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REVIEW

NLRP3 Inflammasome Pharmacological Inhibitors in *Glycyrrhiza* for NLRP3-Driven Diseases Treatment: Extinguishing the Fire of Inflammation

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Abstract: Inflammation is the tissues' defense response after the body is stimulated by microbial infection or damage signals, and it is initiated when pattern recognition receptors recognize pathogen-related molecular patterns and danger-related molecular patterns. The hyperactivation of NLRP3 inflammasome, the main driving force of immune outbreaks, is involved in a wide range of inflammatory diseases. Meanwhile, growing evidence has indicated that the development of NLRP3-targeted therapies offers great potential and promise for the treatment of related diseases. The search for and development of efficacious anti-inflammatory prodrugs from natural sources of plants and traditional Chinese medicines (TCMs) have received extensive attention. *Glycyrrhiza*, an important minister in the kingdom of TCMs, has high activity and a wide range of therapeutic effects. Studies have shown that a variety of active components found in *Glycyrrhiza*, such as licochalcone A, echinatin, isoliquiritigenin, and glycyrrhizin, produce a wide range of anti-inflammatory effects by discouraging NLRP3 inflammasome activation. Here, we summarize the role and mechanism of the active ingredients in *Glycyrrhiza* that target the NLRP3 inflammasome and treat related inflammatory diseases. We describe a favorable approach for the development of natural, safe, and efficient drugs that exploit these naturally occurring active ingredients to treat NLRP3-driven diseases.

Keywords: NLRP3 inflammasome, *Glycyrrhiza*, inflammatory diseases, anti-inflammatory

Introduction

Inflammation is a tissue defense response after the body is stimulated by external microbial infection or by damage signals from itself. The pathological manifestations include tissue exudation, degeneration, and hyperplasia in the inflammatory area, and are characterized by redness, swelling, heat, pain, and dysfunction. The inflammatory response is initiated when cell surface or intracellular pattern recognition receptors (PRRs) recognize pathogen-related molecular patterns (PAMPs) and danger-related molecular patterns (DAMPs).[1] Many common clinical diseases, such as cardiovascular diseases, autoimmune diseases, wound repair, are characterized by inflammation.[2–4] In clinical treatment, anti-inflammatory drugs are the second largest class of drugs after anti-infective drugs; these drugs mainly consist of steroidal anti-inflammatory drugs and non-steroidal anti-inflammatory drugs. However, due to the strong adverse side-effects of many synthetic drugs,[5] the search for and development of dependable and efficacious anti-inflammatory drugs from natural sources such as plants has received extensive attention. In

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particular, traditional Chinese medicines (TCMs), the quintessence of disease prevention and control in China for thousands of years, are a very important part of the world medicine treasury and play a vital role in inflammation.

Innate immunity plays an important role in the development of a variety of diseases by regulating the immune and inflammatory responses that depend on PRRs. NLRP3 inflammasome is part of the innate immune response and is activated in response to PAMPs or DAMPs, promoting the expression, maturation and release of multiple pro-inflammatory cytokines that trigger a cascade of inflammatory responses. Recent studies have shown that the activation of NLRP3 inflammasome is the main driving force behind excessive immune outbreaks.[6–8] The aberration of NLRP3 inflammasome activation participate in the development of human diseases, such as metabolic pathologies, cardiovascular diseases, inflammatory issues, and neurologic disorders.[9–11] *Glycyrrhiza*, also known as "Guo Lao" in Chinese, is an important minister in the kingdom of TCMs. It is not only the most commonly used TCM in tonics and food, but also one of the most important TCMs with high levels of activity and a wide range of therapeutic effects. A wide range of pharmacological effects makes *Glycyrrhiza* useful for treating multi-system inflammatory diseases, allergic diseases, and immunocompromised diseases.[12–15] A variety of active components in *Glycyrrhiza* exert a wide range of anti-inflammatory effects by inhibiting NLRP3 inflammasome. Therefore, in this review, we mainly focus on the role and mechanism of the active ingredients in *Glycyrrhiza* and how they target the NLRP3 inflammasome to treat related inflammatory diseases.

The Activation of NLRP3 Inflammasome

Inflammasomes are protein polymer complexes that coordinate the host's defense mechanism against pathogens and physiological abnormalities. The assembly of inflammasome complexes is initiated by the nucleotide-binding domain and leucine-rich repeat receptors (NLRs) or absent in melanoma 2 (AIM2) like receptors (AIM2-like receptors, ALRs), etc.[16,17] NLRs and ALRs mediate the recognition of PAMPs and DAMPs during bacterial, viral, fungal and cellular damage. In most cases, activated NLRs and ALRs will recruit the dimeric protein of apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) which participates in caspase-1 activation.[18] NLRP3 (also called CIAS1, Cryopyrin, NALP3 or Pypaf1) is composed of an amino-terminal pyrin domain (PYD), nucleotide-binding and oligomerization domain (NOD), C-terminal leucine-rich repeat domain.[19–21] The activation of the canonical NLRP3 inflammasome requires the completion of two signals (Figure 1). Signal 1 (priming stage) is characterized by toll-like receptors (TLRs), NOD2, tumor necrosis factor receptor 1 (TNFR1), TNFR2, etc., that induce NF-κB-mediated precursor protein production, including NLRP3, pro-IL-1β, and pro-IL-18. Signal 2 (activation stage) is the stage when a variety of PAMPs and DAMPs induce the assembly of the NLRP3 inflammasome complex (NLRP3-ASC-pro-caspase-1). Subsequently, pro-caspase-1 auto-cleaves to form active caspase-1, and caspase-1 then cleaves and activates the precursor proteins pro-IL-1β and pro-IL-18 into mature forms IL-1β and IL-18, which are secreted into the extracellular to participate in the subsequent inflammatory response. At the same time, the activation of NLRP3 inflammasome also leads to the occurrence of a programmed cell death, called pyroptosis.

Pharmacological Inhibitors of NLRP3 Inflammasome in *Glycyrrhiza*

Licochalcone A (Lico A)

Lico A (Figure 2A) is a chalcone occurring in *Glycyrrhiza* that has a wide range of pharmacological activities, including anti-inflammatory, anti-tumor, and anti-bacterial.[14] Here, we focus on the anti-inflammatory effect of Lico A via targeting NLRP3 inflammasome. Osteoarthritis (OA) is the most common arthritis in the elderly and is characterized by subchondral bone hyperplasia and articular cartilage degeneration, leading to the loss of joint function.[22,23] NLRP3 inflammasome is a potentially novel therapeutic target for the management of OA.[24,25] In vitro, Lico A suppresses NLRP3 inflammasome activation and GSDMD expression in primary mouse OA chondrocytes via nuclear factor erythroid-2 related factor 2 (Nrf2)/heme oxygenase-1 (HO-1)/NF-κB axis (Figure 3), indicating that Lico A attenuates LPS-induced chondrocyte pyroptosis.[26] In vivo, Lico A significantly attenuates the LPS-induced IL-1β and IL-18 protein expression in an air pouch mouse model.[26] The above studies indicate that Lico A may have therapeutic potential in OA.

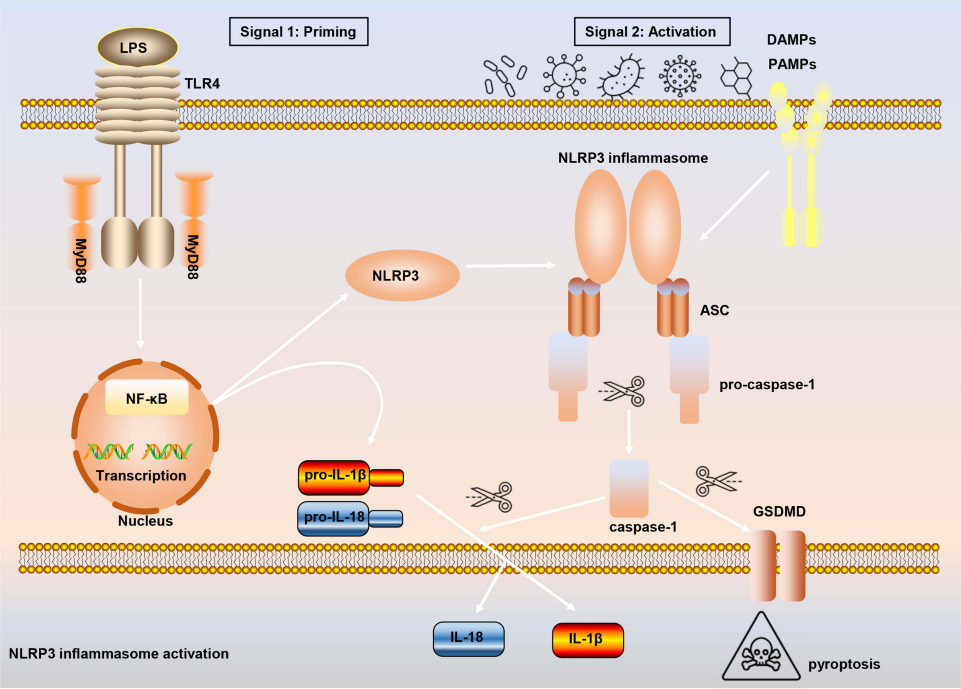

Figure 1 The process of canonical NLRP3 inflammasome activation. The priming signal (signal 1) is provided by microbial components, such as lipopolysaccharide (LPS), leading to the activation of the transcription factor NF-κB and subsequent upregulation of NLRP3, pro-interleukin-1β (pro-IL-1β), and IL-18. The activation signal (signal 2) is provided by a variety of stimuli including extracellular adenosine triphosphate (ATP), nigericin, pore-forming toxins, viruses et al, to induce the assembly of NLRP3-ASC-pro-caspase-1. Pro-caspase-1 then auto-cleaves and activates the precursor proteins pro-IL-1β and pro-IL-18 into mature forms IL-1β and IL-18. Moreover, active caspase-1 also leads to the occurrence of pyroptosis.

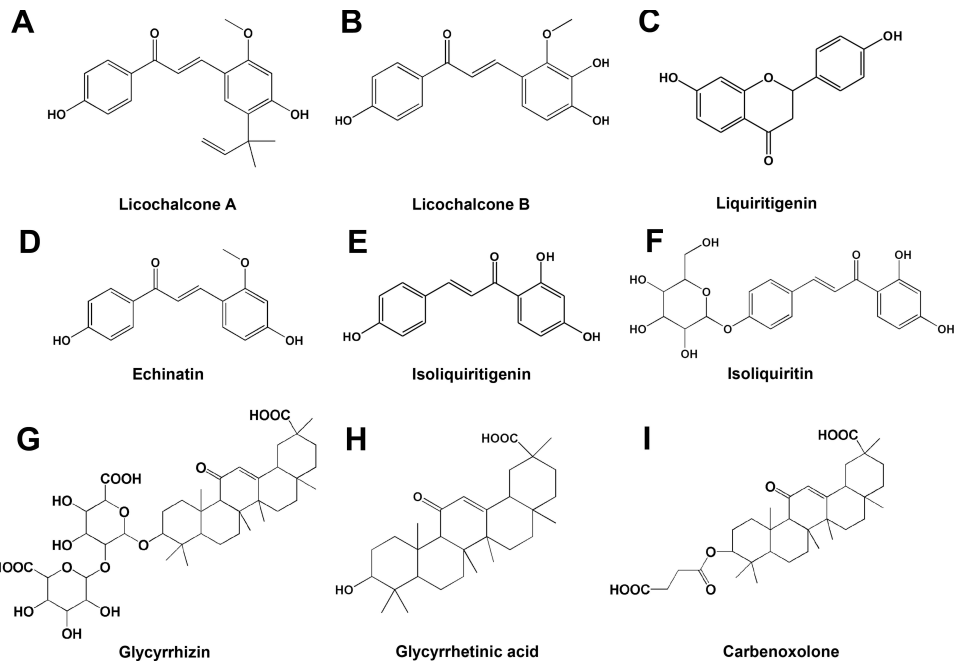

Figure 2 Chemical structure of compounds from *Glycyrrhiza*. (**A**) Licochalcone A; (**B**) Licochalcone B; (**C**) Liquiritigenin; (**D**) Echinatin; (**E**) Isoliquiritigenin; (**F**) Isoliquiritin; (**G**) Glycyrrhizin; (**H**) Glycyrrhetinic acid; (**I**) Carbenoxolone.

Cell stress causes excessive accumulation of reactive oxygen species (ROS), leading to the separation of thioredoxin interacting protein (Txnip) from thioredoxin-1 (Trx-1).[27] Then, Txinp binds to NLRP3, triggering the activation of NLRP3 inflammasome, which has been proven to be a key signaling molecule connecting oxidative

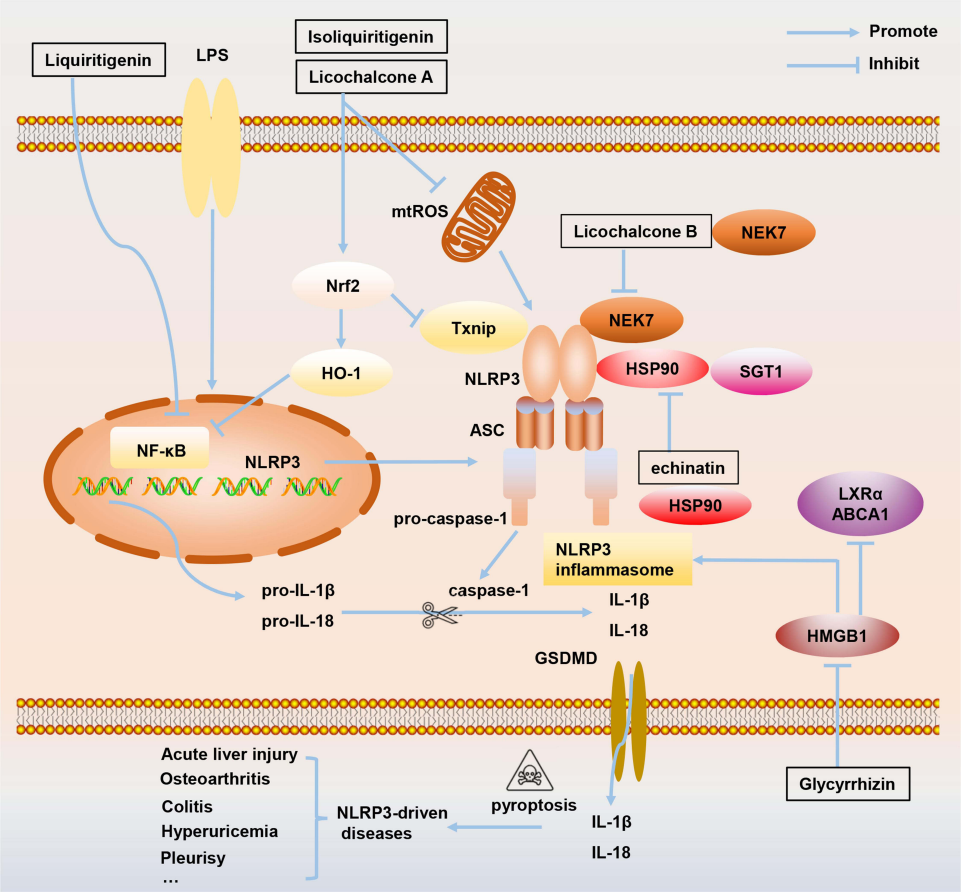

Figure 3 The mechanism of how active ingredients in *Glycyrrhiza*, including licochalcone A, licochalcone B, echinatin, liquiritigenin, isoliquiritigenin, and glycyrrhizin, target NLRP3 inflammasome to treat inflammation-related diseases.

Abbreviations: ABCA1, ATP-binding cassette transporter; HMGB1, High mobility group Box 1; HO-1, Heme oxygenase-1;HSP90, Heat shock protein 90; LXRα, liver X receptor α; mtROS, Mitochondrial reactive oxygen species;NEK7, NIMA-related kinase 7; Nrf2, Nuclear factor erythroid 2-related factor 2; SGT1, Suppressor of G2 allele of skp1; Txnip, Thioredoxin-interacting protein.

stress and inflammasome activation.[27,28] The LPS/GalN-induced inflammatory response is closely related to NLRP3 inflammasome activation.[29–31] Studies have shown that Lico A treatment notably decreases Txnip, NLRP3, ASC, caspase-1 p20, and IL-1β p17 protein expression but enhances the expression of thioredoxin-1 (Trx-1) protein in LPS/GalN-induced acute lung injury (ALI) (Figure 3),[32] indicating that inflammation inhibited by Lico A may be responsible for suppressing activation of the Txnip-NLRP3 inflammasome.

NLRP3 inflammasome activation triggered by *Propionibacterium acnes* (*P. acnes*) is vital for inducing inflammatory response and worsening the development of acne.[33–35] Lico A has been shown to suppress *P. acnes*-induced NLRP3 inflammasome activation via inhibition of ASC speck formation and mitochondrial reactive oxygen species (ROS) in primary mouse BMDMs and immortalized human SZ95 sebocytes (Figure 3).[36] Importantly, external use of Lico A on mouse ear skin reduces skin inflammation caused by *P. acne*, and blocks caspase-1 activity and IL-1β production.[36] These results provide a theoretical basis for the development of natural, safe, and efficient health care products or drugs derived from Lico A raw materials.

Licochalcone B (Lico B)

Lico B is known to have strong pharmacological properties, such as anti-inflammatory, antibacterial, and anticancer.[14,37] Although the content of Lico B (Figure 2B) in *Glycyrrhiza* is relatively low, it has a strong anti-NLRP3 inflammasome effect. Our previous studies have shown that Lico B could specifically suppress NLRP3 inflammasome activation via binding to NEK7 and inhibiting the interaction between NLRP3 and NEK7 in BMDMs, THP-1 cells and human peripheral blood mononuclear cells (PBMCs)[38] (Figure 3). In vivo

experiments show that Lico B ameliorates LPS-induced septic shock characterized by improving survival rate, inhibiting IL-1β production, reducing the number of peritoneal exudative cells and peritoneal macrophages; Meanwhile, MSU-induced peritonitis, and methionine- and choline-deficient (MCD) diet-induced nonalcoholic steatohepatitis are significantly ameliorated by Lico B through targeting NLRP3 inflammasome.[38] Taking these studies into consideration, we firmly believe that with further investigation of its pharmacological effects will lead to Lico B becoming a promising candidate in the treatment of NLRP3-related diseases.

Liquiritigenin

Hyperuricemia, a metabolic disease with a high prevalence rate, is typically related to high serum uric acid that could cause monosodium urate crystals to be deposited in the joints and kidneys, seriously endangering the life and health of patients.[39,40] A large amount of evidence indicates that the inflammatory response mediated by the NLRP3 inflammasome plays a crucial role in the renal injury of rodent models for hyperuricemia and clinical patients.[41–43] Liquiritigenin (Figure 2C), one of the flavonone compounds extracted from *Glycyrrhiza* plants, reduces the level of uric acid in the serum and urine, and decreases renal inflammation in potassium oxonate-induced hyperuricemic rats by inhibiting the activation of the renal AQP4/NF-κB/IκBα signaling pathway and NLRP3 inflammasome.[44] Hyperglycemia is considered a crucial element in the pathogenesis and progression of diabetic nephropathy (DN).[45,46] Liquiritigenin suppresses high glucose-induced extracellular matrix accumulation, oxidative stress, and inflammation in the rat glomerular mesangial cell line HBZY-1 by inhibiting NF-κB and NLRP3 inflammasome pathways,[47] thus showing potential for preventing the development of DN.

Echinatin

Echinatin is a bioactive flavonoid in *Glycyrrhiza*. It has been reported that echinatin exhibits strong scavenging activity and suppresses the production of nitric oxide, interleukin-6 and prostaglandin E2 in LPS-induced macrophage cells.[48] Moreover, echinatin could attenuate CCl_4-induced liver injury and may be responsible for the hepatoprotective activity of *Glycyrrhiza*.[49] Our previous studies have shown that echinatin (Figure 2D) inhibits NLRP3 inflammasome activation by binding to heat-shock protein 90 (HSP90), inhibiting its ATPase activity and disrupting the association between the cochaperone SGT1 and HSP90-NLRP3[50] (Figure 3). In vivo experiments demonstrated that echinatin treatment could suppress NLRP3 inflammasome activation and ameliorate LPS-induced septic shock, dextran sodium sulfate-induced colitis, and MCD diet-induced nonalcoholic steatohepatitis in mice,[50] making it a favorable candidate approach for therapeutic interventions in NLRP3 inflammasome-driven disease.

Isoliquiritigenin (ILG)

ILG (2',4',4'-trihydroxychalcone) (Figure 2E) is an isoflavone compound extracted from the Chinese herbal medicine *Glycyrrhiza*. It has been proven that ILG is biologically safe and has high levels of biological activity. Although *Glycyrrhiza* contains only low concentrations of ILG, ILG has a wide range of pharmacological properties, such as anti-inflammatory, anti-tumor, and antioxidant.[51–53] In particular, the anti-inflammatory effect of ILG has been a rapidly growing research topic in recent years. Therefore, the following sections mainly explains the anti-inflammatory effect of ILG from the perspective of inhibiting NLRP3 inflammasome.

ILG plays a powerful role in repairing neuroinflammation damage. ILG pretreatment prevents cognitive impairment, reverses synaptic dysfunction, alleviates neuronal injury, attenuates microglia and astrocyte activation, and reduces the production of TNF-α, IL-1β, and IL-18 by promoting Nrf2 signaling and suppressing NLRP3 inflammasome activation in a kainic acid-induced seizure rat model.[54] A study has shown that chronic nicotine exposure increases the protein levels of caspase-1, ASC, IL-1β, and exacerbates ischemic brain damage via activation of the inflammasome in the brains of female rats.[55] As an NLRP3 inflammasome inhibitor, ILG could decrease nicotine-induced ischemic neuronal death in hippocampal organotypic slice cultures after oxygen-glucose deprivation.[55] Furthermore, spontaneous intracerebral hemorrhage (ICH) is a fatal cerebrovascular disease that accounts for a relatively high proportion of all stroke types and is usually accompanied by high morbidity and mortality.[56,57] ILG administration after collagenase IV–induced ICH decreases early brain impairments and neurological deficits, and the mechanism is related to triggering Nrf2 activity and Nrf2-induced antioxidant system to regulate the activation of NLRP3 inflammasome pathway[58] (Figure 3). The results of this experiment also indicate that ILG is a potential drug candidate for a new treatment strategy for ICH.

Organs and tissues are susceptible to self-injury or infection by foreign pathogens, and these lead to the occurrence of the inflammatory response. ILG can reduce the inflammatory response by inhibiting NLRP3 inflammasome activation, thus avoiding the occurrence of serious diseases. NLRP3 inflammasome and its regulatory mechanisms play an important role in the pathological process of ALI.[59–61] By activating AMP-activated protein kinase (AMPK)/Nrf2/antioxidant response element (ARE) signaling and inhibiting the activation of NLRP3 inflammasome and NF-κB pathways, ILG significantly reduces lung injury in LPS-induced ALI mice, and it decreases the exudation of inflammatory cells and the levels of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in bronchoalveolar lavage fluid,[62] highlighting the beneficial effects of ILG and its related mechanisms in LPS-induced ALI and providing new insights for its application. Non-steroidal anti-inflammatory drug indomethacin could induce small intestinal damage and increase the protein levels of cleaved caspase-1 and mature IL-1β in the small intestine.-[63] ILG treatment improves indomethacin-induced small intestinal damage by suppressing NLRP3 inflammasome activation.[63] Therefore, there is an urgent need to carry out relevant clinical studies to evaluate the effectiveness and safety of ILG in the treatment of intestinal diseases caused by non-steroidal anti-inflammatory drugs.

In addition, ILG also plays an important role in other inflammatory diseases. Chronic periodontitis is a common disease, and its incidence and severity increase with age.[64] Periodontal ligament fibroblasts are the primary cell type in periodontal ligament tissues and play a vital role in the occurrence and development of periodontitis, including tissue repair and reconstruction.[65,66] ILG markedly recovers the migration dysfunction induced by *Porphyromonas gingivalis* lipopolysaccharide by reducing NLRP3 inflammasome activation, caspase-1 activation, IL-1β and HMGB1 release in cultured mouse periodontal ligament fibroblasts.[67] Pleurisy refers to inflammation of the pleura caused by a variety of infectious and noninfectious factors such as tumors, allergies, chemical substances, and trauma. ILG significantly reduces histopathological damage and increases the levels of inflammatory cell exudation, protein leakage and pro-inflammatory mediators in carrageenan-induced pleurisy by inhibiting the NLRP3/NF-κB pathway and high levels of iNOS and COX-2.[68] ILG strongly inhibits NLRP3 inflammasome activation in macrophages and reduces HFD-induced obesity, lipid homeostasis, insulin resistance, and the accumulation of inflammatory cells and adipose tissue inflammation.[69] Moreover, ILG treatment inhibits HFD-induced IL-1β and caspase-1 production in epididymal white adipose tissue culture.[69]

Isoliquiritin

Depression is a common and debilitating mental illness. It is characterized by poor mood, loss of pleasure, and avoidance of social interactions, all of which cause a major social and economic burden.[70] Although a variety of antidepressant drugs can be used for the treatment of depression, most have a low cure rate, a wide range of side effects and poor treatment compliance.[71] Therefore, there is an urgent need for new therapies with high curative effects and few adverse reactions. Current evidence indicates that the development of depression is related to pyroptosis mediated by the activation of NLRP3 inflammasome.[72–74] Isoliquiritin (Figure 2F) protects against LPS and ATP elicited NLRP3 inflammasome activation in primary microglia.[75] In vivo data show that isoliquiritin administration effectively ameliorates LPS or chronic social defeat stress (CSDS)-induced depressive symptoms by suppressing NLRP3-mediated pyroptosis via miRNA-27a/spleen tyrosine kinase (SYK)/NF-κB axis,[75] and this provides a new treatment strategy for the treatment of depression.

Glycyrrhizin (GL)

Glycyrrhizin (Figure 2G) (also called glycyrrhizic acid) is a triterpenoid compound extracted from *Glycyrrhiza*. GL-related derivatives are mainly used as sweeteners in the food industry. As a medicine, GL preparation is a powerful liver cell membrane protector that has the effects of anti-inflammatory, immune regulation, and hepatocyte protection.[76] It has been used clinically for many years as an effective drug for chronic hepatitis and has achieved good curative results.[77,78]

Metabolic disease is caused by disorders of amino acid, glucose and lipid metabolism in the body, and chronic inflammation is one of its main characteristics. Studies have shown that GL has significant therapeutic effects on metabolic diseases because of its ability to regulate NLRP3 inflammasome activation. Non-alcoholic steatohepatitis (NASH) is a progressive stage of non-alcoholic fatty liver disease (NAFLD) that may lead to liver cirrhosis and liver cancer.[79,80] NASH seriously threatens the health of patients, and there is currently a lack of effective treatment options. In recent years, studies have shown that

NLRP3 inflammasome plays an important biological role in the occurrence and development of NASH.[81–83] GL preparations are currently one of the first-line drugs used for anti-inflammatory and hepatoprotective treatments of liver diseases. GL could inhibit deoxycholic acid-induced NLRP3 inflammasome-associated inflammation in macrophage cells.[84] Importantly, an in vivo experiment shows that GL administration significantly attenuates MCD diet-induced hepatic steatosis, inflammation, and fibrosis and inhibited the activation of NLRP3 inflammasome. Moreover, both intraperitoneal injection of GA and oral administration of GL significantly reduce MCD-induced liver injury,[84] suggesting that GL may attenuate NASH via its active metabolite GA. Atherosclerosis is the pathological basis of many vascular diseases, such as aneurysms, atherosclerotic obliterans and carotid artery disease.[85] Lipid metabolism disorder is the pathological basis of atherosclerosis. Inhibiting the atherosclerotic process is beneficial for controlling the development of the above-mentioned vascular diseases. GL significantly attenuates LPS/high-fat diet-induced atherosclerosis and NLRP3 inflammasome-dependent high-mobility group Box 1 (HMGB1) secretion in male ApoE$^{-/-}$ mice.[86]

In addition, GL has been shown to be effective in a variety of acute inflammatory injury models. *Streptococcus aureus* (*S. aureus*) infection facilitates pro-inflammatory cytokines production and induces damage to multiple organs, including ALI.[87] GL treatment reduces serum and lung tissue IL-6, TNF-α, IL-8, IL-1β and HMGB1 levels, as well as lung tissue neutrophil and macrophage infiltration in *S. aureus*-induced ALI by inhibiting NF-κB, p38/extracellular signal-related protein kinases (ERK1/2) pathways, and NLRP3 inflammasome dependent pyroptosis.[88] In a corneal injury mouse model, it has shown that GL treatment attenuates the expression of IL-1β by directly inhibiting extracellular HMGB1 functions, suppressing the NF-κB-p65/NLRP3/IL-1β signaling pathway, resulting in the cornea regaining transparency and integrity[89] (Figure 3). Acute glaucoma is a cause of irreversible blindness that seriously threatens vision and is characterized by a sudden and significant increase in intraocular pressure followed by the death of retinal ganglion cells.[90,91] HMGB1 is increased in ischemic retinal tissue during acute glaucoma, and the HMGB1 inhibitor, GL, reduces the severity of the disease via regulating the activation of NLRP3 and caspase-8 inflammasomes.[92] These results provide new insights toward understanding the role of the innate immune response in the pathogenesis of acute glaucoma and provide research strategies for new therapeutic targets for acute glaucoma. Traumatic spinal cord injury can lead to a large amount of nerve cell necrosis and severe functional-behavioral defects in the injured area.[93] In addition to the primary injury, the subsequent inflammatory process also contributes to secondary injury.[94] Functional recovery is promoted by GL treatment in rat model subject to traumatic spinal cord injury. The GL treatment results in recovery accompanied by decreased expression of NLRP3 inflammasome components, such as ASC, NLRP3, and cleaved caspase-1, as well as IL-1β and IL-18.[95]

Glycyrrhetinic Acid (GA)

GA (Figure 2H), a triterpene saponin extracted from *Glycyrrhiza* plants, reduces LPS-induced ALI pathological damage, macrophage infiltration and pulmonary edema, and inhibits NLRP3 inflammasome and IL-1β secretion mediated by the ROS-PI3K/AKT pathway.[96] This suggests that it may serve as a potent NLRP3 inflammasome inhibitor with great promise toward the attenuation of ALI-related inflammation and pathological status. Parkinson's disease (PD) is one of the most common neurodegenerative diseases. It has clinical manifestations including resting tremor, rigidity, bradykinesia, and postural instability, and is characterized by the loss of dopaminergic neurons in the substantia nigra region and the presence of Lewy bodies containing α-synuclein.[97,98] A large amount of evidence confirms the relationship between Parkinson's and NLRP3 inflammasome.[99–101] GA, *Glycyrrhiza inflata*, and Shaoyao Gancao decoction (a formulated Chinese medicine) all exhibit anti-inflammatory effects that ameliorate neurotoxicity induced by α-synuclein in BV-2 and A53T SNCA-GFP SH-SY5Y cells by suppressing NLRP1/NLRP3 inflammasome, IL-1β-mediated IκBα/P65, JNK/JUN, P38/STAT1, and IL-6-mediated JAK2/STAT3 pathways;[102] This indicates that related components and preparations of licorice may be used as drugs for the treatment of neurodegenerative diseases such as PD.

Carbenoxolone (Figure 2I), a synthetic derivative of GA, is frequently used in the treatment of gastric ulcers, psoriasis, and wound healing. The NLRP3 inflammasome is a culprit behind the chronic inflammation that accompanies insulin resistance in obese mice.[103–105] Carbenoxolone ameliorates insulin resistance in the liver and skeletal muscle of high-fat diet-induced obese mice by inhibiting IκB-α/NF-κB pathway and NLRP3

inflammasome activation,[106] and it deserves further study for the treatment of obesity related diseases.

Licorice Extract

Glycyrrhiza plants, especially flavonoids, induce strong anti-inflammatory and immunomodulatory activities. The major flavonoid components in *Glycyrrhiza uralensis* are liquiritin apioside, liquiritin, naringin, liquiritigenin, quercetin, Lico A and glabridin, as measured by high-performance liquid chromatography analysis.[107] The upregulated mRNA and protein levels of TNF-α, IL-1β, and IL-6, are significantly decreased by all of the flavonoids from *Glycyrrhiza uralensis* in the colonic tissue of irinotecan-induced colitis mice, and the flavonoids also inhibit the activation of NLRP3 inflammasome triggered by irinotecan.[107] Huangqi decoction (Astragali Radix and Glycyrrhizae Radix et Rhizoma), a classic Chinese herbal formula, ameliorates 3,5-diethoxycarbonyl-1,4-dihydrocollidine-induced cholestatic liver injury, and alleviates the increased hepatic expression of pro-inflammatory factors and NLRP3 inflammasome activation.[108]

Discussion

Since NLRP3 inflammasome is involved in the occurrence of a variety of inflammatory diseases, NLRP3 inflammasome may become a potential drug target for these diseases.[27,109,110] Therefore, exploring the pathogenesis of these diseases from the perspective of inflammation and NLRP3 inflammasome activation, and then developing related drugs may bring new hope for treatment. At present, therapeutic strategies targeting NLRP3 inflammasome mainly block the interaction between IL-1β and its receptor using antibodies or antagonists that inhibit the inflammatory response. However, due to the pro-inflammatory cytokines produced by the activation of NLRP3 inflammasome, there are other pro-inflammatory factors in addition to IL-1β, such as the presence of IL-18. Therefore, the treatment strategy of blocking IL-1β requires further investigation, especially in diseases of complex etiology that may not respond as well to therapy. For this reason, the development of drugs targeting NLRP3 inflammasome itself and its related signaling pathways will become a rapidly growing area of research. However, to date, the understanding of NLRP3 inflammasome activation and its regulatory mechanisms is still very limited, and there is a lack of clinical drugs targeting NLRP3 inflammasome. In recent years, good progress has been made in research on intervention strategies targeting NLRP3 inflammasomes. Recent research in our lab has found that many active ingredients in TCMs could serve as candidate therapeutic drugs for NLRP3-driven diseases by suppressing NLRP3 inflammasome activation. Cardamonin (from *Alpinia katsumadai*) could reduce lethal LPS-induced mortality and attenuate IL-1β production in the septic-shock mouse model by inhibiting the activation of NLRP3 inflammasome.[111] In addition, the active components carnosol and cryptotanshinone reduce caspase-1 activation and IL-1β secretion in MCD-induced NASH mouse model by regulating NLRP3 inflammasome activation.[112,113] Therefore, the development of small molecule compounds targeting NLRP3 inflammasome may provide new treatment strategies for complex diseases.

Glycyrrhiza contains a variety of active ingredients and is one of the most commonly used Chinese medicines. A common Chinese idiom is nine out of ten prescriptions contain *Glycyrrhiza*. Ancient documentation on Chinese herbal classics record that *Glycyrrhiza* could "harmonize all kinds of drugs and cure all kinds of toxins", but it is unclear how to regulate these activities. This review details the extensive anti-inflammatory effects of various components in *Glycyrrhiza* via inhibition of NLRP3 inflammasome activation. Our previous studies also show that the drugs carbamazepine, isoniazid and nevirapine, as well as Chinese medicines such as Epimedium folium and Psoraleae fructus, can promote the activation of NLRP3 inflammasome and lead to liver injury.[114–116] Therefore, we believe that one of the scientific connotations of the description of *Glycyrrhiza's* ability to "harmonize all kinds of drugs and cure all kinds of toxins" is the broad spectrum of antagonistic effects: abnormal activation of NLRP3 inflammasome signaling pathway is involved in the occurrence and development of various diseases, and active ingredients in *Glycyrrhiza* slow the process and reduce the development of related diseases by inhibiting NLRP3 inflammasome, and thus are capable of "mediating various drugs and eliminating all toxins".

The overall concept of TCMs and the characteristics of low adverse reactions have received more attention. The current application of *Glycyrrhiza's* anti-inflammatory effects has demonstrated the unique advantages of reducing side effects, improving prognosis during disease treatment, and improving the survival rate of patients. This review summarizes current research on active ingredients

in *Glycyrrhiza*, such as Lico A, echinatin, GL, and ILG, that inhibit the activity of NLRP3 inflammasome in the treatment of ALI, DN, NASH, and other NLRP3-driven inflammatory diseases (Table 1). However, the pharmacological mechanism and clinical application of *Glycyrrhiza* via suppression NLRP3 inflammasome activation have not been systematically and thoroughly studied, and the specific action links are not yet detailed enough, especially at the cellular and molecular levels. As the chemical composition of *Glycyrrhiza* is complex and contains a variety of anti-inflammatory components, it is not clear whether these components have a synergistic or an antagonistic effect on inflammatory responses. Therefore, in-depth research in this area still needs to be conducted. Since *Glycyrrhiza* is one of the most frequently used TCMs, clarifying the molecular biological mechanisms and signal transduction pathways explaining how *Glycyrrhiza* inhibits NLRP3 inflammasome will better characterize its anti-inflammatory effect, and provide the basis for developing new indications and for guiding clinical use of *Glycyrrhiza*. This has important theoretical and practical significance.

Table 1 NLRP3 Inflammasome Inhibitors as Well as Their Effects in *Glycyrrhiza* for NLRP3-Driven Diseases

Agent	Cell/Animal Model	Effect and Function	Ref.
Lico A	LPS/GalN-induced acute liver injury mouse model	Acute liver injury↓, TNF-α↓, IL-6↓, IL-1β↓, Txnip-NLRP3 inflammasome signaling pathway↓	[32]
	Primary mouse chondrocytes	IL-1β↓, IL-18↓, pyroptosis↓, Nrf2/HO-1 signal pathway↑	[26]
	Air pouch mouse model	IL-1β↓, IL-18↓	[26]
	Bone marrow-derived primary macrophages (BMDMs) and human SZ95 sebocytes	Caspase-1(p10) ↓, IL-1β↓, mitochondrial reactive oxygen species production↓	[36]
	Intradermal infection of P. acnes mouse mode	Skin inflammation↓, caspase-1 activity↓, IL-1β↓	[36]
Lico B	BMDMs, THP-1 cells, and human PBMCs	IL-1β↓, caspase-1 activity↓, caspase-1 p20↓, bind to NEK7↑, the interaction between NLRP3 and NEK7↓	[38]
	LPS-induced septic shock	Mouse survival↑, IL-1β↓, the number of peritoneal exudative cells↓, peritoneal macrophages↓	[38]
	MSU-induced mouse peritonitis	IL-1β↓, the number of peritoneal exudates↓, neutrophils↓	[38]
	MCD diet-induced NASH mouse model	Liver steatosis↓, balloon dilatation↓, fibrosis↓, the protein level of active caspase-1 in liver tissue↓, the pro-fibrotic marker alpha smooth muscle actin (α-SMA) ↓, mRNA expression of col1a1↓, TNF-α↓, IL-1β↓ and IL-18↓, serum IL-18↓	[38]
Liquiritigenin	Potassium oxonate-induced hyperuricemic rat model	The level of uric acid in serum and urine↓, IL-1β↓, IL-6↓, TNF-α↓, renal AQP4/NF-κB/IκBα signaling and NLRP3 inflammasome activation↓	[44]
	The rat glomerular mesangial cell line HBZY-1	High glucose-induced extracellular matrix accumulation↓, oxidative stress↓, IL-6 and IL-1β production↓, NF-κB and NLRP3 inflammasome pathways↓	[47]
Echinatin	Mouse BMDMs and human PBMCs	Bind to heat-shock protein 90↑, ATPase activity↓, the association between the cochaperone SGT1 and HSP90-NLRP3↓	[50]
	LPS-induced septic shock mouse model	IL-1β↓, TNF-α production↓, mouse survival↑	[50]
	Dextran sodium sulfate-induced colitis mouse model	Colonic inflammation↓, mucosal barrier and inflammatory cell infiltration↓, caspase-1 activation↓, IL-1β production↓	[50]
	MCD diet-induced NASH mouse model	Morphological changes↓, hepatic steatosis↓, ballooning↓, fibrosis↓, caspase-1 activation↓, mRNA expression of proinflammatory genes IL-1β and TNF-α↓	[50]

(*Continued*)

Table 1 (Continued).

Agent	Cell/Animal Model	Effect and Function	Ref.
ILG	Kainic acid-induced seizures rat model	TNF-α↓, IL-1β↓, IL-18↓, NLRP3↓, Caspase-1↓	[54]
	Carrageenan-induced pleurisy mouse model	TNF-α↓, IL-1β↓, IL-6↓, the NLRP3/NF-κB pathway↓, iNOS↓, COX-2↓	[68]
	The mouse periodontal ligament fibroblasts	Chronic periodontitis↓, caspase-1 activation↓, IL-1β↓, HMGB1↓, ROS/TXNIP/Nlrp3 inflammasome pathway↓	[67]
	Collagenase IV–induced intracerebral hemorrhage rat model	Neurological deficits↓, histological damages↓, blood-brain barrier disruption↓, brain edema↓, neuronal degeneration↓, the NF-κB and NLRP3 inflammasome pathways↓, Nrf2-mediated antioxidant system↑	[58]
	LPS-induced ALI mouse model	Recruitment of inflammatory cells↓, COX-2↓, iNOS↓, TNF-α↓, IL-1β↓, IL-6↓, the AMPK/Nrf2 signaling and its downstream antioxidant enzymes↑, the NLRP3 inflammasome and NF-κB pathways↓	[62]
	In vitro model of ischemia in organotypic slice cultures	Ischemic neuronal death↓, NLRP3 inflammasome activation↓	[55]
	Indomethacin-induced small intestinal damage mouse model	Small intestinal damage↓, cleaved caspase-1↓, mature IL-1β protein levels↓	[63]
	Ex vivo culture of epididymal white adipose tissue	Adipose tissue inflammation↓, IL-1β↓, caspase-1 production↓	[69]
	HFD-induced adipose tissue inflammation	The accumulation of inflammatory cells↓, adipose tissue inflammation↓	[69]
Isoliquiritin	LPS or CSDS-induced depression mouse model	The protein levels of SYK↓, p-NF-κB↓, NLRP3↓, caspase-1↓, IL-1β↓, GSDMD-N↓; the concentration of IL-1β↓, IL-6↓, TNF-α↓	[75]
	Mouse primary microglia	Protein levels of p-NF-κB↓, NLRP3↓; cleaved caspase-1↓, IL-1β↓, GSDMD-N↓	[75]
GL	MCD diet-induced NASH mouse model	NASH-induced liver injury↓, liver fibrosis↓, hepatic lipid accumulation↓, bile acid accumulation↓, NLRP3 inflammasome activation and Meta-inflammation↓	[84]
	Raw 264.7 macrophage cells	Deoxycholic acid-induced NLRP3 inflammasome-associated inflammation↓	[84]
	LPS/HFD-induced atherosclerosis in $ApoE^{-/-}$ mice	Atherosclerosis↓, serum HMGB1 levels↓, NLRP3 inflammasome activation↓	[86]
	Streptococcus aureus-induced ALI mouse model	Serum and lung tissue IL-6↓, TNF-α↓, IL-8↓, IL-1β↓, HMGB1↓, lung tissue neutrophil and macrophage infiltration↓, NF-κB↓, p38/ERK pathways↓, pyroptosis↓	[88]
	A corneal injury mouse model	The expression of IL-1β↓, extracellular HMGB1 functions↓, the NF-κB-p65/NLRP3/IL-1β signaling pathway↓	[89]
	An acute glaucoma mouse model	The severity of the disease↓, the activation of NLRP3 and caspase-8 inflammasomes↓	[92]
	Traumatic spinal cord injury rat model	Expression of NLRP3 inflammasome components↓, ASC↓, NLRP3↓, cleaved caspase-1↓, IL-1β↓, IL-18↓	[95]
GA	Mouse BV-2 microglial cells	Nitric oxide↓, IL-1β maturation↓	[102]
	LPS-induced ALI mouse model	ALI↓, the activation of NLRP3 inflammasome↓, ROS-PI3K/AKT pathway↓	[96]

(*Continued*)

Table 1 (Continued).

Agent	Cell/Animal Model	Effect and Function	Ref.
Carbenoxolone	HFD-induced obese mouse model	Insulin sensitivity↓, the IκB-α/NF-κB pathway and NLRP3 inflammasome↓,	[106]
Licorice extract	Irinotecan-induced colitis mouse model	The mRNA and protein levels of TNF-α↓, IL-1β↓, and IL-6↓	[107]

Notes: ↓, inhibition; ↑, promotion.

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Disclosure

The authors report no conflicts of interest in this work.

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