic parameters of the participants with CYP2D6*10/*10 genotype.

CONCLUSION:

These data demonstrated that administration of Zuojin Pill inhibited moderately CYP2D6-mediated metabolism of dextromethorphan in healthy volunteers. The inhibitory influence of CYP2D6 was greater in CYP2D6*1/*1 and CYP2D6*1/*10 groups than CYP2D6 *10/*10 group.

TarNet: An Evidence-Based Database for Natural Medicine Research.

http://www.ncbi.nlm.nih.gov/pubmed/27337171
PLoS One. 2016 Jun 23;11(6):e0157222.
By Hu R.

BACKGROUND:

Complex diseases seriously threaten human health. Drug discovery approaches based on "single genes, single drugs, and single targets" are limited in targeting complex diseases. The development of new multicomponent drugs for complex diseases is imperative, and the establishment of a suitable solution for drug group-target protein network analysis is a key scientific problem that must be addressed. Herbalmedicines have formed the basis of sophisticated systems of traditional medicine and have given rise to some key drugs that remain in use today. The search for new molecules is currently taking a different route, whereby scientific principles of ethnobotany and ethnopharmacognosy are being used by chemists in the discovery of different sources and classes of compounds.

RESULTS:

In this study, we developed TarNet, a manually curated database and platform of traditional medicinal plants with natural compounds that includes potential bio-target information. We gathered information on proteins that are related to or affected by medicinal plant ingredients and data on protein-protein interactions (PPIs). TarNet includes in-depth information on both plant-compound-protein relationships and PPIs. Additionally, TarNet can provide researchers with network construction analyses of biological pathways and protein-protein interactions (PPIs) associated with specific diseases. Researchers can upload a gene or protein list mapped to our PPI database that has been manually curated to generate relevant networks. Multiple functions are accessible for network topological calculations, subnetwork analyses, pathway analyses, and compound-protein relationships.

CONCLUSIONS:

TarNet will serve as a useful analytical tool that will provide information on medicinal plant compound-affected proteins (potential targets) and system-level analyses for systems biology and network pharmacology researchers. TarNet is freely available at http://www.herbbol.org:8001/tarnet, and detailed tutorials on the program are also available.

Astragalus-containing Traditional Chinese Medicine, with and without prescription based on syndrome differentiation, combined with chemotherapy for advanced non-small-cell lung cancer: a systemic review and meta-analysis.

http://www.ncbi.nlm.nih.gov/pubmed/27330356.

Curr Oncol. 2016 Jun;23(3):e188-95.
By Wang SF

OBJECTIVE:

Traditional Chinese Medicine (tcm) is used in China as part of the treatment for non-small-cell lung cancer (nsclc) and often includes prescription of herbal therapy based on syndrome differentiation. Studies of various Astragalus-based Chinese medicines combined with platinum-based chemotherapy in the treatment of lung cancer are popular in East Asia, particularly in China. The aim of the present study was to perform a systematic review and meta-analysis comparing platinum-based chemotherapy alone with platinum-based chemotherapy plus Astragalus-basedChinese botanicals, with and without prescription based on syndrome differentiation, as first-line treatment for advanced nsclc.

METHODS:

We searched the Chinese Biomedical Literature database, the China National Knowledge Internet, the VIP Chinese Science and Technology Periodicals Database, PubMed, embase, the Cochrane databases, and abstracts presented at meetings of the American Society of Clinical Oncology, the World Conference on Lung Cancer, the European Society for Medical Oncology, and the Chinese Society of Clinical Oncology for all eligible studies. Endpoints were overall survival; 1-year, 2-year, and 3-year survival rates; performance status; overall response rate; and grade 3 or 4 adverse events. Subgroup analyses based on herbal formulae individualized using syndrome differentiation or on oral or injection patent medicines were performed using the Stata software application (version 11.0: StataCorp LP, College Station, TX, U.S.A.) and a fixed-effects or random-effects model in case of heterogeneity. Results are expressed as a hazard ratio (hr) or relative risk (rr), with corresponding 95% confidence intervals (cis).

RESULTS:

Seventeen randomized studies with scores on the Jadad quality scale of 2 or more, representing 1552 patients, met the inclusion criteria. Compared with platinum-based chemotherapy alone, the addition of Astragalus-based tcm to chemotherapy was associated with significantly increased overall survival (hr: 0.61; 95% ci: 0.42 to 0.89; $p = 0.011$); 1-year (rr: 0.73; 95% ci: 0.65 to 0.82; $p < 0.001$), 2-year (rr: 0.3344; 95% ci: 0.237 to 0.4773; $p < 0.001$), and 3-year survival rates (rr: 0.30; 95% ci: 0.17 to 0.53; $p < 0.001$); performance status (rr: 0.43; 95% ci: 0.34 to 0.55; $p < 0.001$); and tumour overall response rate (rr:

0.7982; 95% ci: 0.715 to 0.89; p < 0.001). Subgroup analyses indicated that Astragalus herbal formulae given based on syndrome differentiation were more effective than Astragalus-based oral and injection patent medicines. Side effects-including anemia, neutropenia, thrombocytopenia, fatigue, poor appetite, nausea, and vomiting-were significantly more frequent with platinum-based chemotherapy alone than when platinum-based chemotherapy was combined with Astragalus-based tcm.

CONCLUSIONS:
Astragalus-based Chinese botanical therapy, especially when based on syndrome differentiation, is associated with increased efficacy of platinum-based chemotherapy and decreased platinum-derived toxicities for patients with advanced nsclc.

Comprehensive Qualitative Ingredient Profiling of Chinese Herbal Formula Wu-Zhu-Yu Decoction via a Mass Defect and Fragment Filtering Approach Using High Resolution Mass Spectrometry.

http://www.ncbi.nlm.nih.gov/pubmed/27213316

Molecules. 2016 May 19;21(5). pii: E664.
By Xu H

Abstract
The Wu-Zhu-Yu decoction is a traditional Chinese medicine formula for the treatment of headache. To reveal its material basis, a rapid and reliable liquid chromatography-high resolution mass spectrometry method was established for comprehensive profiling of the chemical ingredients in the Wu-Zhu-Yu decoction. The method was used on a quadrupole time-of-flight mass spectrometer along with an advanced data processing procedure consisting of mass accuracy screening, mass defect filtering and fragment filtering. After eliminating interference with a filtering approach, the MS data profiling was made more distinct and accurate. With the optimized conditions of only 35 min LC separation and single sample injection of each positive or negative ion mode, a total of 168 compounds were characterized, including 23 evodiamine and its analogous alkaloids, 12 limonoids, 17 gingerols, 38 ginsenosides, 15 flavonoids, 16 organic acids, 14 alkaloids, 5 saponins, 3 2,2-dimethylchromenes and 25 other compounds. The fragmentation patterns of representative compounds were illustrated as well. Integrative qualitative analysis of the Wu-Zhu-Yu decoction by high resolution mass spectrometry was accomplished and reported for the first time. The study demonstrated that the established method was a powerful and reliable strategy for comprehensive detection and would be widely applicable for identification of complicated components from herbal prescriptions, and may provide a basis for chemical analysis of other complex mixtures.

Use of Plant-Based Therapies and Menopausal Symptoms: A Systematic Review and Meta-analysis.

http://www.ncbi.nlm.nih.gov/pubmed/27327802

JAMA. 2016 Jun 21;315(23):2554-63.

By Franco OH

IMPORTANCE:

Between 40% and 50% of women in Western countries use complementary therapies to manage menopausal symptoms.

OBJECTIVE:

To determine the association of plant-based therapies with menopausal symptoms, including hot flashes, night sweats, and vaginal dryness.

DATA SOURCES:

The electronic databases Ovid MEDLINE, EMBASE, and Cochrane Central were systematically searched to identify eligible studies published before March 27, 2016. Reference lists of the included studies were searched for further identification of relevant studies.

STUDY SELECTION:

Randomized clinical trials that assessed plant-based therapies and the presence of hot flashes, night sweats, and vaginal dryness.

DATA EXTRACTION:

Data were extracted by 2 independent reviewers using a predesigned data collection form.

MAIN OUTCOMES AND MEASURES:

Hot flashes, night sweats, and vaginal dryness.

RESULTS:

In total, 62 studies were identified, including 6653 individual women. Use of phytoestrogens was associated with a decrease in the number of daily hot flashes (pooled mean difference of changes, -1.31 [95% CI, -2.02 to -0.61]) and vaginal dryness score (pooled mean difference of changes, -0.31 [95% CI, -0.52 to -0.10]) between the treatment groups but not in the number of night sweats (pooled mean difference of changes, -2.14 [95% CI, -5.57 to 1.29]). Individual phytoestrogen interventions such as dietary and supplemental soy isoflavones were associated with improvement in daily hot flashes (pooled mean difference of changes, -0.79 [-1.35 to -0.23]) and vaginal dryness score (pooled mean difference of changes, -0.26 [-0.48 to -0.04]). Several herbal remedies, but not Chinese medicinal herbs, were associated with an overall decrease in the frequency of vasomotor symptoms. There was substantial heterogeneity in quality across the available studies, and 46 (74%) of the included randomized clinical trials demonstrated a high risk of bias within 3 or more areas of study quality.

CONCLUSIONS AND RELEVANCE:

This meta-analysis of clinical trials suggests that composite and specific phytoestrogen supplementations were associated with modest reductions in the frequency of hot flashes and vaginal dryness but no significant reduction in night sweats. However, because of general suboptimal quality and the heterogeneous nature of the current evidence, further rigorous studies are needed to determine the association of plant-based and natural therapies with menopausal health.

Cardioprotective effects of Notoginsenoside R1 against ischemia/reperfusion injuries by regulating oxidative stress- and endoplasmic reticulum stress- related signaling pathways.

http://www.ncbi.nlm.nih.gov/pubmed/26888485
Sci Rep. 2016 Feb 18;6:21730.
By Yu Y.

BACKGROUND:

Recent reports suggested the involvement of oxidative stress- and endoplasmic reticulum stress (ERS)-associated pathways in the progression of ischemia/reperfusion (I/R) injury. Notoginsenoside R1 (NGR1) is a novel saponin isolated from P. notoginseng, which has a history of prevention and treatment of cardiovascular diseases.

OBJECTIVE:

We aimed to examine the cardioprotective effects of NGR1 on I/R-induced heart dysfunction ex vivo and in vitro.

METHODS:

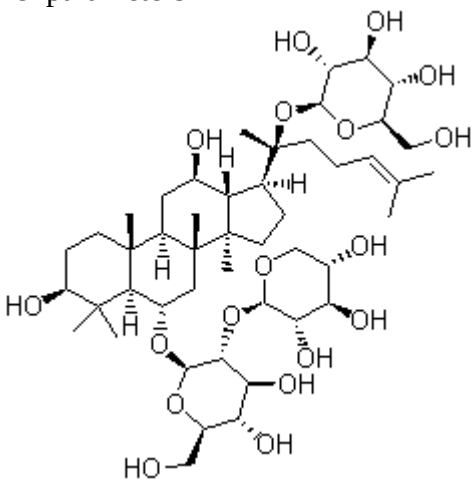
H9c2 cadiomyocytes were incubated with NGR1 for 24 h and exposed to hypoxia/reoxygenation. Isolated rat hearts were perfused by NGR1 for 15 min and then subjected to global ischemia/reperfusion. Hemodynamic parameters were monitored as left ventricular systolic pressure (LVSP), heart rate, and maximal rate of increase and decrease of left ventricular pressure (±dP/dt max/min).

RESULTS:

NGR1 pretreatment prevents cell apoptosis and delays the onset of ERS by decreasing the protein expression levels of ERS-responsive proteins GRP78, P-PERK, ATF6, IRE, and inhibiting the expression of pro-apoptosis proteins CHOP, Caspase-12, and P-JNK. Besides, NGR1 scavenges free radical, and increases the activity of antioxidase. NGR1 inhibits Tunicamycin-induced cell death and cardic dysfunction.

CONCLUSION:

We elucidated the significant cardioprotective effects of NGR1 against I/R injuries, and demonstrated the involvement of oxidative stress and ERS in the protective effects of NGR1.



The ginseng's fireness is associated with the lowering activity of liver Na+-K+-ATPase.

http://www.ncbi.nlm.nih.gov/pubmed/27288755

J Ethnopharmacol. 2016 Jun 8. pii: S0378-8741(16)30381-6.

By Xu X

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE:

Ginseng is an herbal medicine used worldwide that possesses a wide range of pharmacological activities. However, its side effects are rarely discussed. The experience of Chinese medicine has revealed that taking ginseng at a high dose chronically can cause fireness, i.e., the ginseng-abuse syndrome. Here, we explored the mechanism of ginseng's fireness by comparing the energy metabolism of mice affected by red ginseng (RG), ginseng (GS), ginseng leaves (GL) and American ginseng (AG), which exhibit different drug properties according to the theory of TCM.

MATERIALS AND METHODS:

KM mice were randomly divided into five groups ($n \geq 30$ per group) and administered distilled water or drugs, respectively. Mice receiving RG, GS, or GL received 4.5g/(kg·day), while the mice receiving AG received 3g/(kg·day). Control mice received distilled water. The duration of exposure for all groups was 31 days. The mice's physical characteristics, such as eye condition, rectal temperature, saliva secretion, urine, stool weight, blood coagulation time and swimming time, were measured at different times after administration. Energy metabolism indexes were measured via TSE phenoMaster/LabMaster animal monitoring system, including the mice' 24h oxygen consumption (VO_2), carbon dioxide production (VCO_2), heat production (H) and energy expenditure (EE). Biochemical indices were measured by ultraviolet spectrophotometer and microplate reader, including pyruvic acid content in serum and succinate dehydrogenase (SDH) activity, lactate dehydrogenase (LDH) activity, the Na^+-K^+-ATPase activity and the content of glycogen in the liver tissue.

RESULTS:

After 31 days of drug administration, mice in the RG and GS groups exhibited obviously more eye secretions, less saliva secretion and less urine. Compared with the control group, the swimming times of mice in the GS, AG and GL groups were significantly prolonged; the clotting time of mice in the GL was extended significantly; VCO_2, H and EE of mice in the GS group were obviously increased; Pyruvate content of mice in the RG group showed an initial decrease followed by an increase; SDH activity of mice in the AG and GL groups was significantly inhibited; LDH activity of the mice showed no significant difference among different groups; Na^+-K^+-ATP enzyme activity of the RG and GS groups showed up-regulation initially and then down-regulation; the content of hepatic glycogen of mice in the GS and GL groups increased significantly.

CONCLUSION:
The results demonstrated that RG and GS with their warm drug nature could enhance the body's energy metabolism to produce their dryness to the body. The liver Na^+-K^+-ATP enzyme activity may be the primary index for indicating the fireness of ginseng. In addition, our results demonstrated that ginseng, especially red ginseng, is not suitable for long time application with a higher dose.

Guizhi-Shaoyao-Zhimu decoction attenuates rheumatoid arthritis partially by reversing inflammation-immune system imbalance.

http://www.ncbi.nlm.nih.gov/pubmed/27277474

J Transl Med. 2016 Jun 8;14(1):165.
By Guo Q

Abstract

BACKGROUND:
Guizhi-Shaoyao-Zhimu decoction (GSZD) has been extensively used for rheumatoid arthritis (RA) therapy. Marked therapeutic efficacy of GSZD acting on RA has been demonstrated in several long-term clinical trials without any significant side effects. However, its pharmacological mechanisms remain unclear due to a lack of appropriate scientific methodology.

METHODS:
GSZD's mechanisms of action were investigated using an integrative approach that combined drug target prediction, network analysis, and experimental validation.

RESULTS:
A total of 77 putative targets were identified for 165 assessed chemical components of GSZD. After calculating the topological features of the nodes and edges in the created drug-target network, we identified a candidate GSZD-targeted signal axis that contained interactions between two putative GSZD targets [histone deacetylase 1 (HDAC1) and heat shock protein 90 kDa alpha, class A member 1 (HSP90AA1)] and three known RA-related targets [NFKB2; inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta (IKBKB); and tumor necrosis factor-alpha (TNF-α)]. This signal axis could connect different functional modules that are significantly associated with various RA-related signaling pathways, including T/B cell receptor, Toll-like receptor, NF-kappa B and TNF pathways, as well as osteoclast differentiation. Furthermore, the therapeutic effects and putative molecular mechanisms of GSZD's actions on RA were experimentally validated in vitro and in vivo.

CONCLUSIONS:
GSZD may partially attenuate RA by reversing inflammation-immune system imbalance and regulating the HDAC1-HSP90AA1-NFKB2-IKBKB-TNF-α signaling axis.