REVIEW ARTICLE

BioMed Research International Study Quality on the Role of Pyroptosis Bionic in Gouty Arthritis and Traditional Chinese Medicine Biomechanics Intervention

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ABSTRACT

Gouty arthritis (GA) cause great harm to patients. Cellular pyroptosis, a mode of programmed cell death associated with inflammatory response, is closely related to GA. Both cysteamine aspartate-1-dependent and non-dependent pathways are involved in the progression of GA. During GA development, high blood uric acid levels leads to excessive biologically-inspired NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation to drive caspase-1 activation for promoting the maturation of interleukin-1β precursors, and caspase-1 activation disrupts the amino terminus in gasdermin D-N (GSDMD-N) and carboxy-terminal gasdermin-C structural domains, causing pores in the membrane and thus inducing the onset of scorch death. Therefore, modulating the onset of scorch death may become an important target for drug intervention in diseases. Chinese medicine is substantially biologically inspired and used synergistically to treat GA through multiple pathways and targets, which may regulate the relevant pathways through cellular pyroptosis quality. This study focuses on the interpretable regulatory mechanism of cellular pyroptosis bionic in GA and the role of Chinese medicine on GA, which provides a new scientific basis and strategy for targeting cellular pyroptosis bionic as the prevention and treatment quality of GA. (*Altern Ther Health Med.* 2024;30(4):82-89)

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INTRODUCTION

Gouty arthritis (GA) is an inflammatory disease associated with uric acid sodium salt crystals deposition in the joints.[1] When the concentration of uric acid in the body exceeds the solubility of uric acid and reaches supersaturation, MSU crystals are deposited in the cartilage, synovial membrane, and surrounding tissues and irritate the synovial membrane, resulting in a series of pathological reactions that lead to inflammatory reactions in the joint.[2] At present, the prevalence of GA is increasing year by year worldwide with typical symptoms, including redness, swelling or edema, fever, and pain in the joints and adjacent tissues, and the pain is unbearable, which seriously affects people's daily life and work.[3] It is closely related to elevated uric acid, involvement of inflammatory factors, weakened antioxidant stress, apoptosis, dysbiosis of intestinal flora, and imbalance of bone metabolism.[4] Although significant progress has been made in the treatment of GA, there are still major challenges, and therefore, exploring new therapeutic targets provides more valuable theoretical support for clinical treatment.

Recent studies have confirmed[5] that cellular pyroptosis is a programmed cell death critically associated with inflammatory response, and its associated signaling substantially regulates the growth of arthritis; therefore, cellular pyroptosis should be targeted by novel drugs to treat arthritis. At first, Cookson proposed cellular pyroptosis in 2001 as a novel form of Caspase-1 mediated cell death, which in turn releases large amounts of pro-inflammatory factors and thus accelerates cell death.[6] In the last few years, cellular pyroptosis has gained extraordinary expansion in the research field as a novel mode of cell death present in the pathological processes of several diseases. However, recently stated that cellular pyroptosis critically regulates the pathogenesis of GA, and targeted regulation of cellular pyroptosis may provide a new strategy to improve GA. Currently, the first-line agents used in the clinical treatment of gout include Non-steroidal anti-inflammatory drugs(NSAIDs), Colchicine, and Glucocorticoids. Although they have shown good efficacy in gout attacks, their clinical use is limited by various adverse effects, including drug resistance, suppression of endogenous hormones, gastrointestinal discomfort, and other side effects.[7-9] Thus,

there is a need to find drugs that are less toxic, highly effective, and mild in action.

In the treatment of GA, traditional Chinese medicine (TCM) embodies evidence-based treatment under the guidance of a holistic view, with the characteristics of multi-target, long-lasting action, safety, and stability, which can reduce the recurrence rate of GA, improving the life-span of GA patients, and play a role in treating both the symptoms and the root cause of GA. Chinese medicine has unique advantages in the treatment of GA, with precise efficacy and high safety, and has made great research progress in both clinical trials and experimental studies. In addition, Chinese medicine and its monomers and herbal compounds have certain regulatory effects on cellular pyroptosis, which have important roles in preventing and clinically treating GA. In China, TCM has been adopted for GA prevention and treatment for thousands of years. Gout patients are usually treated with TCM according to their different conditions, and long-term results can be achieved by improving their physical condition. How to use cellular pyroptosis theory to guide the effective prevention and treatment of GA in Chinese medicine has become a new research hotspot. Therefore, a brief review of the pathogenesis of cellular pyroptosis and the research progress of GA is conducted to provide a new research direction and theoretical basis for treating GA in TCM.

At this stage of research, the main focus is on the Toll-like receptor pathway, NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammatory vesicle signaling axis, etc. In addition, there may be more signaling pathways and target genes involved in cellular pyroptosis, therefore, there is a need to further investigate the mechanism of cellular pyroptosis in the development of GA to help develop precise therapeutic approaches. This study aims to investigate the role of specific signaling pathways and target genes in cellular pyroptosis during the development of GA and how this knowledge can inform precise therapeutic approaches in TCM.

The Concept of cellular pyroptosis

Pyroptosis, a programmed cell death, leads to the formation of pores in the cell membrane for releasing pro-inflammatory cytokines such as interleukin-18 (IL-18) and interleukin-1β (IL-1β) to control inflammation. Cell pyroptosis is divided into two main types: Classical caspase-1-dependent and non-classical caspase-1-dependent.

The classical pyroptosis pathway associated with Caspase-1 is closely linked to inflammatory vesicles, with NLRP3 as the major upstream inflammatory vesicle, consisting of the NOD-like receptor thermal protein domain associated protein 3 (NLRP3), the Apoptosis-associated speck-like protein (ASC), and the Cysteine aspartate protein hydrolase-1 precursor (pro-Caspase-1).[10] Under the action of pathogen-associated molecular patterns or risk-associated molecular patterns, it forms a functional NLRP3 inflammatory vesicle complex through two processes, initiation and activation, which in turn induces pro-Caspase-1 to self-shear into activated Caspase-1. mature Caspase-1 promotes the release and activation of IL-1β and IL-18, and can also shear The dissociated GSDMD-N can perforate the cell membrane, promote K+ efflux, and secretes IL-1β and IL-18, which ultimately stimulates the cellular pyroptosis and inflammatory signaling cascades.[11] Monosodium urate (MSU)-mediated inflammation is closely related to gouty arthritis. Also, MSU could induce the activation of NLRP3.

The non-classical pyroptosis/non-classical caspase-1-dependent pathway. In contrast to the classical pyroptosis pathway, a non-Caspase-1-dependent cellular pyroptosis pathway exists in the atypical pyroptosis pathway, in which Cysteinyl aspartate-specific proteinase-4/5/11 (Caspase-4/5/11) bind with lipopolysaccharide (LPS), which in turn causes inflammatory signaling for cellular necrosis. This Caspase-4/5/11-dependent programmed cell death mechanism is linked to the non-classical pyroptosis pathway. Similar to Caspase-1, Caspase-11 is associated with cell membrane perforation by cleaving GSDMD after its activation. In addition, activated Caspase-11 promoted K+ efflux not only by stimulating GSDMD cell membrane perforation but also by cleaving pannexin-1/adenosine triphosphate/purinergic P2X7 (Pannexin-1/ Adenosine triphosphate/purinergic P2X7, Pannexin-1/ATP/P2X7) signaling, activating NLRP3/ASC/Caspase-1 signaling axis, stimulating IL-1β maturation and secretion to induce inflammatory responses in cellular levels.[12]

In summary, both classical and non-classical pathways eventually shear the GSDMD, which in turn induces pyroptosis.

The mechanism of cellular pyroptosis. The classical caspase-1-dependent phenotype is mainly based on the NLRP3 pathway, which is associated with the stimulation of NLRP3, including pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). The induction of inflammatory microsomal receptors by PAMPs or DAMPs triggers the recruitment of Caspase-1 to macromolecular compounds, which activates Caspase-1 among these compounds and drives Caspase-1 for cleaving pro-IL-1β and pro-IL-18 to produce mature IL-1β and IL-18 which ultimately triggering the cellular pyroptosis, which also causes GSDMD-NT cleavage to form a membrane-based cavity, mediates the secretion of contents, contacts the cell membrane, releases its membrane perforating activity, and induces cellular pyroptosis; meanwhile, oxidative stress produces reactive oxygen species (ROS)[13] to stimulate NLRP3, and structurally changed NLRP3 inflammatory vesicles for inducing Caspase-1 activation. Caspase-1 activated in inflammasomes triggers a programmed necrosis called pyroptosis, which is mediated by gasdermin D (GSDMD). The activated caspase-1 converted the Gasdermin D to a polypeptide having nitrogen capped active structural domain of Gasdermin D, leading to porous membrane and cell membrane damage, resulting in the secretion of molecules for causing inflammatory response, thus inducing cellular pyroptosis. The development of GA is mainly associated with the deposition of MSU, and the formation of MSU stimulates the development of NLRP3-mediated cellular pyroptosis, as shown in (Figure 1).

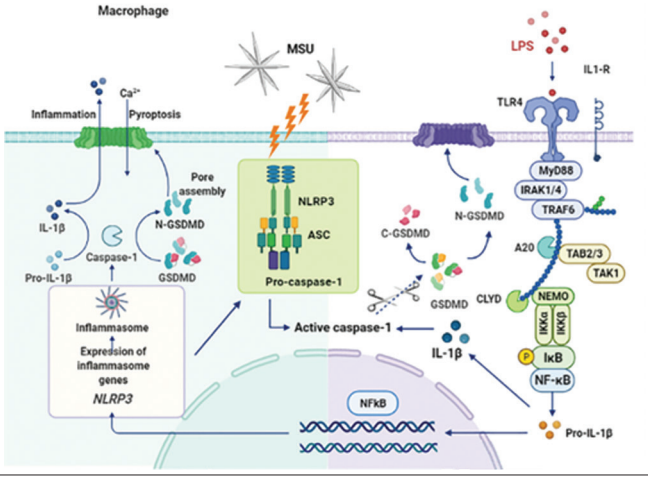
CELLULAR PYROPTOSIS AND GOUTY ARTHRITIS (GA)

Gouty arthritis is an inflammatory disease caused by the deposition of monosodium urate (MSU) crystals in the joint. Studies reported that gallic acid enhances the Nrf2 signaling to suppress NLRP3 inflammasome activation and pyroptosis and alleviate NLRP3-dependent gouty arthritis.[1] The mechanism of cellular pyroptosis is a highly pro-inflammatory and programmed cell death process, which is mediated by Caspase-1, GSDMD, regulated by NLRP3 and Toll-like receptor pathway, and associated with BDR4, Nrf2, oxidative stress, mitochondrial dysfunction, etc. BRD4 in MSU-induced pyroptosis by regulating NF-κB/NLRP3/GSDMD signaling pathway and can be a potential target for treatment of acute gouty arthritis. These mechanisms all lead to the release of inflammatory factors, and the accumulation of ROS, disrupting the body's redox response and mitochondrial function, thus inducing cellular pyroptosis, which plays an important role in the development of GA. The following will describe the relevant proteins and pathways involved in cellular pyroptosis in GA, and provide directions for new drug development.

GSDMD, the key protein in cellular pyroptosis

GSDMs are a family of proteins encoded by six paralogous homologous human genes, including gasdermin A (GSDMA), gasdermin B (GSDMB), gasdermin C(GSDMC), gasdermin (DGSDMD), gasdermin E (GSDME) (or DFNA5), and DFNB59 (or PJVK). In mice, there are three Gsdma genes (Gsdma1, Gsdma2, and Gsdma3), four Gsdmc genes (Gsdmc1, Gsdmc2, Gsdmc3, and Gsdmc4), one Gsdmd gene, and one Gsdme gene. There are two structural domains (NT domain and CT domain) in GSDM A-E, which can bind to each other through flexible connectors and are activated when the NT domain and CT domain are separated; they interact with acidic phospholipids regions of the intracellular membrane after polymerizing, forming pores that act as channels for the release of cytokines (e.g., IL-1β, IL-18). Chemokines enter the extracellular space from the cellular pyroptosis, disrupting cellular membrane integrity, causing cellular pyroptosis, and stimulating inflammation, which then activates an immune response in response to an emergency (infection or injury).[14] Studies[15-16] showed that GSDMD, a shared substrate of caspase-1,4,5,11, is a key performer in triggering pyroptosis. It was shown[17] that the NH2-terminus of GSDMD has a role in inducing cell death, while the COOH-terminus inhibits the NH2-terminal induction of cell death. In healthy cells, the interaction between the two structural domains leaves the GSDMD in a functional inactivation state. During pyroptosis, it is a direct substrate for the cytokine caspase-1 downstream of inflammatory vesicles, which is sheared by stimulated caspase-1 or caspase-11/4/5 to the NH2-terminal cleavage product with pore-forming properties (GSDMD-NT). GSDMD-NT is translocated to the membranes of plasma and mitochondri. Through these transmembrane pores, cellular contents such as inflammatory cytokines (e.g. IL-1β and IL-18) are secreted, which disrupts the membranous osmotic potentiality for triggering the cellular membrane rupture,

Figure 1. Schematic illustration of the regulatory signaling mechanisms of cellular pyroptosis, cited from reference.



ultimately leading to cellular pyroptosis.[18] A recent study[19-20] showed that oxidation of GSDMD is the initiating mechanism of mitochondrial ROS promoting cellular pyroptosis. Currently, the exact role of oxidative stress in cellular pyroptosis is unclear, and a deeper study of the relationship between the two is of great importance.

Toll-like receptor Pathway and Gouty Arthritis (GA)

Toll-like receptors (TLRs), such as TLR2 and TLR4, are activated following MSU activation during the development of GA.TLRs are typing I transmembrane proteins that are potent activators of the inflammatory response, and they can bind with myeloid differentiation factor 88 (MyD88) for recruiting interleukin 1 receptor-associated kinase (IRAK), MyD88 and interleukin 1 receptor-associated kinase (IRAK). Nuclear factor kappa-B (NF-κB) is ultimately activated or stimulated by the catalytic action of IKB kinase. Stimulated NF-κB entered into the nucleus for transcribing the inflammatory mediators, which then promotes the production of precursors such as NLRP3, IL-18, and IL-1β.[21] The classical Toll-like receptor 4 (TLR4) pathway is activated during the activation of NLRP3 inflammatory vesicles and is another pattern recognition receptor that can be activated by MSU. Related studies have also confirmed[22-23] that gout attacks are associated with the TLR4 and its downstream signaling axis TLR4-MyD88-NFκB activation in vivo via urate activation, which is involved in the regulation of immune and inflammatory responses in GA. It was shown[24] that TLR4 suppression is critically linked with the reduction of severe arthritis in mice. The level of TLR4 and NF-κB was substantially elevated in acute GA than in healthy subjects,[25] indicating the association of TLR4 with inducing gout. X Chen et al.[26] found that MiR-146a, through TLR4 / MyD88 / NF-κB signaling pathway to alleviate joint inflammation in acute arthritis in rats.

NLRP3 inflammasome axis and Gouty arthritis (GA)

NLRP3 inflammasomes, as pattern recognition receptors (PRR), recognize endogenous and exogenous danger signals

and are an important component of intrinsic immunity.[27] MSU, as an endogenous danger signal molecule, is recognized as a danger signal by the body's intrinsic immunity through pattern recognition receptors. The C-terminus of NLRP3 protein is activated upon recognition of MSU resulting in a conformational change that exposes the nucleotide-binding oligomerization structural domain (NACHT), polymerizes via ATP into NLRP3 protein oligomers.[28] Matured caspase-1 breakdown the GSDMD protein for the secretion of the NT structural domain and generates a non-selective membranous pore, while mature IL-1β and IL-18 are synthesized by caspase-1 after cleaving the IL-1β and IL-18 precursors. The latter is released from the pore along with other cellular contents, leading to cellular pyroptosis.[29-30] Activated NLRP3 inflammatory vesicles and interleukin-1β (Interleukin-1β. IL-1β) release are critically associated with the progression of gout.[31]

There are two-step processes for activating the NLRP3 inflammatory vesicles. Firstly, LPS (TLR agonists) activated the NF-κB pathway to promote the transcription of NLRP3 and IL-1β. In the second step, NLRP3 inflammatory vesicle activation stimuli (Monosodium urate crystals) stimulated the synthesis of protein complexes that converted the pro-Caspase-1 into its mature form (p10 and p20 subunits). Then, mature Caspase-1 synthesized the IL-1β from pro-IL-1β. At the same time, mature Caspase-1 also converted gasdermin D (GSDMD) into its N-terminal fragment (GSDMD-N). GSDMD-N then forms membranous pores, leading to a cleaved form of cell death called pyrophosphorylation and secreted the mature IL-1β.[32-35] In addition, mitochondria ROS (mtROS) can promote the activation of NLRP3 inflammatory vesicles.[36-37]

Monosodium urate (MSU) is a potent activator of NLRP3, and the role of NLRP3 and its upstream and downstream cytokines has been validated in GA studies, and NLRP3 has become an important therapeutic target for GA. Yuqin Lin et al[38] found that Gallic acid inhibited NLRP3 inflammatory vesicle stimulation by suppressing Caspase-1 activation and IL-1β secretion; blocking NLRP3/NEK7 interaction and ASC oligomerization exerted its inhibitory effects, thus limiting inflammatory vesicle assembly and thus alleviating GA symptoms. In addition, Gallic acid induced the level of nuclear factor E2-related factor 2 (Nrf2) and suppressed the synthesis of mtROS, which in turn suppressed the NLRP3 inflammatory vesicle stimulation and pyroptosis associated with Nrf2 signaling, indicating that Gallic acid has therapeutic potentiality for the GA treatment. Chih-Chien Wang et al[39] found that cardamomycin could improve the symptoms of GA by inhibiting NLRP3 inflammatory vesicle activity, attenuating IL-1β secretion, and caspase-1 activity. Reports showed that palmatine protects against MSU-induced gouty arthritis via regulating the NF-κB/NLRP3 and Nrf2 Pathways, which suggested the important role of NF-κB in the GA.

Bromodomain proteins 4

The BET (bromodomain and extra-terminal) family of proteins includes BRD2, BRD3, BRD4, and BRDT. These protein families interacted with acetylated lysine residues in histone tails through their N-terminal bromodomains, altering chromatin structure and exerting important effects on a variety of physiological processes. The BET family respond to infection and sterile inflammation, and abnormally expressed or dysfunctional BETs are involved in the activation of pattern recognition receptor. The multifunctional Brd4 belongs to the BET family of proteins containing two tandem bromine structural domains and an additional terminal (ET) structural domain[40] and is an epigenetic regulator that recognizes and binds to acetylated histones,[41] of which well-studied, bromodomain-containing protein 4 (BRD4) interacted with acetylated histones through the N-terminal bromine structural domain and transcriptional-BRD4 interacted with acetylated histones and transcription factors via the N-terminal bromine domain and regulates inflammatory processes. A BET protein familyBRD4 is associated with the regulation of NF-κB signaling through acetylated-RELA.[42] Immunoprecipitation results showed that the two bromodomains of BRD4 interact with lysine-310/acetylated RELA and that the double bromodomain inhibitor JQ1 suppresses the molecular interaction of BRD4 and acetylated RELA, thereby inhibiting NF-κB-induced transcription.[43] NF-κB is critically associated with inflammatory processes and failure of energy and regulates the synthesis of pro-inflammatory cytokines. The inflammatory responses detach the NF-κB from IκBα for translocating into the nucleus and regulating the transcriptional machinery of pro-inflammatory cytokines, which would induce the stimulation of the NLRP3 inflammatory vesicle.

The BET inhibitor JQ1 is a relatively specific inhibitor of BRD4, and related studies have shown that JQ1 has an important role in the inflammatory response.[44] The selective BET bromodomain inhibitor compound 38 can block the Janus kinase-signal transducer and activator of transcription and mitogen-activated protein kinase pathways in macrophages,thus decreasing their secretion of proinflammatory cytokines in a dose-dependent manner. Recent studies have shown that the BRD4 inhibitor JQ-1 is significantly potent via suppressing IκB kinase-associated NF-κB translocation in GA fibroblast-like synoviocytes. Meanwhile, it was shown that JQ1 inhibition of BRD4 could inhibit vasculitis by suppressing NF-κB activation[45] syndrome. One study reported that BRD4 inhibition attenuated the production of pro-inflammatory cytokines in microglia.[46] In addition, JQ1 disrupts the molecular binding of BRD4 with acetylated lysine-310 residues on RelA and inhibits TNF-α-mediated activation of inflammatory cytokines.Tong Hua et al[47] showed that BRD4 reduced GA by controlling the NFκB-NLRP3-GSDMD signaling axis in the extent of cellular pyroptosis.

Oxidative stress

Oxidative stress critically causes tissue damage in our body, and the cellular damage it causes triggers a complex

antioxidant protection mechanism in the body. Oxcessive ROS production can cause immune cell infiltrationa and aggregated inflammatory cells, like neutrophils, monocytes, macrophages, and other immune cells. Also, it could secrete inflammatory cytokines, chemokines, and cell adhesion molecules which are responsible for hyperinflammation, angiogenesis, and bone erosion. Under normal conditions, the body usually maintains a balance between its production of free radicals and antioxidants, which is disrupted by severe oxidative stress.[19] The PRR acts as a sensor for various risk factors (such as NLRP1, NLRP3, NLRC4, NLRP6, NLRP7, NLRP9b, NLRP12, pyrin, and AIM2) and can be stimulated by various factors, including viruses, bacterial toxins, fungi, parasites, nucleic acids, crystalline substrates, silica particles, long-chain saturated fatty acids, ROS, and various endogenous signaling by damage. Also, studies have shown[48] that the dysregulation of NLRP3 inflammasomes is mediated by oxidative stress, and MSU can enhance the activation of NLRP3 inflammatory vesicles through the overproduction of ROS. Meanwhile, ROS-mediated signaling is associated with the synthesis and activation of IL-1β and caspase-1. The limited level of ROS is associated with cellular signaling and physiological responses, but the excess level of ROS potentially leads to cell death. These ROS-activated signaling pathways regulate senescence or cell death and are linked to cancer. Moreover, previous studies have shown[49] that IL-1β can accumulate cellular ROS after uncoupling the antioxidant enzymes. Taking these ideas into consideration, we found that inflammatory response and oxidative stress are correlative for the development of disease, for example, synthesis of MSU-induced pro-inflammatory cytokines, infiltrations of inflammatory cells, and the stimulation of NLRP3 inflammasome.

Mitochondrial dysfunction

Mitochondrial dysfunction in tissue-specific mesenchymal stem cells plays an important role in cell fate and the morbidity of chronic inflammation-associated bone diseases, such as GA. Caspase-1-dependent mitochondrial damage is initiated by the absence of NLRP3 inflammasome. Mitochondrial dissociation is promoted by Caspase-1 mediated multiple pathways, leading to mitochondrial ROS synthesis, and disrupting the membrane potentiality, permeabilization, and communication of mitochondria.[50] In addition, Caspase-1 inhibits mitochondrial autophagy to amplify mitochondrial damage, mediated in part by cleavage of Parkin, a key mitochondrial autophagy regulator. Without Parkin activity, increased mitochondrial damage increases cellular pyroptosis, as indicated by induced plasma membrane permeabilization and secretion of hazard-related molecular patterns.[51-52] Thus, as with other initiating cystathionine, activation of caspase-1 by inflammatory vesicles leads to mitochondrial damage. Weimin Fan et al,[77] found that it is possible to promote mitochondrial autophagy and thus inhibit mitochondrial autophagy by increasing the membranous potentiality of mitochondria, inhibiting the P62 and Pink1 level, and enhancing the expression of LC3B-II, Parkin, and TOMM20 NLRP3 inflammatory vesicle activation to prevent and control GA. Therefore, future studies should address the role of mitochondrial damage in cellular pyroptosis in various physiological and pathophysiological stages and explore the clues to manipulate mitochondrial damage or mitochondrial autophagy as a means to control this cellular pyroptosis and inflammatory response.

Nuclear factor E2-related factor 2

NRF2 abundance within the cell is tightly regulated and is mainly controlled by four E3 ubiquitin ligase complexes-mediated ubiquitylation and proteasomal degradation. NRF2 is expressed in all cell types. In the antioxidant stress system, the transcription fact Nrf2 is substantially associated with cytoprotection by exerting anti-inflammatory effects that negatively regulate the activation of NLRP3 inflammasome vesicles, and NRF2 siRNA plays a role in promoting IL-1β secretion.[53] It was discovered that Nrf2 prevents NLRP3 inflammatory vesicle activation by controlling the quantity of ROS, thioredoxin system, and glutathione-based antioxidative system, thus reducing oxidative stress levels and decreasing the incidence of pyroptosis, thereby reducing inflammatory symptoms in GA.[54-55] Modified Simiaowan has potent anti-inflammatory and antioxidant effects on gouty arthritis. MSM could be a treatment target of GA through Nrf2/HO-1/ROS/NLRP3 signaling pathway.

TRADITIONAL CHINESE MEDICINE (TCM) REGULATES CELLULAR PYROPTOSIS TO PREVENT AND TREAT GOUTY ARTHRITIS (GA)

TCM has remarkable efficacy in the clinical treatment of many diseases, and it is a natural treasure trove of compounds with many active ingredients, wide sources, guaranteed safety, and a stable composition structure. Whether it is a single flavor or a Chinese medicine compound, it has a multi-target, multi-faceted, and multi-level "holistic" effect in the treatment of GA. At present, there are few studies on the mechanism of Chinese medicine to regulate GA cellular pyroptosis. " "Chinese medicine", "heart failure", "Gouty arthritis " etc. as keywords. The relevant literature published in the past five years was searched in the databases of CNKI, Wan Fang Data, Chongqing Vipu Full Text Database (VIP), China Biomedical Literature Service (CBM), PubMed, and Elsevier, etc., and is shown in Table 1. The mechanism of action of TCM for the prevention and treatment of GA was summarized to provide further clinical application.

Traditional Chinese Medicine Herbal Compositions

Several studies revealed that herbal decoction is substantially associated with the management of GA. Guo Yuqin et al.[56] found that all dose groups of Jiawei Xuanbi Decoction/Soup could reduce the level of joint swelling in GA rat model induced by potassium oxyzincate combined with Monosodium urate, and downregulated the expression of serum SUA,CRP,IL-1β, tumor necrosis factor (TNF)-α as well as toll-like receptor (TLR)-4 in joints of model rats,

Table 1. Traditional Chinese Medicines, Compounds, and Monomers for GA Regulation

Chinese Herbal Recipe	Structure/Composition	Animal Species	Model Preparation Method	Dose of Drug Administration	Test Indicators	References
Jiawei Xuanbi Decoction/ Soup	Stephania tetrandra S. Moore, prunus armeniaca L., fors.	Wistar Male rats	Sodium pentobarbital, Monosodium urate suspension	High, medium, and low doses (40, 20, 10g/kg)	Decreased levels of serum SUA, CRP, IL-1β, TNF-α, TLR4, MyD88, IRAK4 mRNA expression in joints	[56]
Decoction of Five drugs including Astragalus and Cinnamon (Huangqi Guizhi five things soup)	Astragalus, cinnamomi ramulus, paeonia lactiflora Pall., zingiber officinale, ziziphus jujuba Mill.	SD Male rats	Monosodium urate crystal suspension	5.98g/kg	Decreased levels of serum UA, CRP, PTGS2, Mapk1, and IL-6 mRNA in synovial tissue	[57]
Sanmiao Wan	Phellodendri chinensis cortex, rhizome of swordlike atractylodes, achyranthes bidentata	SD Male rats	Homemade hypoxanthine-containing diet, uricase inhibitor, exhaustive swimming	30g herbal medicine/kg	Decreased serum SUA, IL-1β, IL-6 levels	[61]
Jiawei Sanmiao Wan	Smilacis glabrae rhizoma, phellodendri chinensis cortex, rhizome of swordlike atractylodes, achyranthes bidentata	Human-derived mononuclear leukemia cell line THP-1	Co-induction of Monosodium urate and lipopolysaccharide	High, medium, and low doses (0.4, 0.2, 0.1 mg/mL)	Decreased IL-1β level, NLRP3, ASC, NF-KB, Caspase-1, TLR2, and TLR4 protein expression in THP-1 cells	[58]
Phellodendri chinensis cortexrhizome of swordlike atractylodes Decoction	Phellodendri chinensis cortex, rhizome of swordlike atractylodes, rhizoma arisaematis, cinnamomi ramulus, clematidis radix et rhizoma, stephania tetrandra S., et al.	SD Male rats	50 μL of 80 mg/mL urate solution	High, medium, and low doses (12, 6, 3g/kg)	Downregulation of TNF-α, IL-1β, IL-8, and IL-6 in joint fluid	[60]
Cangshu Baihu Decoction	Gypsum, anemarrhena asphodeloides bunge, rhizome of swordlike atractylodes, glycyrrhiza uralensis Fisch., polished japonica rice	Wistar Male rats	Joint cavity punctured with Monosodium urate solution	High, medium, and low doses (16.3, 9.8, 3.3 g/kg)	Decreased serum IL-1β, TNF-α levels	[62]
Simiao Wan	Rhizome of swordlike atractylodes, phellodendri chinensis cortex, achyranthes bidentata, coicis semen	SD Male rats	Injection of MSU in hind limb	High, medium, and low doses group (1.2, 0.6, 0.3 g/kg)	Serum IL-1β level decreased and IL-10 level increased; iNOS protein expression level decreased and Arg-1 protein expression level increased in joint tissues	[83-84]
Jiawei Simiao Decoction	Rhizome of swordlike atractylodes, achyranthes bidentata, coicis semen, smilacis glabrae rhizoma, dioscorea, plantaginis herba, sinapis alba L., Rhei radix et rhizoma, Rhizoma Atractylodis Macrocephalae, crataegus pinnatifida Bge.	Wistar Male rats	Ankle joint puncture	High, medium, and low dose groups were given 67.2, 33.6, 16.8 g/(kg-d) respectively	Serum IL-1β, IL-6 levels decreased, and IL-10 increased; decreased protein levels of TLR2, TLR4, MyD88, NF-κB p65, TNF-α, IL-6, and iNOS in synovial tissue	[85-86]
Jiawei Simiao Pill	Rhizome of swordlike atractylodes, achyranthes bidentata, coicis semen, smilacis glabrae rhizoma, dioscorea, plantaginis herba, sinapis alba L., Rhei radix et rhizoma, Rhizoma Atractylodis Macrocephalae, crataegus pinnatifida Bge.	Wistar Male rats	Intracavitary injection of urate suspension	High, medium, and low dose groups (1.4, 0.7, 0.35 g/kg)	Serum IL-1β, IL-6, TNF-α levels decreased; TNF-α, IL-6, iNOS protein expression decreased in synovial tissue	[87-88]
Flos Lonicerae Japonicae and Forsythiae Fructus Decoction	Flos lonicerae, fructus forsythiae, smilacis glabrae rhizoma, and rhizome of swordlike atractylodes	SD Male rats	Monosodium urate crystal suspension	High, medium, and low doses (15, 7.5, 3.75g/kg)	Decreased serum UA, IL-1β, IL-6 levels; suppressed NLRP3 inflammasome activation	[59]

MyD88,IRAK4 mRNA expression levels in the joints, the results showed that Jiawei Xuanbi Decoction/Soup achieved the therapeutic effect on GA by inhibiting TLR4,MyD88,IRAK4 pathway; Zhao et al.[57] showed that Astragalus-cinnamomi ramulus Wu Yi Tang significantly reduced UA, C-reaction protein(CRP) levels in the serum of GA rats induced by potassium oxyzincate combined with Monosodium urate, and down-regulated the expression of PTGS2,Mapk1,IL-6 mRNA in the synovial tissue of model rats; Zhang et al.[58] showed that Jiawei Sanmiao Wan significantly suppressed the secretion of IL- 1β secretion level of THP-1 cells in the model group, and also significantly down-regulated the expression of NLRP3,ASC,NF-κB,Caspase-1,TLR2,TLR4 proteins in the model group; Yang Fan et al.[59] found that all dose groups of Cangshu Baihu Decoction could reduce the level of IL-1β,TNF-α in the model rats, and then achieve anti- GA; Yang Hong et al.[60] found that all dose groups of phellodendri chinensis cortexrhizome of swordlike atractylodes soup could reduce the levels of TNF-α,IL-1β,IL-8,IL-6 in the joint fluid of model rats by decreasing the expression of TNF-α,IL-1β,IL-8,IL-6, thus substantially improved the inflammatory response of acute GA in a dose-dependent manner; Liu Longlong et al.[61] detected that Sangshangwan could inhibit the degree of joint swelling as well as the release of IL-1β in the serum of model rats; Du Shibai et al.[62] found that giving MSU-induced GA rats Xinjia Baihu Tang 20g/kg for 7 d substantialy downregulated the model serum expression of IL-6,TNF-α in rats.

Monoherbal medicines

There are increasing numbers of herbal medicines with unique advantages in the treatment of GA. Relevant literature suggested that herbal medicines can be used to prevent and treat GA by regulating cellular pyroptosis. Recently, it was found that some herbal compound containing rhizome of swordlike atractylodes has a potential therapeutic effect on GA. Chao Li et al[63-64] detected that rhizome of swordlike atractylodes in all dose groups could reduce the expression of IL-1β, IL-6, TNF-α, XOD, PGE2, UA, and TGF-β1 in modeled rats and slowed down the degree of pathological synovial damage; Gentiana dahurica Fisch. has anti-inflammatory, antioxidant, and other physiological activities, and the results of Gao Xiangxiang et al[65] showed that Gentiana dahurica Fisch. can reduce joint damage in rats, and the mechanism is associated with the reduction of serum TNF-α, IL-1β, IL-6, PGE2, and MMP-3 levels. Dioscorea nipponica has anti-inflammatory, immunomodulatory, and uric acid-reducing efficacy, Jing Lu et al[66] found that Dioscorea nipponica critically downregulated the serum IL-1β expression in rats. Therefore, monoherbal medicines had the potential to treat GA.

Active ingredients of Chinese herbal medicines

Chinese herbal extracts also have certain regulatory mechanisms on cellular pyroptosis, and studies have shown that Total saponins of Dioscorea nipponica, the main active ingredient of Dioscorea nipponica, have anti-inflammatory and analgesic, anti-tumor, anti-viral, modulating the immune system, improving cardiovascular function, hypoglycemic, It

showed numerous pharmacological efficacies, including anti-inflammatory, analgesic, anti-tumor, anti-viral, immune system regulating, cardiovascular function improving, hypoglycemic, lipid-lowering.[67-69] Zhou Qi et al.[70] showed that Total saponins of Dioscorea nipponica could improve the histopathological damage of synovial membrane in model rats, significantly reduce CD68 and iNOS expression, and significantly augment the level of anti-inflammatory factors IL-4, TGF-β1.[71] Total saponins Achyranthes (TSA) had a significant anti-inflammatory effect and could suppress the level of cytokine IL-1β.[72] Nasha et al[73] showed that total saponins of achyranthes decreased IL-1β, IL-6, and IL-18 expression in rat joint fluid in all dose groups, and regressed the level of NLRP3, ASC, as well as Caspase-1 protein in synovial tissue. Its anti- GA mechanism may be the inhibition of NLRP3 inflammatory vesicle assembly. Studies have confirmed the anti-inflammatory effect of Gallic acid, and LinYu Qing et al[74] revealed that Gallic acid inhibits ROS production, thereby reducing NLRP3 inflammatory vesicle maturation and pyroptosis associated Nrf2 signaling; Resveratrol (Veratrum grandiflorum) (Res), which has hypo-uric acid,[75] anti-GA effects.[76] Weimin Fan et al[77] demonstrated that Res is associated with the reduction of IL-1β, IL-18, and Caspase-1 levels for inhibiting the MSU-induced maturation of NLRP3 inflammatory vesicles. Also, Res augmented the membranous potentiality of mitochondria, suppressed the level of P62 and Pink1, enhanced LC3B-II Parkin and TOMM20 expression, promoting mitochondrial autophagy, while inhibitors of mitochondria reverse the suppressing effect of Res on NLRP3 inflammatory vesicle maturation. Res significantly ameliorates GA, and the potential mechanism may be to suppress NLRP3 inflammatory vesicle maturation by triggering the Pink1 / Parkin pathway to promote mitochondrial autophagy; increasing evidence suggests[78-79] that Isovitexin is associated with the mechanisms of anti-inflammatory and antioxidant activities. Isovitexin attenuates inflammatory responses in LPS-induced RAW 264.7 macrophage cell lines. Recent results suggest that Isovitexin can inhibit the progression of osteoarthritis, Xiaofen Hu et al[80] showed that Isovitexin attenuated the infiltration of inflammatory cells, improved the proliferation of synovial cells, substantially downregulated the expression of TNF-α, IL-1β, and IL-6 in the serum of model rats, and TLR4 in the synovial tissue of model rat ankle joints, The level of TLR4, MyD88, and phosphorylated-nuclear factor κB (p-NF-κB p65) in the synovial membranes. of ankle joints of model rats was significantly reduced, suggesting that Isovitexin ameliorates GA through suppressing the TLR4-MyD88-NFκB regulatory axis and improving joint inflammation in acute GA. Luteolin (luteolin) has various pharmacological activities, including anti-inflammatory, antioxidant, anti-immune T cell proliferation, and angiogenesis, etc. It shows effective anti-inflammatory activity by blocking the NF-κB signaling pathway downregulating pro-inflammatory cytokines in macrophages and inhibiting nitric oxide and pro-inflammatory arachidonate production.[81] Luteolin has shown effective anti-inflammatory activity against acute GA rats and showed significant anti-inflammatory effects,[82] Ruiming Shen et al. revealed that Luteolin downregulates the TLR-MyD88-NFκB signaling axis to attenuate the inflammatory response in acute.

However, there are still many shortcomings in the treatment of GA by TCM, which are highlighted by the unknown interactions between TCM components, the toxicology of TCM, and the difficulty in controlling the quality of TCM. Therefore, it is important to deepen the existing research, explore the unknown research, and strengthen the research of TCM in the treatment of GA. In further researches, it is crucial to explore the relevant molecular pathways and drug targets of traditional Chinese medicine in the regulation of cellular pyroptosis.

CONCLUSIONS

This study reviewed the recent progress of the cellular pyroptosis pathway involved in the development of GA and the related research progress of Chinese medicine in GA treatment. It was found that oxidative stress, mitochondrial damage and cellular pyroptosis is mainly associated with GA in terms of inflammatory release.The mechanisms and interactions between oxidative stress and mitochondrial damage are not yet clarified and need to be further investigated. Understanding the molecular signaling pathways and the interactions between target genes will be the main direction of our future research. Meanwhile, with the continuous development of Chinese medicine, other mechanisms of action of TCM in the prevention and treatment of GA will also gradually come into the view of scholars.

DATA AVAILABILITY

The data could be obtained by contacting the corresponding author.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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