doi.org/10.36721/PJPS.2026.39.8.232.1

Exploring the anti-gout mechanism of Erding granules based on network pharmacology and experimental verification

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Abstract: **Background**: Gout is a common form of inflammatory arthritis. **Objectives**: This study aimed to explore the mechanism of Erding granules in gout. **Methods**: The anti-gout components and targets of Erding granules were identified using network pharmacology. Molecular docking predicted the degree of binding between compounds and targets. Cell experiments confirmed changes in target expression levels and preliminary anti-inflammatory effects. **Results**: Erding granules contain 14 potential active ingredients and 18 possible targets for fighting gout. Using KEGG and GO enrichment analyses, two signaling pathways were identified, namely PI3K/AKT and MAPK. Two cellular components, GO: 0035866, alpha-beta3 integrin-PKCalpha complex and GO: 0035867, alpha-beta3 integrin-IGF-1-IGF1R complex, were identified. The key signaling pathways and two cellular components were traced to identify the corresponding genes and experiments were designed to verify them. Through RT-qPCR, it was found that monosodium urate (MSU) can cause increases in the expression levels of INSR, PRKCA and IGF1R mRNA; however, Erding granules can reverse these increases. Under the action of Erding granules, the increased release of IL-1β and IL-18 induced by MSU was reversed. **Conclusion**: Erding granules may alleviate gout by reducing the release of pro-inflammatory factors via targeting INSR, PRKCA and IGF1R.

Keywords: Erding Granules; Gout; IGF1R; INSR; NLRP3; PRKCA

Submitted on 01-01-2025 – Revised on 14-03-2025 – Accepted on 25-08-2025

INTRODUCTION

Gout is a metabolic disease caused by excessive accumulation of uric acid (Song *et al*., 2023). An epidemiological study shows that there has been a huge increase in the overall incidence and prevalence of gout in recent years (Ashiq *et al*., 2021). Prevalence has been reported to range from 0.68% to 3.90% in adults in population-based studies from Asia, Europe and North America (Dalbeth *et al*., 2021). The pathological process of gout is relatively complex. It is mainly due to excessive accumulation of uric acid, uric acid with excretion disorder, inflammatory response caused by uric acid accumulation and the interaction of these factors (Sun *et al*., 2023). Uric acid is a by-product of the conversion of purine in the human body through the purine metabolism pathway (Shi *et al*., 2020). If excessive amounts of purine-rich foods are consumed, the accelerated production of uric acid will be triggered within our bodies through related pathways, such as the conversion of adenosine 5'-triphosphate (ATP) and adenosine diphosphate (ADP) (Liu *et al*., 2024). Insufficient clearance of uric acid will lead to an increase in uric acid levels in the serum and excretion of uric acid is dependent the kidneys (Chou *et al*., 2020). Both glomerular filtration and tubular reabsorption in the kidney rely on transport proteins (Zitt *et al*., 2020). If these proteins are abnormal, this affects the timely excretion of uric acid. Uric acid also triggers signaling pathways in various cells in the body, ultimately causing inflammation. Related factors and cells in inflammation will work together to accelerate the progression of gout (Deng *et al*., 2023). If gout attacks are prolonged, serious conditions, such as tophi, urinary stones and kidney function damage, can occur (Dalbeth *et al*., 2021). In recent years, the incidence of gout has gradually increased and it has become the second most common metabolic disease in the world (Kang *et al*., 2023). More and more people are suffering from gout. Studies have shown that people with gout are getting younger (Wu *et al*., 2024). This makes gout a major public health problem. There are currently no drugs that cure gout. Although some Western medicines can temporarily relieve the symptoms of gout, they also have serious side effects (Zhang *et al*., 2022). For instance, allopurinol can cause the rare but potentially life-threatening allopurinol hypersensitivity syndrome; febuxostat increases the cardiovascular risk (Dalbeth *et al*., 2021). Therefore, finding new and more reliable treatments for gout has become a focus of research.

Erding granules are a widely used Chinese patent medicine in clinical practice. The main ingredients of Erding granules are *Violsse Herba*, *Lobeliae Chinensis Herba*, *Taraxacum officinale* and *Isatidis Radix*. Erding granules have the effect of clearing away heat and detoxifying. Therefore, Erding granules can be used to treat swelling, pain relief and various forms of inflammation.

It is urgent to research and develop a traditional Chinese medicine or Chinese patent medicine to treat gout. However, the mechanism by which Erding granules treat

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gout remains unclear. Therefore, this article uses network pharmacology and cytological methods to explore the mechanism of action of Erding granules in gout, to better apply them in clinical treatment.

MATERIALS AND METHODS

Network pharmacology approach

The TCMSP and HERB (Fang *et al*., 2020) databases were searched for the ingredients of Erding granules, with oral bioavailability (OB)≥20% and Drug-likeness (DL)≥0.1 as cutoffs to obtain active ingredients (Ru *et al*., 2014). Targets of active ingredients were collected in Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), HERB and HIT (Yan *et al*., 2021) databases. The word "gout" was used as the search term to search for disease genes in Therapeutic Target Database (TTD) (Zhou *et al*., 2024), HERB and Online Mendelian Inheritance in Man (OMIM) (Sayers *et al*., 2022) databases. Anti-gout targets in Erding granules were the common targets between disease genes and Erding granule targets. Cytoscape 3.7.1 software was used to plot the herbal medicine-ingredient-anti-gout target network.

Gene annotation

STRING database (Szklarczyk *et al*., 2023) was used for protein-protein interactions (PPI) analysis. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were performed.

Molecular docking

CB-DOCK2 (Liu *et al*., 2022) online docking tool was used for molecular docking. Molecular docking was performed on the identified candidate pockets using AutoDock Vina.

Cell membrane preparation

The treated cells were prepared into a cell suspension and centrifuged. Then, the cells were resuspended in pre-chilled KCL/Hepes relaxation buffer to prepare a cell resuspension of 1.6×10^7 cells/ml. The cell resuspension was sonicated twice (20s each time) and then centrifuged at 700 g for 7 min (Marcil *et al*., 1999). Unbroken cells and cell nuclei were discarded. Then, the sample was centrifuged at 18000 g for 45 min in a Beckman ultracentrifuge. Precipitated cell membrane fragments were washed once and resuspended in a buffer.

Real-time quantitative polymerase chain reaction (RT-qPCR) assay

Total RNA in cells was extracted using TRIzol (Invitrogen). Complementary DNA was reverse transcribed using a complementary DNA (cDNA) synthesis kit (Vazyme, Nanjing, China) following the manufacturer's instructions. RT-qPCR analyses were performed using the miScript® SYBR Green PCR Kit (QIAGEN) on a CFX96™ Real-Time PCR Detection System (Bio-Rad, USA). Data were analyzed using $2^{-\Delta\Delta t}$.

Detection of interleukin (IL)-1β and IL-18 release

The concentrations of IL-1β and IL-18 were determined by ELISA using a commercial kit (BD Biosciences, San Diego, CA, USA) according to the manufacturer's instructions.

Statistical analysis

In this study, the results were repeated at least three times. The data were analyzed and processed using GraphPad Prism 10.1.2 software. $p<0.05$ was considered statistically significant.

RESULTS

Exploration of chemical composition and target of Erding granules

After database search and collection, Erding Granules contain a total of 14 potential chemical components (Table 1). After collecting targets from the database and intersecting them with the "gout" target, a total of 18 potential targets were obtained for Erding Granules against gout. Then, a target network of Erding granules components against gout was constructed (Fig. 1).

Gene annotation

PPI analysis was conducted on these 18 possible targets (Fig. 2A). For KEGG enrichment analysis, the top 20 entries were selected for display, with PI3K/AKT signaling pathway and MAPK signaling pathway specially marked (Fig. 2B). For GO enrichment analysis, the top 20 entries were selected for analysis and two cellular components were found to be related to gout. They are GO: 0035866 alpha-beta3 integrin-PKCalpha complex and GO: 0035867 alpha-beta3 integrin-IGF-1-IGF1R complex (Fig. 2C).

Molecular docking

These two sets of signaling pathways and two cellular components were traced back. Insulin receptor (INSR) can be targeted by kaempferol, luteolin, apigenin and quercetin. Protein kinase C alpha type (PRKCA) was targeted by quercetin and dibutyl phthalate (DBP). Insulin-like growth factor 1 receptor (IGF1R) was targeted by apigenin. After molecular docking, the Vina score of the kaempferol-INSR pair was -7.1 kcal/mol, the Vina score of the luteolin-INSR pair was -7.4 kcal/mol, the Vina score of the apigenin-INSR pair was -7.1 kcal/mol and the Vina score of the quercetin-INSR pair was -7.6 kcal/mol (Fig. 3A); the Vina score of the quercetin-PRKCA pair was -9.6 kcal/mol, the Vina score of the DBP-PRKCA pair was -6.4 kcal/mol (Fig. 3B); and the Vina score of the apigenin-IGF1R pair was -7.5 kcal/mol (Fig. 3C).

Cell experiment detection

Through RT-qPCR, it was found that monosodium urate (MSU) caused increases in the expression levels of INSR, PRKCA, IGF1R and NACHT, LRR and PYD domains-containing protein 3 (NLRP3) mRNA; whereas Erding Granules reversed these increases (Fig. 4A-4D, Table 2).

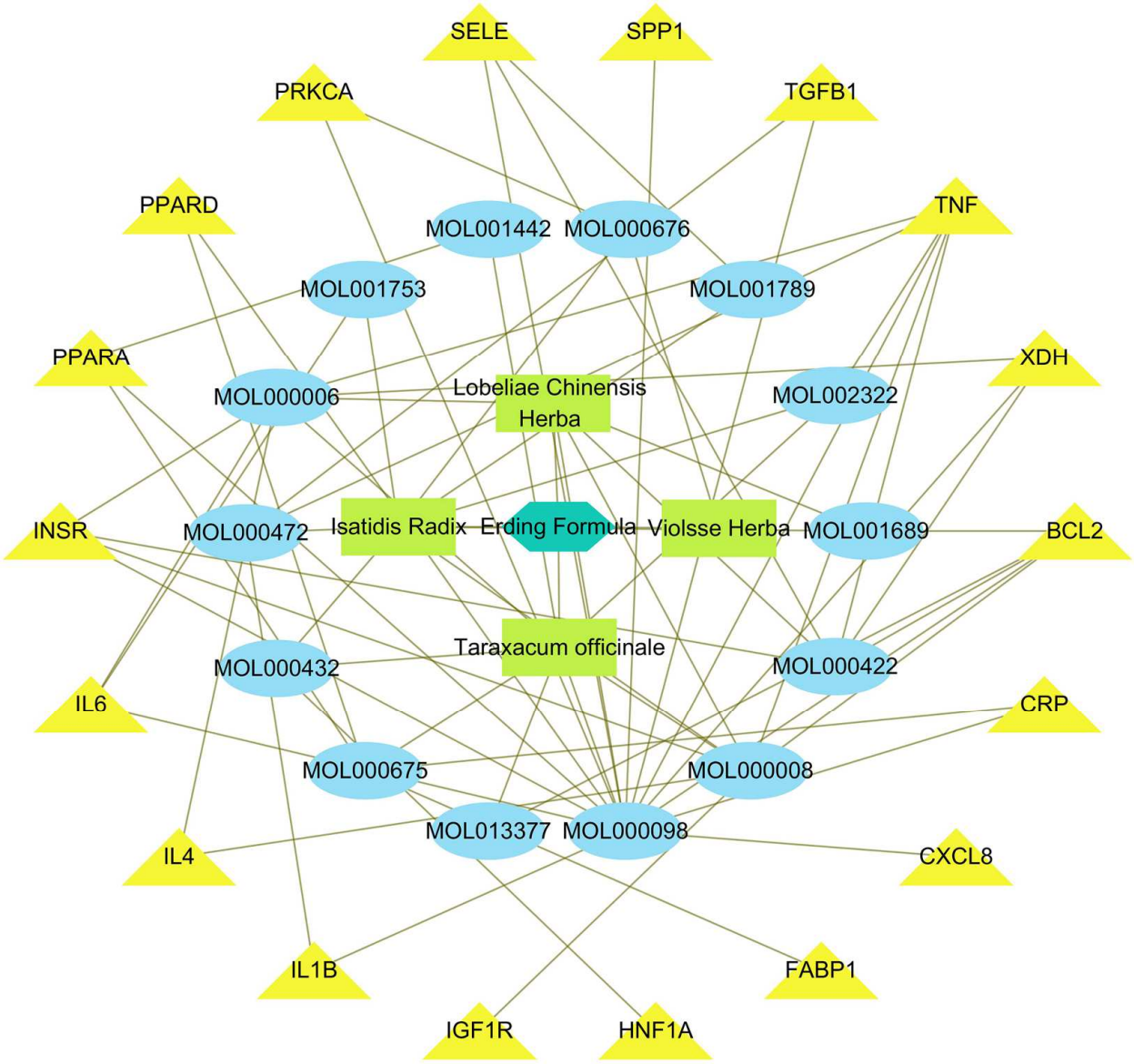

Fig. 1: Erding granules-herb-ingredient-anti-gout target network. In this target network, the hexagon represents the Erding granules, the rectangle represents the herbal medicine, the ellipse represents the active ingredient and the triangle represents the target.

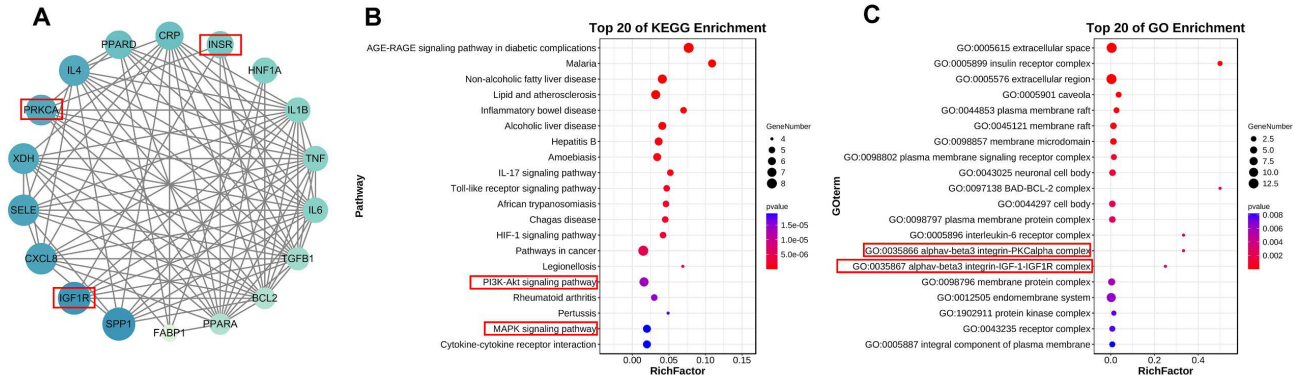

Fig. 2: Gene annotation. (A) Protein-protein interaction diagram (PPI); (B) Top 20 KEGG pathways; (C) Top 20 GO.

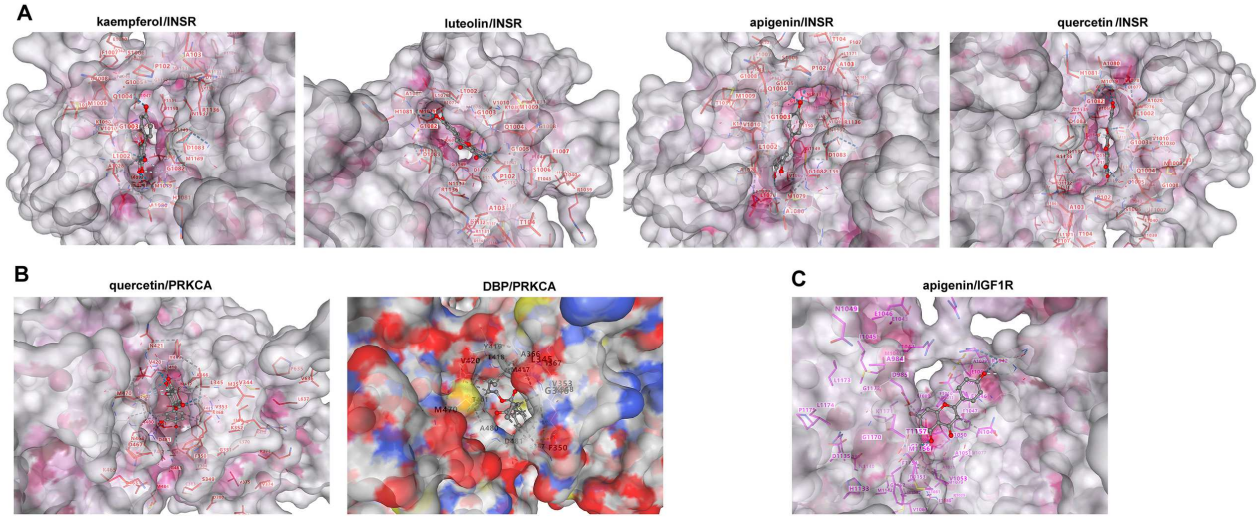

Fig. 3: Molecular docking. Molecular docking results of kaempferol-INSR, luteolin-INSR, quercetin-INSR and apigenin-INSR pairs. (A) Quercetin-PRKCA; (B) DBP-PRKCA pairs; (C) Apigenin-IGF1R pairs.

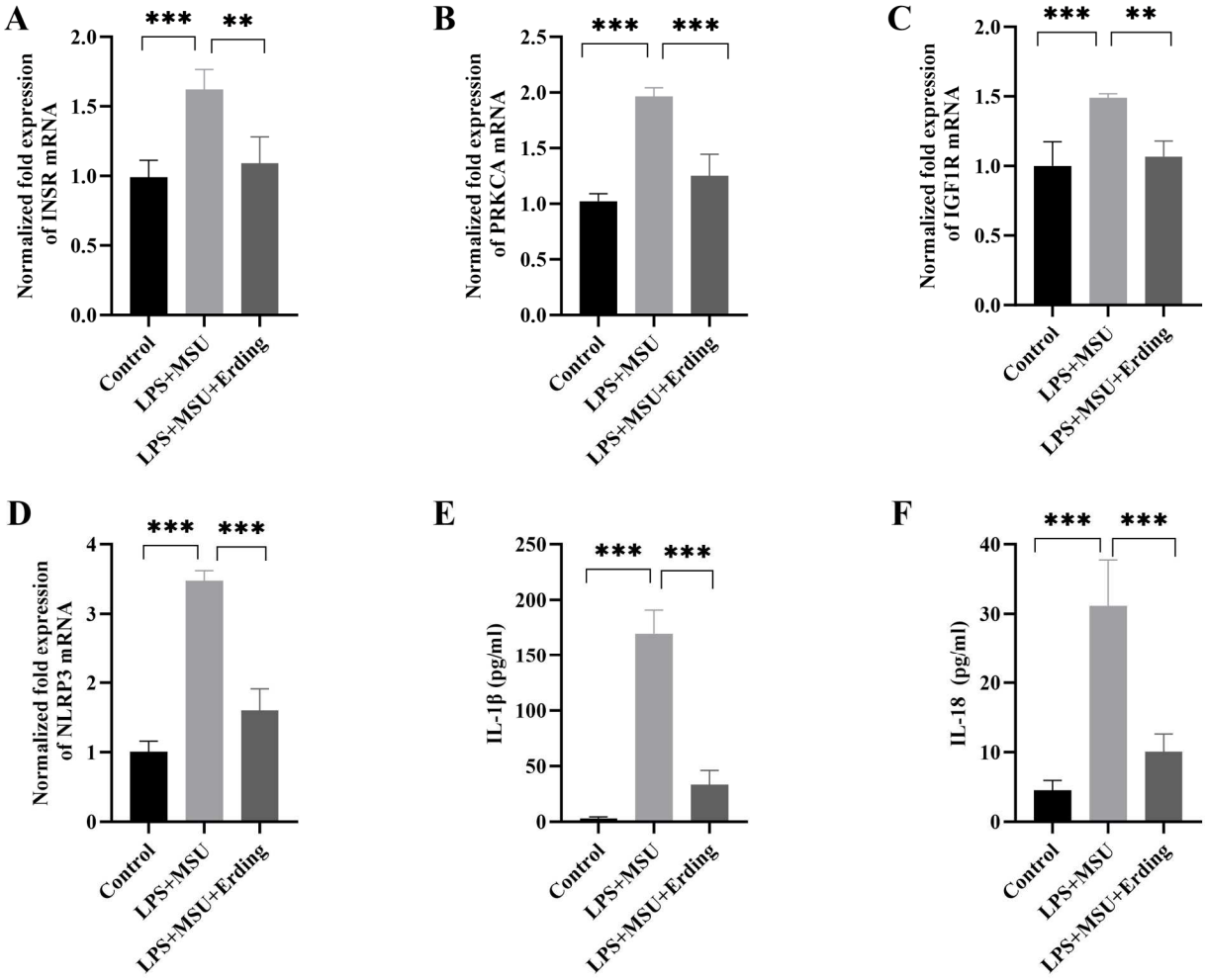

Fig. 4: Cell experimental detection. Effects of Erding granules and MSU on the expression levels of (A-D) INSR, PRKCA, IGF1R, and NLRP3 mRNA; (E-F) Effects of Erding granules and MSU on the release of IL-1β and IL-18. $^{**}p < 0.01$, $^{***}p < 0.001$.

Table 1: Basic information of key compounds.

Mol ID	Molecule name	MW	AlogP	Hdon	Hacc	OB	Caco-2	BBB	DL	FASA-
MOL001689	Acacetin	284.28	2.58	2	5	34.97	0.67	-0.04	0.24	79.9
MOL000422	Kaempferol	286.25	1.77	4	6	41.88	0.26	-0.55	0.24	111.12
MOL000008	Apigenin	270.25	2.33	3	5	23.06	0.42	-0.61	0.21	90.9
MOL000098	Quercetin	302.25	1.5	5	7	46.43	0.04	-0.76	0.27	131.36
MOL000432	Linolenic acid	278.48	5.94	1	2	45	1.2	0.83	0.14	37.29
MOL000472	Emodin	270.25	2.49	3	5	24.39	0.22	-0.66	0.23	94.83
MOL000006	Luteolin	286.25	2.06	4	6	36.16	0.18	-0.84	0.24	111.12
MOL001753	2-Methoxy-4-vinylphenol	522.6	0.55	6	11	21.96	-1.22	-1.86	0.84	167.52
MOL000676	DBP	278.38	4.19	0	4	64.54	0.8	0.55	0.13	52.59
MOL001789	Isoliquiritigenin	256.27	2.9	3	4	85.32	0.43	-0.4	0.14	77.76
MOL002322	Isovitexin	432.41	-0.05	7	10	31.29	-1.24	-2	0.71	181.05
MOL013377	Lutein	568.96	9.46	2	2	22.58	1.13	-0.99	0.54	40.45
MOL000675	Linoleic acid	280.5	6.39	1	2	41.9	1.16	0.9	0.14	37.29
MOL001442	Trans-phytol	296.6	7.33	1	1	33.82	1.22	0.84	0.13	20.22

MW, Molecular weight. OB, Oral bioavailability. BBB, Blood-brain barrier. DL, Drug-likeness. FASA, Fractional accessible surface area. H

Table 2: Details of the interaction of ligands with proteins.

Ligand	Protein	Score	Contact residues
Apigenin	IGF1R	-6.1	Chain A: LEU1005 GLY1006 GLN1007 GLY1008 VAL1013 ALA1031 LYS1033 VAL1063 MET1079 GLU1080 LEU1081 MET1082 THR1083 GLY1085 MET1142 ASP1153
Quercetin	PRKCA	-9.6	Chain C: LEU345 GLY346 LYS347 GLY348 SER349 PHE350 GLY351 LYS352 VAL353 ALA366 LYS368 ILE369 LEU370 LYS371 VAL374 VAL375 ASP378 ASP380 THR384 GLU387 LEU391 THR401 ARG412 PHE415 MET417 GLU418 TYR419 VAL420 ASN421 ASP424 ASP467 ASN468 MET470 ALA480 ASP481 PHE482 GLY483 LEU637
DBP	PRKCA	-6.4	Chain A: LEU345 GLY346 PHE350 VAL353 ALA366 LYS368 GLU387 LEU391 THR401 PHE415 MET417 GLU418 TYR419 VAL420 GLY423 ASP424 ASP467 ASN468 MET470 ALA480 ASP481 PHE482
Kaempferol	INSR	-7.1	Chain A: LEU1002 GLY1003 GLN1004 GLY1005 VAL1010 ALA1028 LYS1030 VAL1060 MET1076 GLU1077 LEU1078 MET1079 ALA1080 HIS1081 GLY1082 ASP1083 SER1086 MET1139 Chain B: PRO102
Luteolin	INSR	-7.4	Chain A: LEU1002 GLY1003 GLN1004 GLY1005 SER1006 VAL1010 ALA1028 LYS1030 VAL1060 MET1076 GLU1077 LEU1078 MET1079 ALA1080 GLY1082 ASP1083 MET1139 ASP1150 Chain B: PRO102
Apigenin	INSR	-7.1	Chain A: LEU1002 GLY1003 GLN1004 GLY1005 SER1006 VAL1010 ALA1028 LYS1030 VAL1060 MET1076 GLU1077 LEU1078 MET1079 ALA1080 GLY1082 ASP1083 MET1139 ASP1150 Chain B: PRO102
Quercetin	INSR	-7.6	Chain A: LEU1002 GLY1003 GLN1004 GLY1005 SER1006 VAL1010 ALA1028 LYS1030 VAL1060 MET1076 GLU1077 LEU1078 MET1079 ALA1080 GLY1082 ASP1083 MET1139 ASP1150 Chain B: PRO102

Under treatment with Erding granules, the increased release of IL-1β and IL-18 caused by MSU was reversed (Fig. 4E-4F, Table 2). Erding granules may alleviate gout by reducing the release of pro-inflammatory factors through INSR, PRKCA and IGF1R.

DISCUSSION

Gout is a common rheumatic disease caused by the deposition of sodium urate crystals in the body of people with hyperuricemia. The significance of traditional Chinese medicine in treating gout is emerging. Gouty tea

can effectively reduce the uric acid and xanthine oxidase levels, effectively improve the vascular endothelial function and inhibit the inflammation in patients with chronic gouty arthritis (Hua *et al*., 2022). In this study, a traditional Chinese formula, Erding granules, was investigated for the treatment of gout using a mechanism-based network pharmacology approach and experimental verification. INSR, PRKCA and IGF1R were found to be the main targets of Erding granules in treating gout.

Under normal conditions, PRKCA is mainly distributed in the cytoplasm and cell nucleus. Under pathological conditions, PRKCA is often activated and transferred to the cell membrane. PRKCA has been reported to be one of the targets for Morus alba L. leaves against gout (Oh *et al*., 2021). Decreased PRKCA expression was found after treatment with Erding granules. Both INSR and IGF1R are insulin-related receptors and share a high degree of sequence homology (Werner, 2023). Both can help clarify the physiological effects of insulin. As a transporter of sugar, insulin helps sugar enter cells to power them (Clerk and Sugden, 2022). If too much sugar is taken in, cells that are already saturated with energy will resist the entry of insulin, leading to insulin resistance (Heo *et al*., 2023). The kidneys begin to excrete sugar but not MSU, resulting in MSU accumulation due to poor excretion. Erding granules can reduce the increase in INSR and IGF1R expression levels caused by MSU.

MSU can play a role in the activation of autoimmune responses as endogenous danger signals, thereby activating inflammatory responses (Xu *et al*., 2023). Through activation of the NLRP3 inflammasome, MSU stimulates macrophages to release IL-1β (Chen *et al*., 2021). PRKCA is associated with chronic pain and osteoarthritis in human osteoarthritis (Oh *et al*., 2021). In this current study, Erding Granules can reduce the expression levels of NLRP3 and the release of IL/1β and IL-18. Erding granules may alleviate gout through targeting PRKCA, INSR and IGF1R, thus alleviating inflammation.

CONCLUSION

In summary, Erding granules may alleviate gout by reducing the release of pro-inflammatory factors or reducing the accumulation of MSU via its targets, including INSR, IGF1R and PRKCA.

Acknowledgments
None.

Authors' contributions
GLW: Responsible for project development, data management, data analysis, manuscript writing and manuscript editing; LH: Responsible for data management, data analysis and manuscript writing; YHZ and XKT: Responsible for data acquisition and data analysis. All authors have read and approved the manuscript.

Funding
There was no funding.

Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This article does not include any studies involving human or animal subjects conducted by any of the authors. Therefore, ethical approval is not required.

Conflict of interest
The authors declare no conflict of interest.

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