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Review

Natural products targeting NLRP3 inflammasome for metabolic dysfunction-associated fatty liver disease: the known unknowns

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ABSTRACT

Metabolic dysfunction-associated fatty liver disease (MAFLD), characterized by fatty acid overload, secondary chronic inflammation, and fibrosis, has become the most prevalent chronic liver disease globally. While no effective pharmacotherapy exists for MAFLD, mitigating inflammatory responses represents a promising approach to preventing the progression from steatosis to severe steatohepatitis. The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, which detects endogenous danger and stress signals, has emerged as a significant target for inflammatory disease treatment, as transcriptional inactivation of its components demonstrates the therapeutic potential for MAFLD. Natural products targeting NLRP3 inflammasome activation have shown promising efficacy in MAFLD therapy. This review synthesizes the current understanding of NLRP3 inflammasome activation and therapeutic targets for NLRP3 homeostasis. Additionally, natural products reported to inhibit NLRP3 inflammasome for MAFLD improvement are categorized according to their mechanisms of action. The review also addresses limitations and future directions regarding natural products targeting NLRP3 inflammasome in MAFLD treatment. Enhanced understanding of NLRP3 inflammasome activation mechanisms in MAFLD and the identification of novel natural products supported by mechanistic research will significantly advance MAFLD treatment.

1. Introduction

Pattern recognition receptors (PRRs) recognize danger- and pathogen-associated molecular patterns (DAMPs and PAMPs, respectively) and initiate the innate immune response, representing the most rapid and conserved defense against pathogenic infections, cell injury, and cellular stress. This response plays a fundamental role in the development of metabolic dysfunction-associated fatty liver disease (MAFLD) and its progression to associated liver diseases, including hepatocellular carcinoma [1]. Current evidence demonstrates that PRRs detect various potentially harmful environmental changes, highlighting the importance of investigating PRR structure, function, and activation in different diseases.

PRRs can be divided into NOD-like receptors (NLRs), Toll-like receptors (TLRs), C-type lectin receptors, retinoic acid-induced gene I-like receptors, and deoxyribonucleic acid (DNA) sensors. NLRs constitute the largest and most diverse PRR family and form the foundation of innate immune response [2]. Mean NLRs respond to various PAMPs and DAMPs originating from dietary factors, endogenous cellular stress, and gut microbiota, thereby initiating inflammatory responses. Research indicates that the extensively studied NLR complex, NLR family pyrin domain containing 3 (NLRP3) inflammasome, contributes to MAFLD progression *via* sensing various metabolites [3]. Notably, NLRP3 inflammasome plays a crucial role in amplifying hepatic inflammation, immune cell activation, hepatocellular damage, and fibrogenesis [4]. This review examines recent advances in NLRP3 inflammasome activation by various factors in MAFLD and explores potential natural products targeting NLRP3 inflammasome for MAFLD management.

2. Overview of NLRP3 inflammasome

NLRP3 inflammasome consists of a sensor (NLRP3), an adapter (ASC), and an effector (procaspase-1), where the NLRP3 protein contains a PYD, a central NACHT domain, and a LRR domain [5]. Upon exposure to various stimuli, NLRP3 functions as a sensor and undergoes self-oligomerization through interactions with homotypic NACHT domains. Oligomerized NLRP3 recruits ASC through homotypic PYD-PYD domain interactions and nucleates helical ASC filament formation, which also occurs *via* PYD-PYD interactions. Multiple ASC filaments combine to form a single macromolecular structure called the ASC speck [6,7]. Subsequently,

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the assembled ASC recruits procaspase-1 through homotypic CARD-CARD domain interactions, enabling procaspase-1 self-cleavage and ultimately activating NLRP3 inflammasome [8]. NIMA-related kinase 7 (NEK7), a serine/threonine-protein kinase involved in NLRP3 inflammasome assembly and activation during mitosis, represents an essential component specific to the NLRP3 inflammasome [5, 9]. Following NLRP3 inflammasome activation, NEK7-NLRP3 interaction increases, with NEK7 binding to the LRR domain of NLRP3, which is essential for ASC speck formation and procaspase-1 activation [10, 11]. This mechanism suggests the potential for inhibiting NLRP3 inflammasome by targeting NEK7.

During NLRP3 inflammasome formation, the induced procaspase-1 initiates its self-cleavage for activation and converts pro-interleukin 1β (pro-IL-1β) and pro-IL-18 into their active forms. Subsequently, activated caspase-1 cleaves a pore-forming protein called gasdermin D (GSDMD), releasing its *N*-terminal domain. The GSDMD-N migrates to the cell membrane and binds to membrane lipids to form pores, facilitating the release of bioactive IL-1β and IL-18 into the extracellular space and inducing a necrotic cell death known as pyroptosis [12].

NLRP3 inflammasome activation serves as a critical mechanism for host defense against pathogen invasion and endogenous stimuli to maintain homeostasis. Moreover, proinflammatory lipids such as palmitate and other fatty acids function as self-derived DAMPs for NLRP3 inflammasome activation [13]. Homocysteine, another DAMP, activates the NLRP3 inflammasome and promotes insulin resistance in adipocytes and adipose tissue macrophages [14]. Furthermore, as a self-derived DAMP, uric acid modulates insulin resistance and hepatic steatosis through NLRP3 inflammasome activation, substantially increasing MAFLD risk [15]. These findings strongly suggest that NLRP3 activation may correlate with metabolic diseases such as MAFLD.

3. Mechanism of NLRP3 inflammasome activation

NLRP3 inflammasome activation occurs in response to diverse stimuli, including PAMPs, such as bacterial ribonucleic acid (RNA), lipopolysaccharide (LPS) and hyphae, and DAMPs, such as ATP, palmitate, soluble uric acid, and cholesterol crystals [8]. Currently, research indicates three distinct NLRP3 inflammasome activation pathways: canonical NLRP3 inflammasome activation, non-canonical NLRP3 inflammasome activation, and alternative NLRP3 inflammasome activation (also known as one-step NLRP3 inflammasome activation).

3.1. Canonical NLRP3 inflammasome activation

Activation of the NLRP3 inflammasome is generally understood as a biphasic process involving a priming phase (signal 1) followed by an activation phase (signal 2). The priming phase is initiated by the recognition of PAMPs or DAMPs, which activates nuclear factor-κB (NF-κB) signaling. This transcriptionally upregulates key inflammasome components, including NLRP3, pro-IL-1β, and pro-IL-18, thereby preparing the cellular machinery for rapid activation upon subsequent stimulation [8]. TLR4 engagement, particularly by LPS, serves as a classical example of this priming signal, facilitating transcriptional enhancement of inflammasome-related genes (Fig. 1A). The priming step also governs essential post-translational modifications of NLRP3, such as phosphorylation and ubiquitination. These modifications contribute to protein stabilization, promote the acquisition of a competent conformational state for oligomerization, and prevent proteasomal degradation, thereby licensing NLRP3 for downstream activation [16]. The activation phase is triggered by specific NLRP3 agonists and involves a conformational change that releases the autoinhibited state of NLRP3. This allows for the oligomerization of its nucleotide-binding and oligomerization domain (NACHT), recruitment of the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), and the subsequent binding and auto-cleavage of procaspase-1. Activated caspase-1 then catalyzes the proteolytic maturation of pro-inflammatory cytokines IL-1β and IL-18, completing the canonical NLRP3 inflammasome activation pathway [5]. Multiple upstream signals have been identified as initiators of this activation process, many of which are not mutually exclusive and may occur concurrently or sequentially. These include ionic fluxes (notably potassium efflux and calcium mobilization), mitochondrial dysfunction, increased production of mitochondrial reactive oxygen species (mtROS), and the cytosolic release of mitochondrial DNA (mtDNA) (Fig. 1A). These events function as key molecular triggers that converge on NLRP3 to facilitate its assembly and activation. The following section explores these upstream mechanisms in detail, elucidating their roles and interactions in the orchestration of NLRP3 inflammasome activation.

3.1.1. Flux of ions

Intracellular K^+ efflux represents a fundamental upstream signal essential for NLRP3 activation induced by various activators, including bacterial pore-forming toxins, nigericin, ATP, and particulate matter. Extensive research indicates that a decline in intracellular K^+ reduction concentration is a critical upstream signal for NLRP3 inflammasome activation, while elevated extracellular K^+ levels exert an inhibitory effect on this process. Nigericin, a microbial-derived ionophore that exchanges K^+ for H^+ ionophore, across cellular membranes, induces potassium efflux, thereby triggering NLRP3 activation and promoting the proteolytic maturation of IL-1β [8]. Extracellular ATP-activated P_2X purinoceptor 7 (P_2X_7), a ligand-gated ion channel of the purinergic receptor family, promotes Ca^{2+} and Na^+ influx and works in conjunction with TWIK2 to mediate K^+ efflux in macrophages [17] (Fig. 1A). Particulate matter, including alum, silica, and calcium pyrophosphate dihydrate crystals, induces K^+ efflux. However, the exact molecular mechanisms underlying K^+ efflux-mediated NLRP3 inflammasome activation by multiple activators remain unclear.

Research indicates that NLRP3 activation triggered by nigericin, alum, silica, and the complement membrane attack complex requires Ca^{2+} mobilization, wherein elevated cytoplasmic Ca^{2+} enhances NLRP3 inflammasome assembly. Ca^{2+} mobilization occurs either through plasma membrane ion channel opening or endoplasmic reticulum Ca^{2+} release into the cytoplasm *via* the calcium-sensing receptor signaling, resulting in decreased cellular cAMP, an inhibitory signal for NLRP3 inflammasome [18]. Additionally, studies reveal that Ca^{2+} mobilization works in concert with K^+ efflux, contributing to mtROS generation and subsequent NLRP3 inflammasome activation [17] (Fig. 1A).

3.1.2. Mitochondrial dysfunction

Mitochondria, the powerhouses of cells, generate the majority of cellular energy in the form of ATP through oxidative phosphorylation. Impaired mitochondria exhibit deficiencies in ATP production and other biosynthetic precursors. Beyond their role in energy metabolism, mitochondria function as the central organelle in NLRP3 inflammasome activation. Research indicates that mitochondrial dysfunction facilitates key upstream events in NLRP3 inflammasome activation through excessive mtROS generation and mtDNA release [19]. Furthermore, evidence demonstrates that mitochondria serve as an assembly platform for NLRP3 inflammasome activation. When stimulated by NLRP3 agonists, the mitochondrial lipid cardiolipin relocates from the inner to the outer mitochondrial membrane and binds to the LRR domain of NLRP3, enabling NLRP3 mitochondrial localization and subsequent inflammasome activation [20]. During RNA viral in-

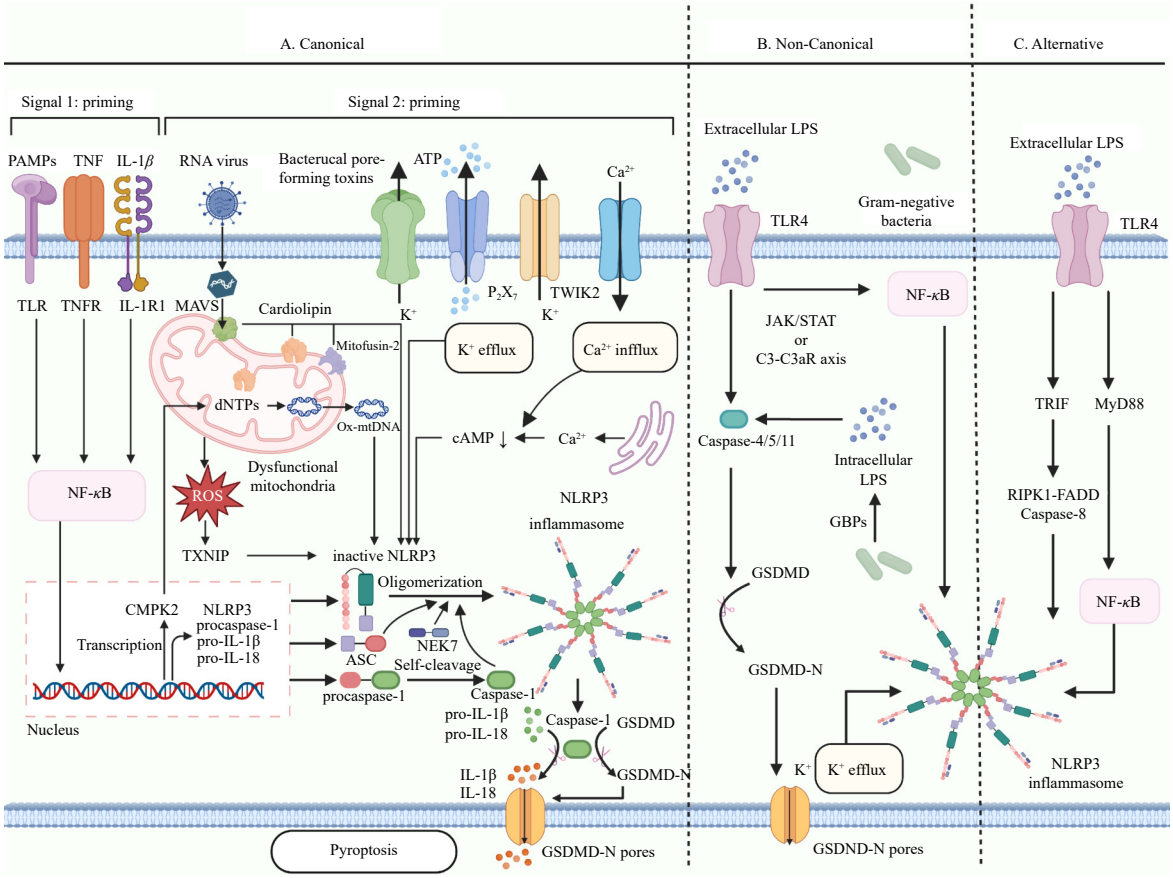

Fig. 1 Mechanism for NLRP3 inflammasome activation. NLRP3 inflammasomes can be activated through three different signaling pathways, including canonical NLRP3 inflammasome activation, non-canonical NLRP3 inflammasome activation, and alternative NLRP3 inflammasome activation. (A) Canonical activation of NLRP3 inflammasome is elicited by signal 1 and signal 2. Activation involves multiple signaling events, including K^+ efflux, Ca^{2+} mobilization, mitochondrial dysfunction, the translocation of cardiolipin to the outer mitochondrial membrane, mtROS production, and the release of oxidized mtDNA. The formation of NLRP3 inflammasome includes oligomerization of NLRP3, formation of ASC speck, recruitment of caspase-1, and the binding of NLRP3 with NEK7. Upon NLRP3 inflammasome assembly, the induced procaspase-1 drives its self-cleavage and activation, which in turn cleaves pro-IL-1β and pro-IL-18 to result in the maturation of the proinflammatory cytokines. GSDMD is also cleaved to release GSDMD-N, inducing pyroptosis. (B) Non-canonical activation of NLRP3 inflammasome is induced by gram-negative bacteria. Extracellular LPS activates TLR4, induces the activation of the transcription factor NF-κB and the production of type I interferon, which upregulates the expression of caspase-11 through the JAK/STAT pathway or the C3-C3aR axis. Activated caspase-4, 5, or 11 specifically cleaves GSDMD, inducing pyroptosis. (C) The alternative pathway is induced by TLR4 agonists like LPS, which activates the TLR4-TRIF-RIPK1-FADD-Caspase-8 signaling, independently of ASC speck assembly and without inducing pyroptosis. (Created with BioRender.com. Agreement number: IN2728SVZ8.)

fections, mitochondrial anti-viral signaling protein (MAVS), located in the outer mitochondrial membrane, initiates type I interferon pathway and NLRP3 inflammasome activation in response to danger signals. The mechanism reveals that MAVS interacts with the *N*-terminus of NLRP3 and induces NLRP3 oligomerization, facilitating its mitochondrial recruitment for activation [21]. Similarly, mitofusin-2, a guanosine triphosphatase in the outer mitochondrial membrane, interacts with NLRP3 to enhance its mitochondrial recruitment and subsequent activation [22]. These findings establish mitochondria's essential role as the central organelle in NLRP3 inflammasome assembly and activation.

3.1.3. Generation of mtROS

NLRP3 inflammasome exhibits unique characteristics in its activation by diverse unrelated stimuli. The common factor among these stimuli is excessive ROS production, resulting in oxidative stress. Mitochondria continuously generate ATP and produce mtROS as a by-product of oxidative phosphorylation during particle phagocytosis by NADH oxidase [23, 24]. Certain mitochondria-targeting small molecules, such as imiquimod, a TLR7 small-molecule ligand, induce ROS bursts, triggering NLRP3 inflammasome activation *via* NEK7. This NLRP3 activation occurs independently of K^+ efflux and lysosomal disruption but requires ROS generation [25]. Research demonstrates that when NLRP3 activators increase ROS levels, thioredoxin-interacting protein (TXNIP) dissociates from oxidized TRX and binds to NLRP3, leading to activation [26]. This indicates that NLRP3 inflammasome activation is suppressed through TXNIP downregulation (Fig. 1A).

3.1.4. Release of mtDNA

NLRP3 inflammasome activators trigger mtDNA release into the cytosol, dependent on mitochondrial permeability transition pore opening through mitochondrial Ca^{2+} overload and ROS [27]. Additionally, mtDNA rapidly enters the cytosol following exposure to NLRP3 activators. The oxidized cytosolic mtDNA specifically binds to and activates NLRP3 inflammasome, playing a crucial role in NLRP3 signaling [28]. Research indicates that oxidized mtDNA colocalizes with NLRP3 and coprecipitates with it, establishing a connection between mitochondria and inflammasome activation. Furthermore, mtDNA synthesis following TLR2, TLR3, or TLR4 agonist priming depends on cytidine/uridine monophosphate kinase 2 (CMPK2), which regulates mitochondrial deoxynucleoside 5'-triphosphate pools and provides deoxyribonucleotide for mtDNA synthesis [29, 30]. The reliance on CMPK2 catalytic activity presents potential opportunities for controlling NLRP3 inflammasome-associated diseases (Fig. 1A).

3.1.5. Altered glycolipid metabolism

The NLRP3 inflammasome demonstrates sensitivity to metabolites, including glucose, uric acid, saturated fatty acids, and cholesterol crystals. Glycolysis participates in NLRP3 inflammasome activation through various metabolites [31]. Hexokinase, the enzyme crucial for glucose phosphorylation in the initial glycolysis step, activates NLRP3 by detecting the *N*-acetylglucosamine

subunit of bacterial peptidoglycan's sugar backbone [32]. Additional research confirms that disruption of glycolytic flux promotes NLRP3 inflammasome activation following the priming step [33].

Lipid metabolism has been associated with NLRP3 inflammasome activation, wherein saturated fatty acid overload activates NLRP3 inflammasomes partially through intracellular crystallization and lysosomal dysfunction [34]. Adenosine 5'-monophosphate-activated protein kinase (AMPK) serves as a crucial mediator of free fatty acids (FFAs) metabolism and inhibits FFAs-induced inflammation. During abnormal conditions triggered by NLRP3 activators and nutritional excess, the expression, activity, and signaling of AMPKα1 in adipose tissue and macrophages become significantly downregulated [35]. Research demonstrates that AMPK negatively regulates lipid-induced inflammation by inhibiting nuclear factor κB (NF-κB) signaling, activating autophagy, and limiting ROS production, thereby suppressing NLRP3 inflammasome [35, 36]. This indicates the potential to inhibit NLRP3 inflammasome activation through AMPK activation (Fig. 1A).

3.2. Non-canonical NLRP3 inflammasome activation

In addition to the canonical pathway, a caspase-11 (caspase-4 and caspase-5 in humans)-dependent non-canonical NLRP3 inflammasome signaling exists during Gram-negative bacterial infection (Fig. 1B). Extracellular LPS activates TLR4 to enhance NF-κB transcription activity and type I interferon production, which increases caspase-11 expression dependent on JAK/STAT pathway or the C3/C3aR axis [37]. Type I interferon additionally induces the expression of small GTPases known as guanylate-binding proteins (GBPs). The interferon-inducible protein IRGB10 targets cytoplasmic bacteria through a GBPs-dependent mechanism that compromises bacterial structural integrity and releases LPS into the cytoplasm to initiate caspase-11 activation [38]. Thus, non-canonical NLRP3 inflammasome activation occurs independently of extracellular LPS, sensed by TLR4. Activated caspase-4, 5, or 11 specifically cleaves the linker between the amino-terminal GSDMD-N and carboxy-terminal GSDMD-C domains in GSDMD, releasing its N-terminal domain and triggering pyroptosis [5]. GSDMD pores may induce K^+ efflux, stimulating NLRP3 inflammasome activation and procaspase-1 along with IL-1β and IL-18 maturation, despite limited efficiency in this process [39].

3.3. Alternative NLRP3 inflammasome activation

Distinct from the canonical and non-canonical pathways, an alternative NLRP3 inflammasome activation pathway exists that is cell- and species-specific (Fig. 1C). In this pathway, single stimulation with TLR ligands fails to activate procaspase-1 in human and porcine monocytes but not murine monocytes. Recent studies indicate that LPS-triggered "alternative inflammasome" activation depends on the upstream signaling of NLRP3 by TLR4-TRIF-RIPK1-FADD-CASP8. However, this "alternative inflammasome" activation, also termed one-step NLRP3 inflammasome activation, lacks the characteristic features of canonical and non-canonical NLRP3 inflammasome activation, including ASC speck formation, pyroptosis induction, and K^+ efflux [40]. This one-step activation occurs in mouse bone marrow-derived cells and splenic dendritic cells, where LPS alone suffices to secrete substantial amounts of mature IL-1β [41].

4. Role of NLRP3 inflammasome in MAFLD

4.1. NLRP3 inflammasome in metabolic diseases

NLRP3 inflammasome functions as a central hub of innate immunity and induces protective immune responses that regulate inflammasome-responsive cytokine release and cell death, such as pyroptosis [4, 19]. Additionally, as an unexpected sensor for metabolic danger and stress, NLRP3 inflammasome contributes to metabolic disorders, including MAFLD, atherosclerosis, gout, type 2 diabetes mellitus, and obesity [42, 43]. For instance, elevated IL-1β secretion and inflammasome component upregulation are observed in subcutaneous or visceral adipose tissue of obese patients [44]. Furthermore, mice lacking inflammasome components demonstrate improvements in hepatic triglyceride level, adipocyte size, adipose macrophage infiltration, and resistance to obesity and insulin resistance [45]. Similarly, exercise and calorie restriction correlate with decreased NLRP3 and IL-1β expression in subcutaneous adipose tissue and enhanced insulin sensitivity. These findings substantiate the beneficial effects of NLRP3 inhibition in ameliorating metabolic diseases [46]. This review primarily addresses MAFLD, the most prevalent liver disease with increasing incidence in recent years.

4.2. Pathogenic role of NLRP3 inflammasome in MAFLD

MAFLD represents a clinicopathological process encompassing a broad spectrum of liver diseases, ranging from steatosis to metabolic-associated steatohepatitis (MASH), which can progress to fibrosis and cirrhosis. Concurrent with the increasing prevalence of metabolic syndromes, particularly obesity and type 2 diabetes mellitus, MAFLD has emerged as the predominant chronic liver disease, with an urgent clinical need for effective therapeutic interventions [47, 48]. The pathogenesis of MAFLD involves complex mechanisms, where hepatic lipotoxicity and multiple factors, including adipose tissue inflammation and altered gut microbial functions, contribute to the progression of inflammation and fibrosis [49]. When FFAs exceed normal supply levels or the liver's capacity to process primary metabolic energy substrates diminishes, lipotoxic lipids accumulate, causing hepatocellular stress, injury, and death, subsequently initiating inflammation and fibrogenesis (Fig. 2). Metabolic stress-induced inflammation, primarily mediated by innate immune signaling following lipid imbalance, plays a crucial role in MAFLD pathogenesis. Liver-resident innate immune cells detect continuously produced DAMPs and PAMPs, initiating the production of effector molecules that exacerbate chronic inflammation, activate hepatic stellate cells (HSCs) to enhance collagen deposition, and induce insulin resistance (Fig. 2). These innate immune responses further deteriorate metabolic homeostasis and serve as a driving force in MAFLD progression [50].

Recent research has highlighted the significant role of NLRP3 inflammasome in MAFLD pathogenesis. Studies reveal elevated messenger RNA (mRNA) levels of hepatic *NLRP3*, *PROCASPASE-1*, *IL-1B*, and *IL-18* in MAFLD and MASH patients compared to healthy controls or non-MASH patients [51, 52]. Experimental evidence demonstrates upregulation of all NLRP3 inflammasome components at the mRNA level in the livers of methionine choline deficiency (MCD) or high-fat diet (HFD)-fed mice [52]. Comparable findings are observed in Kupffer cells (KCs) exposed to palmitic acid (PA) [53]. Research indicates that mice exhibiting only steatosis show increased NLRP3 inflammasome components in the liver exclusively at the mRNA level. However, upon progression to MASH, characterized by enhanced immune cell infiltration in hepatic tissue, both mRNA and protein levels of NLRP3 inflammasome components demonstrate significant elevation [52, 54].

The elevated expression of the NLRP3 inflammasome in the livers of MASH patients and MASH mice suggests its significant role in MASH pathogenesis, as demonstrated through studies of mice lacking NLRP3, ASC, and caspase-1. Research indicates that NLRP3 inflammasome components are expressed in hepatocytes, macrophages, and HSCs, with their activation substantially exacerbating MAFLD. Studies show that MASH development is in-

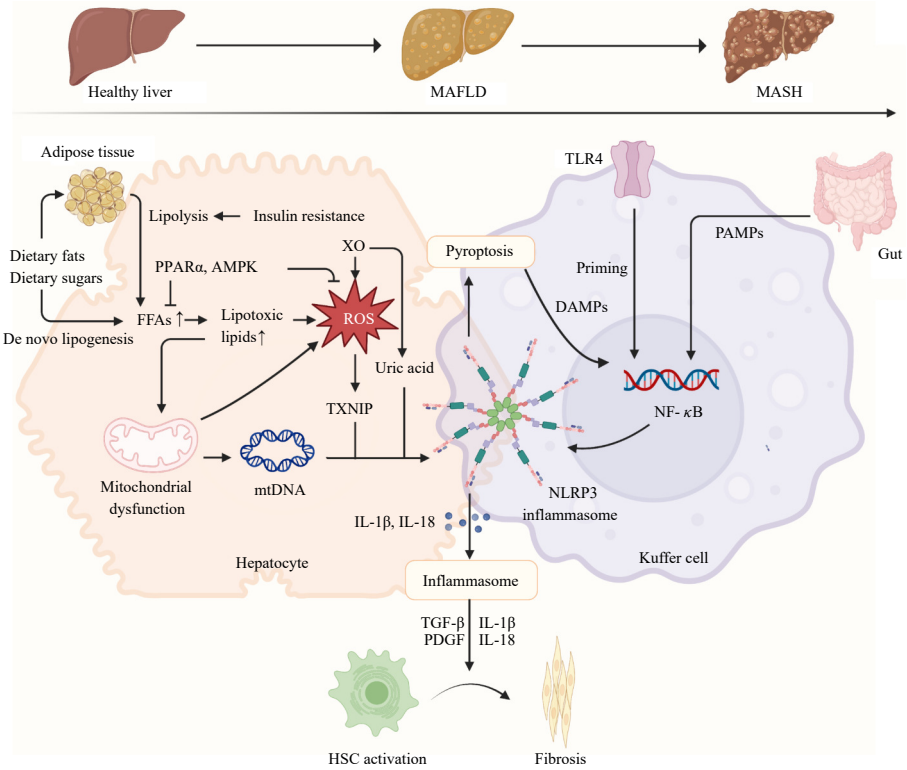

Fig. 2 The involvement of NLRP3 inflammasomes in MAFLD. FFA accumulation or impaired hepatic capacity to metabolize primary energy substrates leads to the buildup of lipotoxic lipids, resulting in hepatocellular stress, mitochondrial dysfunction, increased mtROS production, and mtDNA release, all of which contribute to NLRP3 inflammasome activation. Uric acid also functions as an endogenous DAMP to trigger NLRP3 inflammasome activation. Activation is also potentiated by NF-κB signaling and alterations in gut microbial composition and function. Once activated, the NLRP3 inflammasome promotes the maturation of pro-inflammatory cytokines and initiates downstream signaling cascades that exacerbate chronic hepatic inflammation and activate HSCs, leading to increased collagen deposition and fibrosis. (Created with BioRender.com. Agreement number: KG2728T0H9.)

hibited in NLRP3 knockout mice, and inflammation is reversed in PA-treated KCs. Additionally, NLRP3 inflammasome activation and secretion of IL-1β and IL-18 in KCs are inhibited in cells lacking NLRP3, indicating that KCs NLRP3 is crucial for inflammasome activation and subsequent cytokine secretion [53]. Similarly, NLRP3 knockout mice fed with HFD or choline-deficient amino acid demonstrate decreased hepatic steatosis and liver injury [46, 55]. Conversely, NLRP3 knock-in mice show significantly elevated pro-fibrogenic genes, including *Acta2* and *Col1a1*, and markers of activated HSCs, leading to increased liver fibrogenesis [55]. The NLRP3 selective inhibitor, MCC950, has been shown to inhibit macrophage and neutrophil recruitment, reducing liver inflammation. Moreover, pharmacological inhibition of NLRP3 *in vivo* reduces hepatocyte injury in MAFLD and significantly decreases liver fibrosis [56, 57]. Activated caspase-1, which correlates with disease severity, is detectable in the liver and serum of MASH patients and mice [4, 52]. Furthermore, suppression of caspase-1 activity relates to the dissociation between hepatic triglyceride accumulation, inflammatory reactions, and protection against HSC activation [58]. Notably, ASC-deficient mice on HFD show increased lipid accumulation and ballooning degeneration, potentially linked to gut microbiota dysbiosis and bacterial translocation through the "gut-liver axis" [59, 60]. Research establishes that caspases-1/11 plays a significant role in MAFLD by regulating liver lipid composition and gut microbial community composition [61].

Caspase-11 functions not only to cleave GSDMD and mediate pyroptosis but also specifically protects against gram-negative bacterial infection. Studies show that caspase-11 deficiency reduces bone marrow monocyte-derived macrophage pyroptosis and GSDMD expression on inflammatory monocytes. The absence of caspase-11 decreases hepatic fat deposition and reprograms liver transcriptomes against MAFLD in HFD-fed mice [62]. GSDMD cleavage depends on caspase-1 and leads to pyroptosis through plasma membrane pore formation [63]. Furthermore, hepatic GSDMD and pyroptosis-inducing fragment GSDMD-N levels are significantly elevated in human MASH, with this increase positively correlating with liver fibrosis and MAFLD activity score. This finding is supported by GSDMD$^{-/-}$ mice showing reduced steatosis and inflammation compared to littermate controls after MCD feeding [63]. These findings provide novel insights into the caspase-1/11-GSDMD pathway's role in promoting hepatic macrophage inflammation and MAFLD.

Chronic sterile inflammation induced by NLRP3 inflammasome activation contributes to MAFLD progression. NLRP3 inflammasome activation significantly increases IL-1β and IL-18 secretion, promoting MAFLD development. Research shows that inhibiting pro-IL-1β conversion to bioactive IL-1β protects against MAFLD development and obesity-induced inflammation [64]. MAFLD patients demonstrate significantly higher serum IL-18 levels compared to healthy controls, with serum IL-1β and IL-18 strongly correlating with MAFLD score, hepatic steatosis, and transaminase levels [51]. In MASH patients, *IL-1B* and *IL-18* mRNA levels are significantly elevated compared to non-MASH cases. The expression of *Il-1b* mRNA correlates with *Col1a1* levels, a profibrotic gene expressed by activated HSCs, resulting in reduced liver inflammation and fibrosis in IL-1β-deficient mice [55, 65]. These findings demonstrate IL-1β's crucial role in steatohepatitis and liver fibrosis progression. Conversely, IL-18-knockout mice exhibit dyslipidemia and steatosis compared to littermate controls under HFD. The metabolic alterations in IL-18-deficient mice improve with recombinant IL-18 supplementation, strongly suggesting IL-18's hepatoprotective effects in MAFLD [3, 66]. Fig. 2 summarizes the NLRP3 inflammasome's role in MAFLD.

5. Natural products targeting NLRP3 inflammasome for MAFLD

The significance of NLRP3 inflammasome in MAFLD progression highlights the potential for therapeutic interventions target-

ing this complex. Current understanding of NLRP3 inflammasome activation mechanisms enables the identification of multiple approaches to suppress protein target activation and assess their therapeutic efficacy. Notably, researchers have identified numerous NLRP3 inhibitors that function through both direct and indirect suppression of NLRP3 inflammasome signaling cascades. These inhibitors demonstrate effectiveness both *in vitro* and *in vivo* for MAFLD improvement, though only a limited number have progressed to clinical trials [67, 68].

Natural products remain a crucial source of drugs and lead compounds, maintaining an essential position in drug discovery [69]. Recent research has revealed numerous herbal extracts and their bioactive components exhibiting significant inhibitory effects on NLRP3 inflammasome and potential benefits in MAFLD treatment [70]. The identification of NLRP3 inflammasome inhibitors from natural sources for MAFLD treatment has emerged as a promising research focus (Supplementary table 1). This section summarizes natural products targeting NLRP3 inflammasome for MAFLD improvement, categorized by their mechanisms of action: priming step inhibition, mitophagy enhancement, mtROS and mtDNA production suppression, ASC speck oligomerization blockade, and glycolipid metabolism regulation (Fig. 3).

5.1. Inhibiting the priming

NLRP3 inflammasome activation involves a two-step process, wherein the priming step, initiated by PAMPs or DAMPs, activates NF-κB to enhance the transcription of NLRP3 inflammasome components, facilitating rapid activation in the second step [5]. Research indicates that caffeine ameliorates hepatic steatosis and fibrosis by inhibiting NLRP3 inflammasome activation through downregulation of TLR4/MAPK/NF-κB signaling [71]. Similarly, dieckol, a phlorotannin extracted from *Ecklonia cava*, demonstrates comparable effects in HFD-induced MAFLD [72]. Additionally, lycopene, a carotenoid compound, exhibits a significant reduction of TLR4 at both mRNA and protein levels in HFFD-induced MAFLD, while inhibiting hepatic NLRP3-related inflammatory signaling [73].

Suppressing the priming step of NLRP3 inflammasome may demonstrate therapeutic potential in MASH treatment. Kinsenoside, a bioactive compound isolated from *Anoectochilus roxburghii*, exhibits anti-hepatic steatosis properties. Studies indicate that kinsenoside significantly reduces NF-κB mRNA expression and inhibits NF-κB p65 nuclear translocation in MCD-induced MASH. Corresponding with *in vivo* findings, kinsenoside reduces NLRP3 inflammasome formation by decreasing NLRP3, ASC, and caspase-1 protein expressions in macrophages [74]. Additionally, cannabidiol, a prominent nonpsychoactive component of marijuana, demonstrates protective effects against MASH through inhibition of NF-κB nuclear translocation or deactivation [75]. Similarly, andrographolide significantly downregulates NLRP3 inflammasome through NF-κB inactivation and inhibits LPS-induced IL-1β secretion in fat-laden hepatocytes [76]. Apigenin and naringenin substantially reduce OA-induced lipid accumulation and inhibit NLRP3 activation in OA/LPS-treated hepatocytes. Moreover, treatment with apigenin or naringenin partially reverses hepatic lipid accumulation and inflammation in mice fed with MCD or HFD [77, 78]. *Lycium barbarum* polysaccharides, wolfberry's primary bioactive constituent, demonstrate comparable protective effects in MCD-fed mice [79]. Notably, *Gynostemma pentaphyllum* polysaccharides improve MASH *via* gut microbiota restoration and TLR2/NLRP3 signaling inhibition. In MCD-induced MASH mice, *Gynostemma pentaphyllum* polysaccharides treatment partially ameliorates hepatic steatosis, fibrosis, and oxidative stress [80]. These findings suggest that NLRP3 inflammasome modulation through an NF-κB-dependent mechanism may contribute to MAFLD improvement.

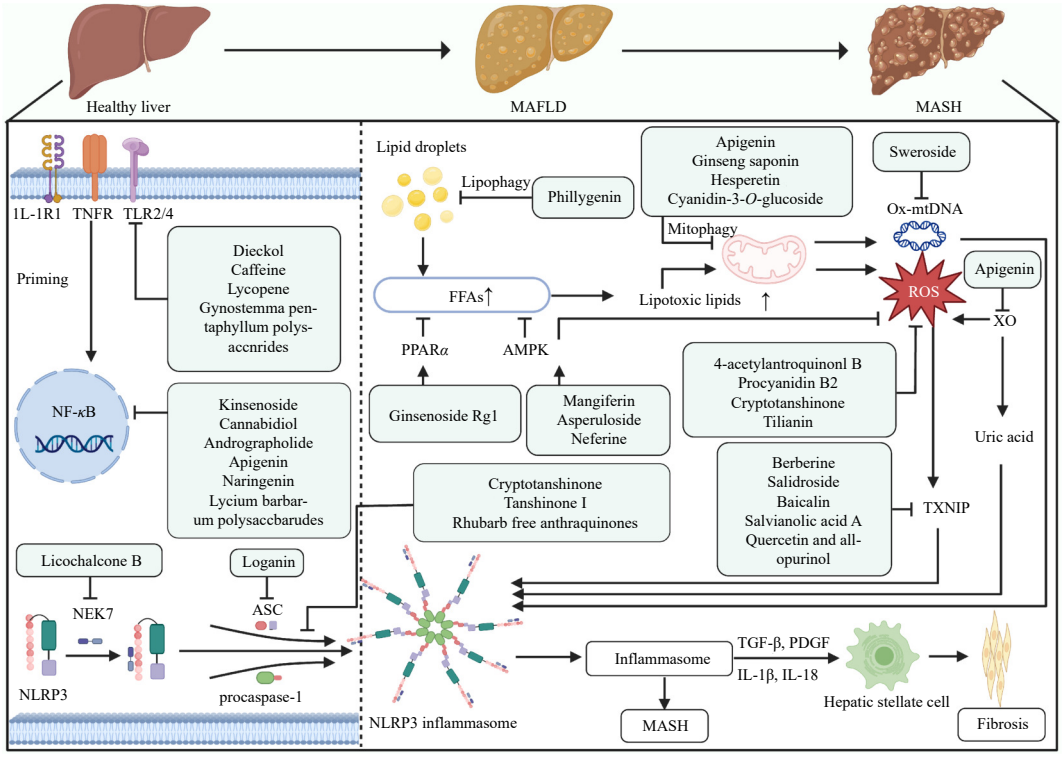

Fig. 3 Natural products targeting NLRP3 inflammasome for MAFLD. Excessive FFAs can serve as substrates to generate lipotoxic lipids, which provoke hepatocellular stress, mitochondrial dysfunction, ROS overproduction, and mtDNA release, further triggering the activation of NLRP3 inflammasome. The activated NLRP3 inflammasome induces chronic inflammation and activates HSCs to promote collagen deposition, thereby promoting the progression of MAFLD. Natural product targets include those that inhibit the NF-κB/NLRP3 pathway, increase mitophagy, suppress ROS overproduction, reduce mtDNA release, block the ASC speck oligomerization, and regulate glycolipid metabolism. (Created with BioRender.com. Agreement number: DQ2728T43W.)

5.2. Inhibiting the activation

5.2.1. Increasing mitophagy

Mitophagy serves as a crucial regulator of NLRP3 activation by selectively eliminating dysfunctional mitochondria and reducing mtROS production and mtDNA release. Effective mitophagy in hepatocytes maintains adequate functional mitochondria, satisfies cellular energy requirements, prevents FFA-induced hepatocyte injury, and mitigates MAFLD progression [81]. Recent studies demonstrate that apigenin eliminates damaged mitochondria through mitophagy, reducing protein expression of NLRP3, caspase-1, GSDMD-N, IL-1β, and IL-18 in HFD-fed mice and PA-treated hepatocytes [82]. In LPS-exposed KCs, ginseng saponin inhibits LPS-induced NLRP3 inflammasome activation by promoting mitophagy, thereby reducing inflammatory response [83]. Additionally, research indicates that under PA stimulation, hesperetin, a bioactive flavonoid from citrus fruit, and cyanidin-3-*O*-glucoside, a natural anthocyanin, restore PA-impaired mitochondrial function *via* enhanced PINK1/Parkin-mediated mitophagy and subsequent dysfunctional mitochondria clearance, thus inhibiting NLRP3 inflammasome activation and improving hepatic steatosis and glucose homeostasis [84, 85].

5.2.2. Suppressing ROS overproduction

The generation of ROS serves as a common mechanism contributing to NLRP3 inflammasome activation across diverse stimuli [23]. Significantly, TXNIP functions as a potential mediator between ROS production and NLRP3 inflammasome activation [26]. The role of TXNIP in NLRP3 inflammasome activation suggests a novel therapeutic approach for MAFLD treatment. Research demonstrates that berberine, an alkaloid extracted from *Coptis chinensis*, reduces lipid accumulation, decreases ROS production, and inhibits TXNIP expression *in vivo* and *in vitro*. Moreover, berberine significantly restores NLRP3 levels, caspase-1 activity, and GSDMD-N expression in hepatocytes. Studies indicate that its inhibitory effect on NLRP3 inflammasome and pyroptosis occurs *via* the ROS/TXNIP axis to improve MASH [86, 87]. Likewise, salidroside, a phenylpropanoid glycoside compound isolated from *Rhodiola rosea*, improves glucose tolerance and lipid deposition while suppressing ROS overproduction in a dose-dependent manner. Salidroside demonstrates therapeutic effects on MAFLD *via* antioxidative stress and regulation of AMPK-dependent TXNIP/NLRP3 signaling [88]. Research reveals that quercetin and allopurinol effectively reduce hepatic inflammatory cell infiltration and lipid deposition in streptozotocin-induced diabetic rats while down-regulating hepatic TXNIP expression, ROS overproduction, NLRP3 inflammasome activation, and IL-1β levels in diabetic rat liver. Furthermore, TXNIP silencing eliminates the suppressive effects of quercetin and allopurinol on caspase-1 and IL-1β secretion in high glucose-exposed hepatocytes [89]. Additionally, baicalin and salvianolic acid A effectively reverse PA-induced cytotoxicity, oxidative stress, and NLRP3 inflammasome activation, accompanied by TXNIP down-regulation [90, 91].

Procyanidin B2, derived from *Cinnamomum cassia*, significantly inhibits ROS production, ER stress, and subsequent NLRP3 inflammasome activation under PA incubation [92]. In LPS-stimulated hepatocytes, 4-acetylantroquinonol B, a bioactive compound from *Androdia cinnamomea*, suppresses ER stress, reduces ROS production, and inhibits NLRP3 inflammasome activation [93]. Similarly, cryptotanshinone, extracted from *Salvia miltiorrhiza* Bunge, inhibits Ca^{2+} mobilization, mtROS production, and NLRP3 inflammasome activation in macrophages exposed to ATP and nigericin. In MCD-fed mice, cryptotanshinone reduces hepatocyte ballooning, inflammatory cell infiltration, and fibrosis. Notably, the inhibitory effect of cryptotanshinone on caspase-1 and IL-1β matches that of MCC950 [94]. In HFHC-fed mice, tilianin administration improves MAFLD by suppressing ROS overproduction, modulating oxidative stress, and inhibiting NLRP3 inflammasome activation [95]. These findings confirm the effectiveness through suppression of ROS overproduction and NLRP3 inflammasome inhibition. Additionally, uric acid functions as a self-derived DAMP activating NLRP3 inflammasome, while xanthine oxidase (XO) serves as a rate-limiting enzyme catalyzing uric acid production [96]. Studies show that apigenin improves HFD-induced MAFLD *via* XO/NLRP3 inhibition. Significantly, apigenin reverses HFD-induced NLRP3 inflammasome activation by down-regulating XO activity and reducing uric acid and ROS levels [97].

5.2.3. Reducing mtDNA production

The synthesis of mtDNA, triggered by TLR engagement, plays a vital role in NLRP3 signaling. Oxidized mtDNA in the cytosol specifically binds to and activates the NLRP3 inflammasome. Inhibition of mtDNA synthesis reduces NLRP3 inflammasome activation induced by stimulants such as ATP and nigericin [29]. Sweroside, a bioactive compound from *Swertia pseudochinensis* Hara, has demonstrated efficacy in reducing hepatic immune cell infiltration, lipid accumulation, and collagen deposition, thereby improving MASH. This improvement correlates with decreased hepatic NLRP3 inflammasome activation, evidenced by reduced hepatic IL-1β and caspase-1 levels. The mechanism underlying sweroside's suppression of the NLRP3 inflammasome involves inhibition of hepatic *de novo* mtDNA synthesis [98]. Given mtDNA's essential role in NLRP3 activation and limited research on natural compounds' effects, identifying natural products targeting hepatic mtDNA to inhibit NLRP3 inflammasome holds significant potential for MAFLD treatment.

5.2.4. Regulating glycolipid metabolism

MAFLD exhibits strong connections with glycolipid metabolism and hepatic inflammation. AMPK functions as a crucial mediator in regulating glycolipid metabolism within liver and adipose tissue, influencing MAFLD progression. When activated, AMPK can suppress lipid-induced inflammation through inhibition of NF-κB signaling, subsequently contributing to NLRP3 inflammasome inhibition [35, 36]. This evidence suggests that targeting AMPK-dependent NLRP3 inhibition represents a promising therapeutic approach for MAFLD.

Mangiferin, a yellow polyphenolic compound abundant in various sources, including Mango leaves, exhibits anti-oxidant, anti-inflammatory, anti-diabetic, and anti-cancer properties. In HFD-induced MAFLD, mangiferin has enhanced glucose tolerance, reduced insulin resistance, and mitigated liver injury while decreasing fat accumulation and hepatic inflammation. Research demonstrates that mangiferin inhibits NLRP3 inflammasome activation and pyroptosis through upregulation of p-AMPKα [99]. Additional studies have shown that asperuloside and neferine activate AMPK to suppress NLRP3 inflammasome and improve MAFLD [100, 101].

Research has also identified opportunities for MAFLD improvement through glycolipid metabolism modulation. Ginsenoside Rg1, a potent bioactive compound extracted from ginseng with hepatoprotective properties, has markedly reduced liver weight and levels of ALT, AST, TG, and FFA in HFD-induced MAFLD. Additionally, ginsenoside Rg1 has increased PPARα expression to enhance fatty acid *β*-oxidation and promoted FFA and TG catabolism. It has also reduced liver inflammation by inhibiting NLRP3 inflammasome activation and decreasing inflammatory cytokine production, including IL-1β and IL-18. These findings indicate that ginsenoside Rg1 may protect against MAFLD through regulation of lipid peroxidation and inflammasome activation [102]. Phillygenin, extracted from *Forsythia suspensa*, has decreased lipid accumulation and reduced intracellular TG and TC levels *in vivo* and *in vitro*. Mechanistically, phillygenin has im-

proved lipid deposition by restoring lipophagy through increased intracellular lipid droplet degradation in lysosomes. Furthermore, phillygenin has inhibited NLRP3 inflammasome activation through enhanced autophagy [103].

5.2.5. Blocking the ASC speck oligomerization

Upon activation, oligomerized NLRP3 recruits ASC to promote its speck formation, leading to the assembly of NLRP3 inflammasome. Studies indicate that cryptotanshinone inhibits ASC oligomerization triggered by ATP and nigericin, thereby blocking NLRP3 inflammasome activation and protecting MASH [94]. Tanshinones, comprising three major constituents, represent the primary lipid-soluble pharmacologically active component of the Chinese medicinal herb *Salvia miltiorrhiza*. Research has demonstrated that tanshinone I inhibits NLRP3 inflammasome activation to alleviate MASH. The mechanism involves tanshinone I disrupting the association between NLRP3 and ASC, thus inhibiting NLRP3 inflammasome activation [104]. Similarly, rhubarb free anthraquinones inhibit the combination between NLRP3 and ASC and subsequent ASC speck formation in mouse bone marrow-derived macrophages to ameliorate MAFLD [105]. These findings confirm that tanshinone I and rhubarb free anthraquinones serve as potential NLRP3 inflammasome blockers to treat NLRP3 inflammasome-related diseases *via* blocking the ASC speck formation. Additionally, research indicates that loganin blocks the speck formation of ASC, thus impairing the assembly of the NLRP3 inflammasome complex and preventing hepatic steatosis [106].

The interaction between NLRP3 and NEK7 is essential for ASC speck formation. Consequently, inhibiting NLRP3 inflammasome by targeting NEK7 presents a viable approach. Licochalcone B, a flavonoid bioactive ingredient isolated from *licorice*, possesses anti-viral, anti-inflammatory, and anti-cancer pharmacological properties. Licochalcone B effectively blocks the nigericin- or ATP-induced NLRP3 activation in macrophages and demonstrates hepatoprotective effects, including MASH. Research has revealed that licochalcone B directly binds to NEK7 and effectively intervenes in the interaction between NEK7 and NLRP3, thus blocking ASC oligomerization and suppressing NLRP3 inflammasome activation [107].

6. Conclusion and future directions

Targeting the NLRP3 inflammasome represents a rapidly evolving and promising therapeutic strategy across a wide range of inflammatory and metabolic disorders. As a central mediator of innate immunity, the NLRP3 inflammasome plays a crucial role in orchestrating inflammatory responses and maintaining metabolic homeostasis. Clinical evidence supports the efficacy of IL-1β-targeted therapies, including FDA-approved agents such as anakinra, rilonacept, and canakinumab, in the treatment of rheumatoid arthritis, cryopyrin-associated periodic syndromes, and other autoinflammatory conditions [108-110]. In parallel, the selective small-molecule inhibitor MCC950 has demonstrated substantial therapeutic potential in preclinical models of Alzheimer's disease, atherosclerosis, and inflammatory bowel disease [68]. The relevance of NLRP3 inflammasome activation in MAFLD has gained increasing attention. Anti-inflammatory strategies targeting the NLRP3 axis have shown encouraging results in both experimental and clinical settings. MCC950, in particular, has yielded favorable outcomes in MAFLD models, and the advancement of NLRP3 inhibitors such as IFM-2427 into clinical trials further underscores their translational promise [56, 67, 68, 111]. NLRP3 inflammasome inhibitors show broad potential in treating multiple metabolic diseases. As outlined above, current natural products targeting NLRP3 inflammasome in ameliorating MAFLD primarily focus on NF-κB pathway-related priming signaling, mitochondrial dysfunction, the production of mtROS and mtDNA, ASC oligomerization, and glycolipid metabolism. Based on advances in understanding NLRP3 activation mechanisms, researchers can better explore new mechanisms to identify more active natural products from traditional Chinese medicine (TCM) to enhance MAFLD treatment.

Several TCM formulas, including Danshen Zexie decoction, Si Miao formula, and Yanggan Jiangmei formula, demonstrate efficacy in treating MAFLD and inhibiting NLRP3 inflammasome [112-114]. However, further detailed experimental evidence is needed to identify their active ingredients exhibiting this therapeutic potential. Recent research has highlighted a range of advanced strategies for identifying bioactive constituents from natural products, including bioaffinity-based screening platforms, magnetically-assisted separation techniques, and optical biosensing technologies [115]. For instance, combining surface plasmon resonance (SPR) with high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) is commonly employed to screen low molecular weight compounds from mixtures, where SPR spectroscopy detects ligand-receptor interactions, and HPLC-MS/MS separates and identifies active ingredients collected from SPR, focusing on real-time detection of accurate biomolecular interactions to elucidate the molecular mechanism of natural products [116, 117]. Additionally, protein-protein interactions can be identified through biological methods. The protein-fragment complementation assay, for example, can screen active compounds that cleave GSDMD to GSDMD-N and GSDMD-C [118, 119]. These advanced technologies will facilitate the refinement of active ingredients and new mechanisms of effective TCM in deactivating GSDMD and ameliorating MAFLD.

Recent studies have explored natural products targeting NLRP3 inflammation; however, mechanistic understanding remains limited, particularly regarding the identification of specific molecular targets. Natural products with well-defined targets are crucial for clinical pharmacokinetic studies and can facilitate the prediction of signal response pathways *in vivo*, enabling the interruption of pathways associated with adverse reactions and minimizing side effects. Consequently, the exploration and identification of novel active targets for natural products hold substantial significance for their therapeutic application. Considering the critical role of NLRP3 inflammasome in disease progression, identifying actual targets and their interactions with NLRP3 through advanced drug target identification technologies merits investigation. A primary approach for drug target discovery involves utilizing molecular probes to couple active targets, followed by confirmatory analyses through chromatography, gel electrophoresis, and mass spectrometry. However, molecular probe labeling methods face limitations due to their reliance on chemical modifications. For natural products lacking covalent cross-linking or chemical modification sites, the development of label-free drug target protein screening technologies becomes essential. One innovative approach combines isobaric tags for relative and absolute quantitation (iTRAQ), a quantitative proteomics method, with clickable activity-based protein profiling (ABPP) to specifically and comprehensively identify drug targets in live cells, significantly enhancing the sensitivity and accuracy of target identification [120].

In conclusion, elucidating novel mechanisms of NLRP3 inflammasome activation, coupled with the identification of diverse ingredients and new targets through advanced technologies, will facilitate the discovery of bioactive compounds in natural products targeting NLRP3 inflammasome for the prevention and treatment of various forms of MAFLD.

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Supplementary data

Supplementary data for this paper is available upon emailrequest to the corresponding authors.

Declaration of competing interest

The authors declare that there are no known conflicts of interest associated with this work.

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