

Traditional Chinese medicine for the treatment of chronic inflammatory diseases: A review of inhibitors for NLRP3 inflammasome

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Abstract

The NLR family pyrin domain-containing 3 (NLRP3) inflammasome is a vital part of the innate immune response, whilst its aberrant activation drives the progression of several noncommunicable diseases. It induces caspase-1 activation and the downstream substrates involved with the processing and secretion of the pro-inflammatory cytokines IL-1 β and IL-18 and TNF- α . Activation of this complex often involves the adapter ASC and upstream sensors including NLRP1, NLRP3, NLRC4, AIM2, and pyrin, which are activated by different stimuli including infectious agents and changes in cell homeostasis, and play key roles in inflammation, development, and related cell death. However, the molecular mechanisms that integrate multiple inflammasome sensors to facilitate optimal host defense remain unknown; therefore, treatment is challenging. Natural medicine and small molecule-based therapies have been well-documented for their effectiveness in modulating inflammatory pathways and reestablishing the lost proteostasis inside the cells to combat several chronic diseases related to inflammation. Traditional Chinese medicines (TCMs) have potent clinical effects against NLRP3 inflammasome activation and could be used as complementary therapy. Therefore, this review summarizes various similar reports and highlights the important effects of nutraceuticals and bioactive compounds derived from medicinal plants on NLRP3 inflammasome activation and their possible mechanisms of action. Thus, TCM prescriptions, herbs, and bioactive compounds can be considered novel, practical, and accessible agents in chronic inflammatory diseases by inhibiting NLRP3 inflammasome activation.

KEYWORDS

chronic inflammatory diseases, NLRP3 inflammasome, traditional Chinese medicine

Yucen Zou and Pei Ma contributed equally to this work.

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INTRODUCTION

The chronic inflammatory diseases (CIDs) describe many disease conditions with a state of non-communicable, persistent, low-grade inflammation, which affect a large group of individuals worldwide [1, 2]. CIDs include infectious, allergic, atherosclerosis, diabetes mellitus, nonalcoholic fatty liver disease, neuroinflammatory/neurodegenerative, autoimmune diseases, and cancer, and they are increasingly found in the aging population [3–6]. The noxious stimuli, including pathogen-associated molecular patterns (PAMPs, such as bacteria, fungi, and viruses) and damage-associated molecular patterns (DAMPs, such as endogenous molecules from dying or dead cells), are recognized by pattern recognition receptors (PRRs), and they initiated the innate immune response. Chronic inflammation occurs if the initiating stimulus is not removed or if the resolution program is disturbed, and the causes include chronic infections, lifestyle and environmental factors, physical inactivity, microbiome dysbiosis, diet, psychological stress, and toxins [7]. PRRs are normally the first sensors for DAMPs and PAMPs and contribute to the resolution of inflammation. Among them, NOD such as receptors (NLRs) serve the largest and most diverse family, and the NOD-like receptor protein 3 (NLRP3) has attracted wide attention in recent years [8]. Emerging evidence suggests that NLRP3 is triggered by multiple endogenous DAMPs in several CIDs, making it an attractive target for near-term interventional studies [9]. Therefore, cutting-edge research for a better understanding of its novel small molecule inhibitors will provide opportunities to develop novel drugs protecting against CIDs.

Upon activation, NLRP3 boosts the release of the inflammatory cytokines, interleukin-1 β (IL-1 β) and IL-18, and induces inflammatory cell death, pyroptosis. Study of NLRP3 inflammasome activation has attracted a lot of interest since its role in an auto-inflammatory disease (cryopyrin-associated periodic syndrome) was elucidated in 2001 [10]. So far, MCC950, a glyburide derivate, is the most potent inhibitor of NLRP3 inflammasome activation, via inhibiting its activation by all known NLRP3 stimuli but not those that activate AIM2, NLRC4, or the TLR-driven priming step. MCC950 has demonstrated significant therapeutic efficacy against CAPS, experimental autoimmune encephalomyelitis, Alzheimer disease, asthma and allergic airway inflammation, atherosclerosis, inflammatory bowel disease, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis, stroke, diabetes, and traumatic brain injury [11]. Meanwhile, active agents from natural medicine are becoming one of the key sources in seeking novel drug candidates, especially those with rich origins, unique structures, and significant activities. Traditional Chinese medicine

(TCM), which uses single herbs or herbal formula for disease treatment, is a well-documented resource utilizing natural products and has a long-lasting history of medical practice and experience. Numerous clinical and animal studies have proven the therapeutic effects of TCMs and formulas on CIDs, including *Lycii Fructus*, Huangkui capsules (HKC), Wenshen–Jianpi recipe, and Huangqi–Guizhi–Wuwu decoction (HQQZWWD). TCM approaches for CID treatment focus primarily on clearing heat and detoxification, controlling water and fluid metabolism to eliminate edema, regulating stomach and spleen function to improve overall immunity, and alleviating the proteinuria issue. Quite a few active ingredients of natural herbs and classic prescriptions have been shown to be able to inhibit NLRP3 inflammasome [12]. Oridonin, a bioactive entkaurane diterpenoid, is a major compound in *Isodon rubescens*, a TCM used for the treatment of inflammatory diseases, and it has been shown to specifically inhibit the NLRP3 inflammasome. Mechanistically, oridonin irreversibly binds NLRP3 Cys279 and blocks the NLRP3–NEK7 interaction. Importantly, oridonin has therapeutic effects in mouse models of peritonitis, gouty arthritis, and type 2 diabetes, via inhibition of NLRP3 activation. Currently, there are several new therapeutics that have been advanced into clinical trials which specifically target NLRP3 inflammasome activation for broad CIDs. Meanwhile, years of basic research have expanded our understanding of the biological processes of NLRP3 activation. Recent discoveries of the NLRP3–NEK7 complex, mitochondrial dysfunction, golgi disassembly, and ionic flux in NLRP3 activation as well as the discovery of GSDMD as the pyroptotic executor provide new insights into the mechanism of action and regulation. The refinement of our understanding of the NLRP3 activation mechanism, a high-resolution structure of protein in complex with inhibitors, as well as determining the mode of action of compounds and potential off-target effects will boost the development of a safe and effective NLRP3 inhibitor.

Increasing evidence emphasize the low toxicity and multi-component synergistic properties of TCMs and formulas for the prevention and therapy of CIDs. Little is known about the role of TCMs and formulas as modulators of NLRP3 for the treatment of CIDs, although an epidemiological study suggested a direct correlation in clinical and animal models. Some previous reviews have discussed NLRP3 inhibitors. However, the authors did not summarize the literature in TCMs and formulas on NLRP3 inflammasome. In this review, we summarize TCMs and formulas that attenuate CIDs with properties of modulating the NLRP3, and their application, pharmacological mechanisms, as well as the limitations. This review intends to serve as a resource for further research.

APPLICATION OF TCM IN CIDS

Generally, modern medicine has adopted a standard treatment mode for CIDs, but it is difficult to completely prevent its occurrence, development, and deterioration. Moreover, these therapies are also frequently reported to have side effects. Practitioners of TCM have a wealth of accumulated experience in CID treatment and have unique views on its etiology and pathogenesis as well as suitable treatment modes. TCM has a set of treatment modes with traditional Chinese medical characteristics. Modern pharmacological studies have found that most of TCMS aim to prevent and treat CIDs by inhibiting the activation of NLRP3 inflammasomes and caspase-1 and by regulating its upstream-related signal pathways, such as TLR4/NF- κ B, ROS/TXNIP, AMPK/Nrf2 or DRP1/NLRP3 to inhibit the occurrence of pyroptosis. At the same time, it is also found that the same monomer or compound prescription can regulate and control the above multiple pathways to improve NLRP3-mediated pyroptosis. Here, we summarize the treatment of CIDs with TCM prescriptions, herbs, and bioactive compounds and their potential mechanisms.

The temporal trend for the top 1000 keywords is shown in Figure 1 based on a logarithm-scaled bubble

plot. Keywords (bubbles) that appeared more frequently in the recent years (2019–2024) relative to the past years (2013–2018) are more likely to be trending up (red color); they tend to be located in the left-upper side from the diagonal line. A trend factor was used to quantify the degree of trending up or trending down in a keyword based on the logarithmic ratio of its normalized cumulative frequency in the current period (Frequency current) to the past period (Frequency past) (Figure 1). Co-occurrence of the top 69 frequent keywords is shown in Figure 2 based on the circos plot. The keywords have been categorized into four distinct groups: Group 1 comprises targets, Group 2 encompasses mechanisms, Group 3 pertains to diseases, and Group 4 pertains to drugs. Edge width and color are used to represent the co-occurrence between keywords; a thicker edge with darker color means that the two keywords have a higher co-occurrence.

TCM PRESCRIPTIONS IN TREATING CIDS

TCM prescriptions are widely used as an independent or adjuvant strategy in treating CIDs. Compared to traditional therapy, TCM methods have shown potent efficacy and fewer adverse effects.

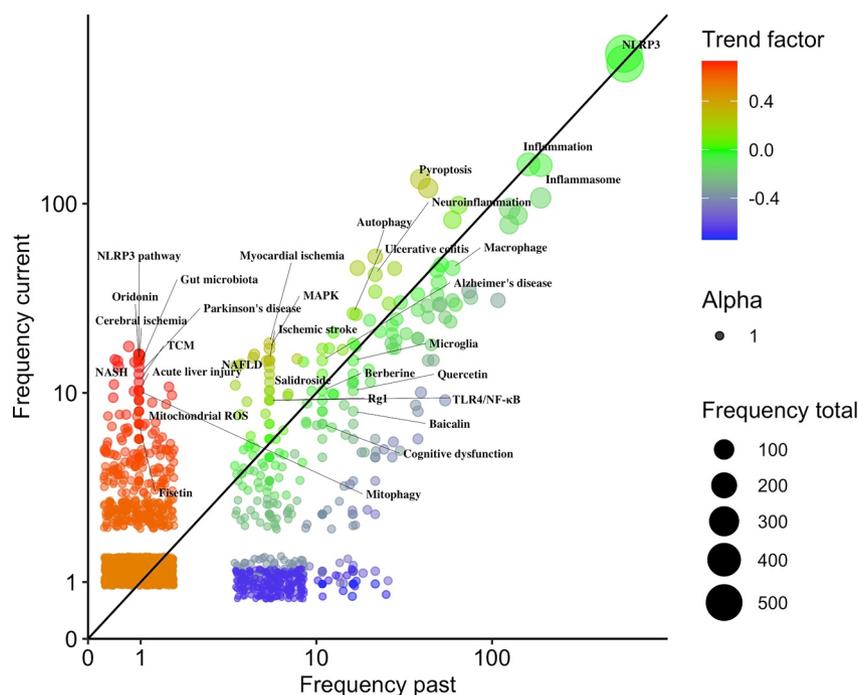


FIGURE 1 Distribution of temporal trend of the top 1000 frequent keywords (bubbles) based on their normalized cumulative frequencies in the past (2013–2018) and recent (2019–2024) years. Trend factor value is shown by color; keywords rendered by red and purple colors are more likely to be trending up and trending down, respectively. The size of bubble reflects the popularity in research of the keyword. Abbreviations: NLRP3, NOD-like receptor thermal protein domain associated protein 3; NASH, nonalcoholic steatohepatitis; TCM, traditional Chinese medicine; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase; Rg1, ginsenoside Rg1; TLR4/NF- κ B, toll-like receptor 4/nuclear factor- κ B.

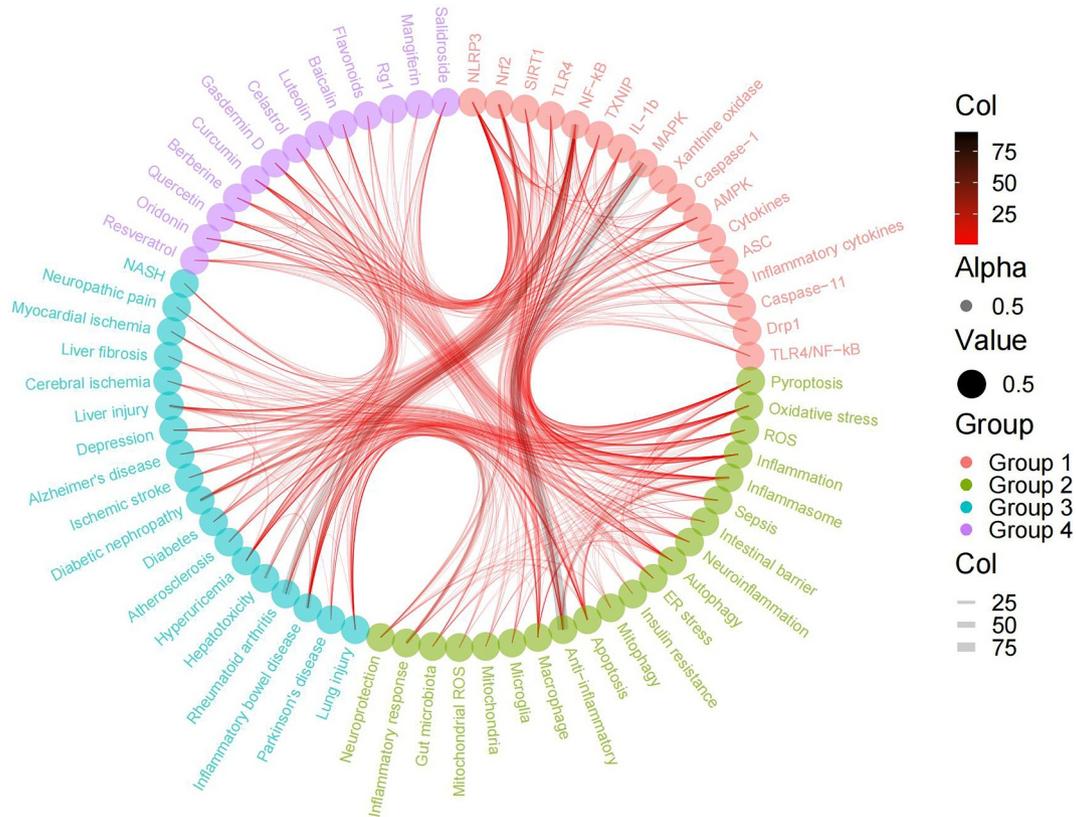


FIGURE 2 Co-occurrence of the top 69 frequent keywords based on the circo plot. The keywords have been categorized into four distinct groups: Group 1 comprises targets, Group 2 encompasses mechanisms, Group 3 pertains to diseases, and Group 4 pertains to drugs. Edge width and color are used to represent the co-occurrence between keywords; a thicker edge with darker color means that the two keywords have a higher co-occurrence. Abbreviations: NLRP3, NOD-like receptor thermal protein domain associated protein 3; Nrf2, nuclear factor erythroid-derived 2-like 2; SIRT1, sirtuin 1; TLR4, toll-like receptor 4; NF- κ B, nuclear factor- κ B; TXNIP, thioredoxin-interacting protein; IL-1 β , interleukin-1 β ; MAPK, mitogen-activated protein kinase; AMPK, AMP-activated protein kinase; ASC, apoptosis-associated speck-like protein containing a CARD; Drp1, dynamin-related protein 1; ROS, reactive oxygen species; ER, endoplasmic reticulum; NASH, nonalcoholic steatohepatitis; Rg1, ginsenoside Rg1.

Here, we summarized the use of TCM prescriptions in treating CIDs. A total of 118 articles related to prescriptions were summarized, involving 99 prescriptions. These prescriptions originated from 39 ancient books, 18 proprietary Chinese medicines, 25 clinically tested formulas, 7 modified formulas, and 10 others. The use frequencies are shown in Figure 3a.

TCM prescription, such as Si-Miao formula, Fufang-Zhenzhu-Tiaozhi, Pien-Tze-Huang, Su-Huang antitussive capsule, and Taohong-Siwu decoction (with a frequency of appearance in the articles ≥ 3), can treat CIDs by inhibiting NLRP3 inflammasomes.

Si-Miao formula is a TCM prescription for the treatment of nonalcoholic fatty liver disease, and research results have confirmed that it has a role in regulating hepatic lipid metabolism pathways [13]. Fufang-Zhenzhu-Tiaozhi targets diabetic cardiomyopathy by mitigating oxidative stress and suppressing the activation of the NLRP3 inflammasome caused by cardiac lipotoxicity [14]. Furthermore, Fufang-Zhenzhu-Tiaozhi also prevents renal injury, inflammation, and fibrosis in hyperuricemic nephropathy mice by promoting uric

acid excretion and inhibiting the PI3K/AKT/NF- κ B signaling pathway [15]. Pien-Tze-Huang effectively mitigates joint inflammation in collagen-induced arthritis mice, possibly by regulating the NF- κ B-signaling pathway and NLRP3 inflammasome [16]. Additionally, it exhibits beneficial liver protection against acetaminophen-induced liver injury, likely through NLRP3 inflammasome inhibition driven by upregulated autophagy activity [17].

Su-Huang antitussive capsule suppresses non-resolving inflammation by inhibiting NF- κ B signaling and NLRP3 inflammasome activation, maintaining mitochondrial homeostasis [18]. This action of Su-Huang antitussive capsule contributes significantly to impairing NLRP3 inflammasome activation and reducing ER stress, leading to the preservation of pulmonary homeostasis [19]. Collectively, these findings suggest that Su-Huang antitussive capsule may play a crucial role in the pharmacological treatment of cough variant asthma (CVA) patients. Recent study has shown that β -hydroxybutyric acid can reduce inflammation and oxidative stress. The increased

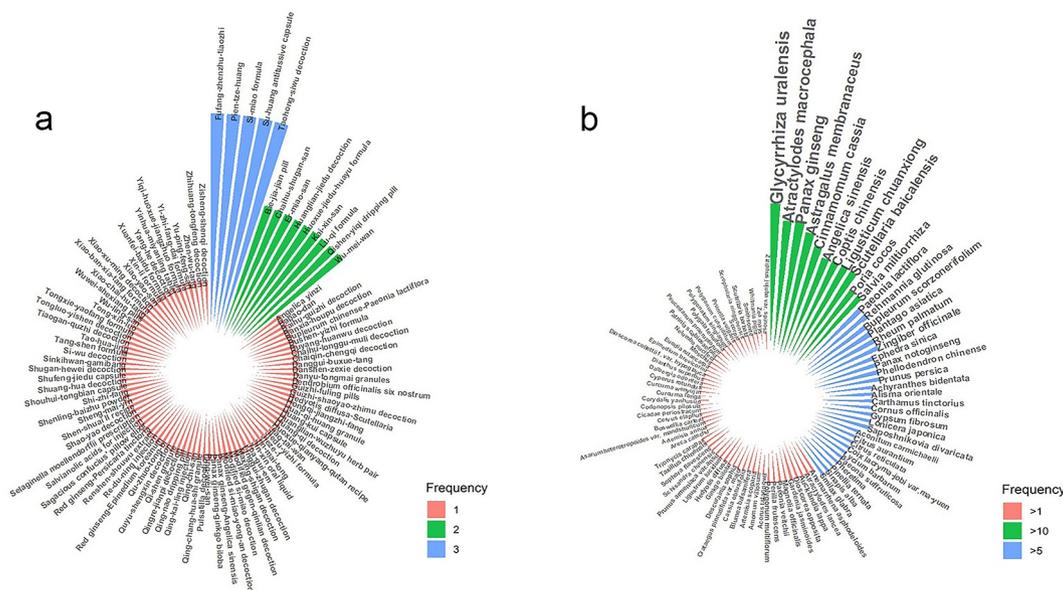


FIGURE 3 TCM prescriptions in treating CIDs. (a) The use frequencies of TCM prescriptions for CID treatment. (b) The use frequencies of TCMs in TCM prescriptions for CID treatment.

production of β -hydroxybutyric acid in serum might be a key factor for Su-Huang antitussive capsule to exert its therapeutic effect in the treatment of CVA [20]. Taken together, these results provide important new experimental data and pharmacological groundwork for the clinical application of Su-Huang antitussive capsule in CVA patients. Taohong-Siwu decoction exerts neuroprotective effects in rats with middle cerebral artery occlusion–reperfusion by reducing the activation level of NLRP3 inflammatory corpuscle and downregulating GSDMD, thereby inhibiting pyroptosis. This neuroprotective action of Taohong-Siwu decoction may be attributed to its inhibitory effect on HMGB1/TLR4/NF κ B and MAPK signaling pathways [21]. Additionally, Taohong-Siwu decoction enhances mitochondrial autophagy, further suppressing NLRP3 inflammasome activation [22]. In PC12 cells, Taohong-Siwu decoction protects against oxygen–glucose deprivation/reperfusion injury by elevating mitophagy and suppressing NLRP3 inflammasome activation [23]. These findings suggest that Taohong-Siwu decoction has potential therapeutic applications in treating neurological disorders associated with inflammation and oxidative stress.

It is important to note that these prescriptions consist of a variety of TCMs, among which *Glycyrrhiza uralensis* is the most frequent and *Atractylodes macrocephala*, *Panax ginseng*, *Astragalus membranaceus* var. *mongholicus*, *Cinnamomum cassia*, *Scutellaria baicalensis*, *Angelica sinensis*, *Coptis chinensis*, *Ligusticum chuanxiong*, *Poria cocos*, and *Salvia miltiorrhiza* appear more than 10 times in the preparations. The use frequencies are shown in Figure 3b.

The bioactive components of *Glycyrrhiza uralensis* primarily consist of flavonoids, triterpenoids, stilbenoids, coumarins, and polysaccharides. In the clinical practice of TCM, *Glycyrrhiza uralensis* is frequently utilized due to its diverse biological activities. These activities include anti-inflammatory (exemplified by β -glycyrrhittic acid), antimicrobial (exemplified by flavonoids), antiviral (exemplified by glycyrrhizic acid), anti-protozoal (exemplified by licochalcone A), antioxidative (exemplified by licochalcones A, B, C, and D), hepatoprotective (exemplified by glycyrrhetic acid), and antitumor activities (exemplified by glycyrrhetic acid). Multiple studies have demonstrated that *Glycyrrhiza uralensis*, acting as an anti-inflammatory agent, can reduce allergic reactions and prevent liver toxicity. Additionally, *Glycyrrhiza uralensis* is also known to be effective in treating fatigue and debilitation. We speculated that most prescriptions in treating CIDs contain *Glycyrrhiza uralensis* because of its anti-inflammatory effect. This notion aligns with the current understanding of CIDs, which often involve hyper-activation of the NLRP3 pathway.

In these TCM prescriptions, the frequency of occurrence of the herbal combinations such as Baishao-Danggui, Baizhu-Fangfeng, Baizhu-Gancao, Chuanxiong-Danggui, Chuanxiong-Gancao, Danggui-Gancao, Danggui-Huangqi, Gancao-Huangqi, and Gancao-Mahuang has exceeded five times. This demonstrates the high frequency of use and importance of these combinations in TCM prescriptions. These combinations may be classic prescriptions formed based on TCM theory and accumulated experience, possessing certain therapeutic effects and a wide range of applications.

TCMS IN TREATING CIDS

We have organized 190 relevant documents on the use of plants in the treatment of CIDs, covering 138 plant species, of which 112 are traditional Chinese medicinal herbs. These herbs primarily originate from plants such as *Panax*, *Artemisia*, *Morus*, and *Abelmoschus*. In terms of the properties of Chinese medicine, they are primarily warm, cool, and neutral drugs, and their meridians mainly involve the kidney, liver, and other meridian systems. The use frequencies are shown in Figure 4a.

Some of these herbs are frequently used in the treatment of CIDs, such as *Panax ginseng* for SARS-CoV2, *Abelmoschus manihot* for kidney injury, *Morus nigra* for colitis, etc. The use frequencies are shown in Figure 4b. COVID-19, a highly contagious disease, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus has the potential to cause clinical manifestations of damage to multiple organs, including various neurological syndromes. The NLRP3 inflammasome, a complex of multiple molecules, is able to detect various pathogen-associated molecular patterns associated with neurological disorders. Activation of NLRP3 stimulates the production of caspase-1-mediated IL-1 β , IL-18, and other cytokines in immune cells. *Panax ginseng*, a medicinal plant widely used due to its safety and anti-inflammatory, antioxidant, and antiviral properties, has traditionally been utilized to enhance the immune system and treat various pathological conditions in the nervous system. Recent reports suggest that *ginseng* and its active components may regulate NLRP3 inflammasome activation in the nervous system [24]. Hyperuricemia has become increasingly common in recent years, leading to a sustained increase in kidney injury cases caused by uric acid (UA). The TCM, *Abelmoschus manihot*, commonly used to treat kidney diseases, has been found to effectively alleviate UA-induced cell damage by inhibiting the ERK1/2/caspase-8/caspase-3/NLRP3/GSDME signaling pathway [25]. Additionally, *Abelmoschus manihot* suppressed NLRP3 inflammasomes via inhibition of ERK1/2 signal transduction, decreased proteinuria and attenuated renal tubule lesions, and inhibited the expression of NLRP3 in tubules in rats with adriamycin nephropathy [26]. The total flavonoids of *Abelmoschus manihot* are widely used in China to treat podocyte injury in diabetic kidney disease (DKD). Studies have shown that it can improve podocyte pyroptosis and injury by adjusting METTL3-dependent m(6)A modification and regulate NLRP3 inflammasome activation and PTEN/PI3K/Akt signaling pathway under hyperglycemic conditions [27]. It has been found that *Morus nigra* may alleviate DSS-induced acute colitis by modifying the gut microbiota and improving mucosal conditions [28].

Bioactive compounds in treating CIDs

The effects of active chemical entities in treating CIDs have been intensively investigated. The various types of compounds studied include albiflorin (terpene glycosides), tanshinone IIA (flavones), koumine (alkaloids), astragaloside IV (steroids), etc. Some of these compounds alleviate the renal pathologic progression of CIDs at low dosages. For example, albiflorin, a major constituent of *Cynanchum otophyllum*, has been shown to attenuate mood disorders under neuropathic pain state by suppressing the hippocampal NLRP3 inflammasome activation during chronic constriction injury [29]. Tanshinone IIA inhibits exosome-induced cardiomyocyte pyroptosis through NLRP3/caspase 1 pathway [30]. Koumine suppresses IL-1 β secretion and attenuates inflammation associated with blocking ROS/NF- κ B/NLRP3 axis in macrophages [31]. Astragaloside IV ameliorates neuroinflammation-induced depressive-like behaviors in mice via the PPAR γ /NF- κ B/NLRP3 inflammasome axis [32]. Additionally, it plays a role in reducing radiation-induced liver inflammation in mice by inhibiting thioredoxin-interacting protein/nod-like receptor protein 3 signaling pathway [33].

The chemical structures of these active chemical entities, which are potential drugs in treating CIDs, are shown in Figure 5. In conclusion, the above components showed positive effects on improving the progression of CIDs, and more details on these are described in Table 1.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

NLRP3 inflammasome plays an important role in the development of CIDs [55]. Most in vitro and in vivo studies in our review have confirmed that inhibition of NLRP3 inflammasome can improve tissue function to a large extent for CID models. A variety of signal molecules lead to early pathological changes through corresponding signaling pathways after CIDs, subsequently activating NLRP3 inflammasome-mediated pyroptosis. These signal-mediated pathological changes include ROS damage, mitochondrial dysfunction, ion imbalance, lysosomal rupture, and trans-Golgi disintegration. The activation of NLRP3 inflammasome consists of two steps, namely the activation and assembly of NLRP3 inflammasome. The signaling pathway involved in the activation step is TLR4/NF- κ B/NLRP3. The signaling pathways involved in the assembly include ROS/TXNIP/NLRP3, AMPK/Nrf2/NLRP3, DRP1/NLRP3, and TAK1/JNK/NLRP3. Current pharmacological studies show that TCM can inhibit NLRP3 inflammasome by regulating

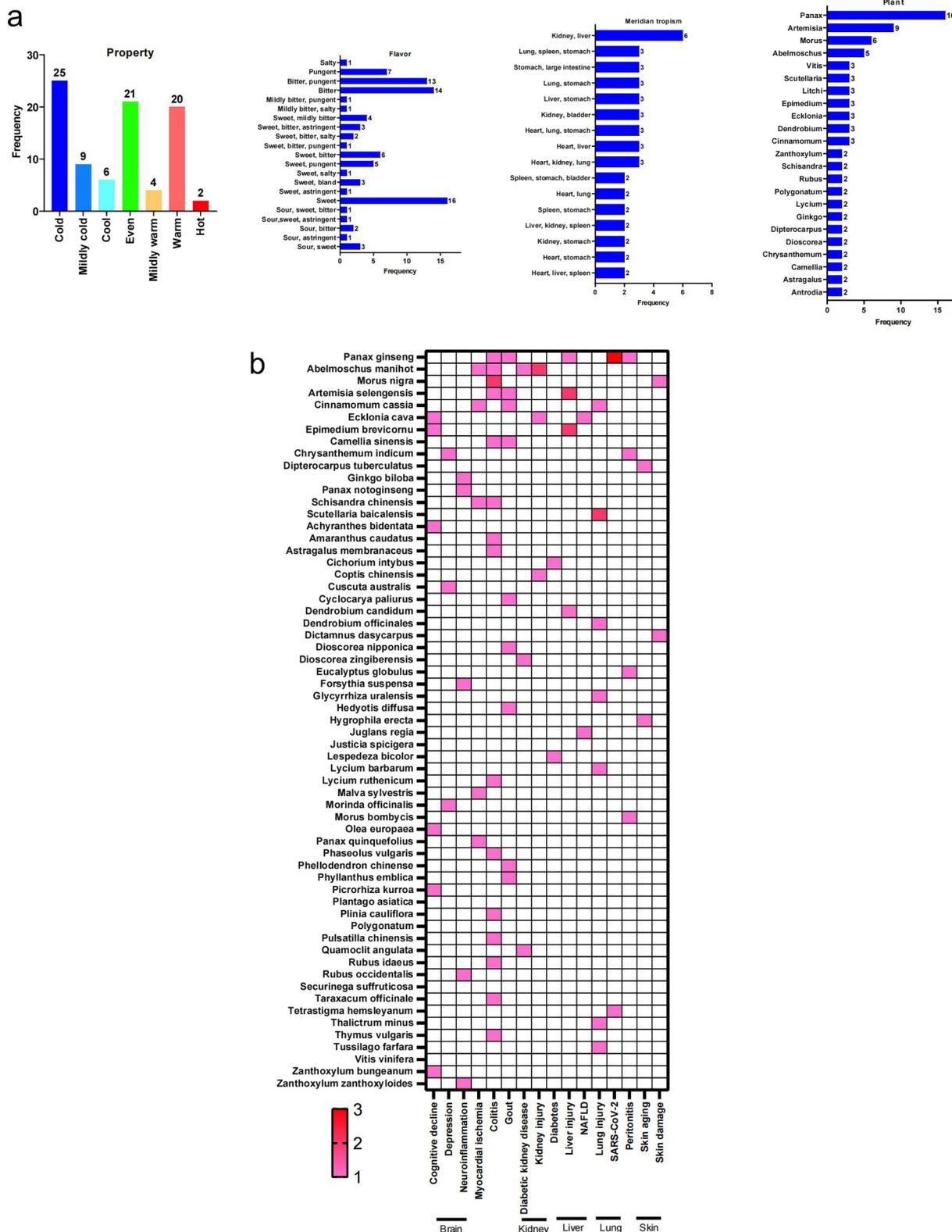


FIGURE 4 TCMs in treating CIDs. (a) The use frequencies of properties, flavors, meridian tropisms, and source plants of TCMs for CID treatment. (b) The use frequencies of TCMs for CID treatment.

the above signal pathways, thus inhibiting pyroptosis and achieving the purpose of alleviating the process of CIDs, showing the characteristics of multi-target

and multi-channel treatment of TCM. This provides a positive signal for exploring the role of TCM in pyroptosis.

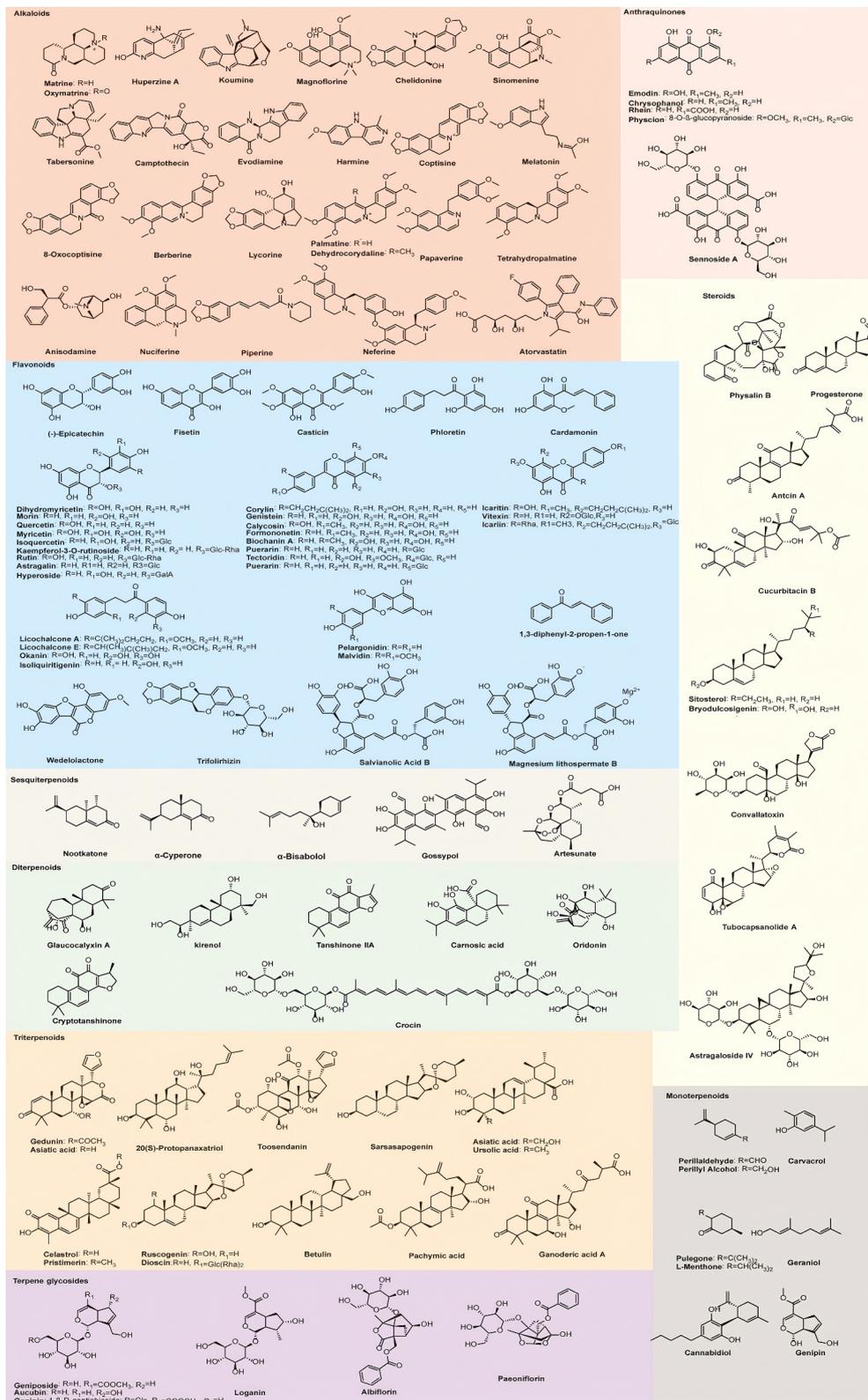


FIGURE 5 The chemical structures of bioactive compounds involved in CID treatment.

We believe that there are still some challenges in the research of the anti-CID effect of TCM based on NLRP3. (1) Strengthen the research of compound prescription and Chinese patent medicine. Our

previous summaries found that compared with TCM monomer, the compound prescription and Chinese patent medicine, as a common clinical form of TCM, has less research reports, which is not conducive to

TABLE 1 TCMs for CID treatment.

Drug	Model	Dosage	Result	Pathway	Ref.
Prescriptions					
Lu-Qi formula	A mouse model of MI	1.78 g/kg/d	NLRP3↓, ASC↓, Caspase-1↓, IL-1β↓, TXNIP↓, Cleaved-caspase-3↓, Bax↓, Bcl-2↑	Inhibiting the activation of the NLRP3/ASC/caspase-1/IL-1β cascade, downregulating caspase-3/Bax signaling	[34]
Qi-Shen granule	MI model, OGD/R, ISO, Ang II and LPS, ATP-induced H9C2 cells	1.65 g/kg/d	P65-NF-κB↓, NLRP3↓, ASC↓, Caspase-1↓, Cleaved IL-18↓, Cleaved IL-1β↓, NT-GSDMD↓	Inhibiting inflammasome activation and pyroptosis	[35]
Xuefu-Zhuyu decoction	Cardiopulmonary bypass-induced acute lung injury rats	8.2 g/kg/day	NLRP3↓, ASC↓, Caspase-1↓, Pro-GSDMD↓, GSDMD↓, IL-18↓, IL-1β↓, p-P65↓, p-IkB-α↓	Inhibiting IkB-α/NF-κB pathway	[36]
Sagacious confucius' pillow elixir	Seven-month-old senescence-accelerated P8 mice	2.3, 4.6, 9.2 g/kg/day	TNF-α↓, NLRP3↓, ASC↓, Caspase-1↓, GSDMD↓, IL-1β↓, IL-6↓, IL-18↓, Aβ↓	Inhibiting IkB-α/NF-κB pathway	[37]
Bie-Jia-Jian pill	ApoE ^{-/-} mice using high-fat diet and streptozotocin	0.9, 1.8, 3.6 g/kg/day	NF-κB↓, TXNIP↓, NLRP3↓, ASC↓, Caspase-1↓, IL-1β↓	Inhibiting of the NLRP3 inflammasome	[38]
Chaihu-Shugan-San	CUMS-induced rats	925, 1850 mg/kg	ALT↓, IL-1β↓, TLR4↓, MyD88↓, NF-κB↓, NLRP3↓, ASC↓, Caspase-1↓, miR-155↑	Suppressing TLR4/MyD88/NF-κB pathway and NLRP3 inflammasome activation	[39]
Kai-Xin-San	CUMS-induced rats	3, 5, 10 g/kg/d	ROS↓	Inhibiting the NLRP3 inflammasome	[40]
Er-Miao-San	A rat model of adjuvant arthritis	3, 1.5, 0.75 g/kg	CD86/CD206↓, IL-10↑, TGF-β↑, IL-1β↓, TNF-α↓	Downregulating the miRNA-33/NLRP3 pathway	[41]
Huanglian-Jiedu decoction	Type 2 diabetes mellitus (T2DM) rats induced via a high-sugar and high fat diet combined with a low dose of streptozotocin	3, 1.5, 0.75 g/kg/day	BDNF↑, ATG7↑, LC3↑, P62↓, NLRP3↓, Caspase-1↓, IL-β↓	Regulating autophagy and NLRP3 inflammasome activation	[42]
Huoxue-Jiedu-Huayu formula	Six-month-old unilateral ureteral obstruction rats	1.92 g/kg/day	Serum creatinine↓, Urea↓	Depressing cell pyroptosis based on the NLRP3/caspase-1/IL-1β pathway	[43]
Herbs and extracts					
<i>Glycyrrhiza uralensis</i> polysaccharides	LPS-induced acute lung injury; LPS-induced BMDM cells	0.5, 1, 2 mg/kg; 0.5–2 mg/mL	IL-1β↓, IL-6↓, TNF-α↓	Suppressing the oligomerization and speckle aggregation of the ASC and the activation and assembly of the AIM2-NLRC4 inflammasomes	[44]
Extracts of <i>Oenanthe javanica</i>	LPS-induced BMDMs or THP-1 cells	1.3, 2.5, 5%	IL-1↓, ASC↓, Caspase-1↓	Inhibiting the activation of the NLRP3, NLRC4, and AIM2 inflammasome	[45]
Bioactive compounds					
Anthocyanins	Diabetic human aortic endothelial (D-HAEC) cells exposed to oxidative stress by hydrogen peroxide and LPS	50 μL/mL	IL-6↓, Caspase-1↓	Inhibiting the NF-κB signaling pathway	[46]
Quercetin, puerarin, and troxerutin	High glucose-induced endothelial cells	10, 50, 100 μmol/L	MCP-1↓, IL-8↓, ROS↓	Suppressing NLRP3 inflammasome activity	[47]
Chlorogenic acid	Cisplatin-induced nephrotoxicity rats	20 mg/kg	NF-κB↓, TNF-α↓, Bax/bcl-2↓	Inhibiting the TLR4/NLPR3/IL-1β/GSDMD pathway	[48]
Resveratrol (RES) and polydatin (PD)	Crystal-induced THP-1 cells	RES (100 μmol/L) and PD (200 μmol/L)	IL-1β↓, ROS↓, NO↓, IL-1↓		[49]

(Continues)

TABLE 1 (Continued)

Drug	Model	Dosage	Result	Pathway	Ref.
Fucoxanthin (FX) and rosmarinic acid (RA)	UVB-irradiated HaCaT keratinocytes	FX (5 $\mu\text{mol/L}$) and RA (5 $\mu\text{mol/L}$)	ROS \downarrow , NLRP3 \downarrow , ASC \downarrow , Caspase-1 \downarrow , IL-1 β \downarrow , Nrf2 \downarrow , HO-1 \downarrow	Downregulating NLRP3-inflammasome and increasing Nrf2 signaling pathway	[50]
Chlorogenic acid methyl ester	LPS-induced mice with acute lung injury; LPS-stimulated mouse macrophage RAW264.7 cells	1 $\mu\text{mol/L}$	PGE2 \downarrow , IL-1 \downarrow , COX-2 \downarrow , NLRP3 \downarrow , p-P65 \downarrow	Blockading the COX-2/NLRP3/NF- κ B signaling pathway	[51]
Dimethyl fumarate	LPS and ATP-induced THP-1 cells	0.001–10 $\mu\text{mol/L}$	Caspase-1 \downarrow , IL-1 \downarrow	Preventing the activation of the pyroptotic molecular cascade	[52]
Isorhamnetin	LPS-induced BMDMs or THP-1 cells	20, 100, 200 $\mu\text{mol/L}$	Caspase-1 \downarrow	Inhibiting the activation of the NLRP3 and AIM2 inflammasome	[45]
Hyperoside	LPS-induced BMDMs or THP-1 cells	20, 100, 200 $\mu\text{mol/L}$	Caspase-1 \downarrow	Inhibiting the activation of the NLRP3 and AIM2 inflammasome	[45]
Morin	An obesity model through a high-fat diet	50 mg/kg	IL-18 \downarrow , Caspase-1 \downarrow , Ppar- γ \downarrow , Srebp-1c \downarrow , Ppar- α \uparrow , Adiponectin \uparrow		[53]

Abbreviations: MI: myocardial infarction; NLRP3: NOD-like receptor protein 3; ASC: apoptosis-associated speck-like protein containing a CARD; IL-1 β : interleukin-1 β ; TXNIP: thioredoxin interacting protein; Bcl-2: B-cell lymphoma-2; Bax: bcl-2 associated X protein; P65-NF- κ B: p65 nuclear factor κ B; IL-18: interleukin-18; NT-GSDMD: gasdermin D N-terminal fragment; Pro-GSDMD: Pro-gasdermin D; GSDMD: gasdermin D; OGD/R: oxygen and glucose deprivation/reoxygenation and reglucose; ISO: isoprenaline; Ang II: angiotensin II; LPS: lipopolysaccharide; ATP: adenosine tri-phosphate; p-P65: phosphorylated nuclear factor- κ B p65 subunit; p-I κ B- α : phosphorylated inhibitor of nuclear factor κ B- α ; I κ B- α : inhibitor of nuclear factor κ B- α ; NF- κ B: nuclear factor- κ B; TNF- α : tumor necrosis factor- α ; ALT: alanine aminotransferase; TLR4: toll-like receptor 4; MyD88: myeloid differentiation primary response gene 88; miR-155: microRNA-155; ROS: reactive oxygen species; ApoE $^{-/-}$: apolipoprotein E knockout; CUMS: chronic unpredictable mild stress; CD86: cluster of differentiation 86; CD206: cluster of differentiation 206; TGF- β : transforming growth factor- β ; miRNA-33: microRNA-33; BDNF: brain-derived neurotrophic factor; ATG7: autophagy related 7; T2DM: type 2 diabetes mellitus; LC3: microtubule-associated protein 1 light chain 3; P62: sequestosome 1; BMDM: bone marrow-derived macrophages; IL-18: interleukin-18; IL-6: interleukin-6; A β : beta-amyloid; AIM2: absent in melanoma 2; NLRP3: NLR family CARD domain containing 3; D-HAEC: diabetic human aortic endothelial; MCP-1: monocyte chemoattractant protein-1; UVB: ultraviolet B; Nrf2: nuclear factor erythroid 2-related factor 2; HO-1: heme oxygenase-1; PGE2: prostaglandin E2; Ppar- γ : peroxisome proliferator-activated receptor- γ ; Ppar- α : peroxisome proliferator-activated receptor- α ; SREBP-1c: sterol regulatory element binding protein-1c; COX-2: cyclooxygenase-2.

providing scientific basis for the clinical application of the compound. In the future, bioinformatics methods can be used to identify the potential effective components and the target of action of the compound prescription and Chinese patent medicine, structural pharmacology methods such as molecular docking technology can be used to further reveal the binding sites of monomer components, and methods such as gene knockout or inhibition of key proteins can be used to verify the target of action of monomer components. Adopt modern pharmacological methods to carry out simultaneous component research and comparative study with compound prescription, so as to clarify the material basis of drug function. (2) The CID body model is diversified. Studies have shown that the selection of models may have an impact on the role of NLRP3-mediated pyroptosis in CIDs. Therefore, different models can be used for comparative study in future studies, and mutual verification can fully illustrate the empirical conclusions. (3) To explore the potential of nonclassical NLRP3 signaling in the study of CID pathological mechanism. There is no in vivo experiment to show the relationship between nonclassical pyrolytic pathway and CID. Moreover, there is little research on nonclassical pyroptosis pathway in TCM.

To sum up, NLRP3 inflammasome may be the switch molecular target of the upstream channel of the mechanism of pyroptosis in CIDs. Deeply exploring the relevant molecular mechanism of NLRP3 inflammasome affecting pyroptosis, summarizing the relationship between NLRP3 mediated-pyroptosis signal pathway and CIDs and the research status of TCM prevention and treatment, clarifying the specific mechanism of TCM, providing new ideas for TCM treatment of CIDs and theoretical basis for TCM to effectively and economically serve human health.

AUTHOR CONTRIBUTIONS

Yucen Zou: Data curation; Formal analysis; Writing—original draft. **Pei Ma:** Data curation; Formal analysis; Writing—original draft. **Bin Li:** Data curation; Formal analysis. **Jiushi Liu:** Formal analysis. **Lifeng Yue:** Methodology. **Bengang Zhang:** Supervision. **Haitao Liu:** Funding acquisition; Supervision; Writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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