

Review Article

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Therapeutic approaches for liver fibrosis/cirrhosis by targeting pyroptosis

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Abstract: Long-term repeated exposure to various stimuli leads to chronic liver damage, inflammation, fibrosis, and eventually cirrhosis. Pyroptosis, a mode of inflammatory programmed cell death, affects the progression of liver fibrosis/cirrhosis. However, current research on drugs targeting the pyroptosis pathway as a therapeutic strategy in liver fibrosis and cirrhosis remains limited. This review aims to explain the relationship between pyroptosis and liver cirrhosis and focuses on methods for the treatment of liver cirrhosis based on targeted pyroptosis. Here, 31 inhibitor drugs that target inflammasomes, gasdermin D, or caspases are discussed. Although the inhibitory effect of these drugs on pyroptosis is indisputable, their efficacy on cirrhosis needs a thorough investigation. Seventeen natural plant compounds that improve liver fibrosis/cirrhosis in cellular and animal models through targeting pyroptosis are also reviewed. In addition, stem cell replacement therapy and exosomes have broad application prospects in liver cirrhosis from the perspective of pyroptosis. In the future, the primary challenges will involve validating the efficacy of the aforementioned drugs in targeting pyroptosis for cirrhosis treatment using human liver organoids as well as determining their potential clinical application.

Keywords: liver fibrosis/cirrhosis, pyroptosis, inhibitors of pyroptosis pathway, natural plant compounds, biomaterials

1 Introduction

Cirrhosis is widely prevalent with a high mortality rate. It is the third leading cause of death in people aged 45–64 years and has become one of the major health problems worldwide [1]. Cirrhosis is the major predisposing risk factor to hepatoma carcinoma and is a consequence of end-stage liver disease, which results from long-term repeated exposure to various stimuli leading to chronic liver damage, inflammation, fibrosis, and eventually cirrhosis [2]. The etiology of cirrhosis mainly includes viral infection (such as hepatitis B virus [HBV], hepatitis C virus [HCV], and hepatitis D virus, either alone or superimposed on HBV); alcohol intake; metabolic and genetic, autoimmune, biliary, vascular, drug-induced (such as vitamin A, amiodarone, methotrexate, and methyl dopa), and cholestatic diseases; and cryptogenic cirrhosis (with uncertain cause) [3,4]. The development of cirrhosis involves multiple cell types, such as hepatocytes, hepatic stellate cells (HSCs), Kupffer cells, and liver sinusoidal endothelial cells. In the treatment of cirrhosis, the primary objective is to address the disease cause as effectively as possible and delay hepatic decompensation because mitigating the cause increases the likelihood of recovery [5]. Despite the complexity and diversity of cirrhosis, promising advances in cirrhosis treatment remain elusive, and to date no treatment with sustained effectiveness has been approved for liver fibrosis. In addition, the unclear pathogenesis of cirrhosis greatly limits the development and application of targeted drugs. Therefore, the pathomechanisms of cirrhosis must be elucidated to facilitate the development of its therapeutic strategies and improve patient benefits.

Pyroptosis refers to inflammatory programmed cell death mediated by inflammasomes that are controlled by classical and nonclassical signaling pathways [6]. In general, inflammasomes trigger the activation of caspases, which leads to the polymerization and cleavage of gasdermin (GSDM) family members, resulting in cell perforation and release of inflammatory factors. Pyroptosis can detect danger signals, such as persistent cell swelling until lysis, resulting in the release of cell contents and triggering of a strong inflammatory response. A distinctive feature of

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pyroptosis is that cell death is accompanied by the release of numerous inflammatory factors such as interleukin (IL)-18 and IL-1 β . Thus, pyroptosis is an important innate immune program of the body and takes on a crucial role in disease resistance and fighting infection. In recent years, numerous studies have suggested that pyroptosis is closely related to various liver diseases, such as cirrhosis, non-alcoholic fatty liver disease (NAFLD), and alcoholic liver disease (ALD) [7,8]. Therefore, targeted regulation of the cellular pyroptosis pathway may be a potential strategy for the treatment of cirrhosis. For example, a study demonstrated that the inhibition of pyroptosis by targeting caspase-1 or NOD (nucleotide-binding and oligomerization domain)-like receptor (NLR) protein 3 (NLRP3) significantly inhibits liver fibrosis or cirrhosis [9]. Therefore, summarizing and predicting the methods and targets that can be utilized for the treatment of cirrhosis based on pyroptosis are clinically important.

Overall, pyroptosis has not been studied much in cirrhosis compared with other diseases, and there are insufficient articles on its relevance. In this review, we summarize the mechanism of pyroptosis and pyroptosis-based approaches for cirrhosis, including inhibitors of the pyroptosis pathway, natural plant compounds, and other effective approaches. This information may provide ideas for research on the treatment of cirrhosis.

2 Pyroptosis mechanism

2.1 Canonical pathway of pyroptosis

In the canonical pathway, inflammasomes can be regulated by pattern recognition receptors (PRRs), such as damage-associated molecular patterns (DAMPs) and

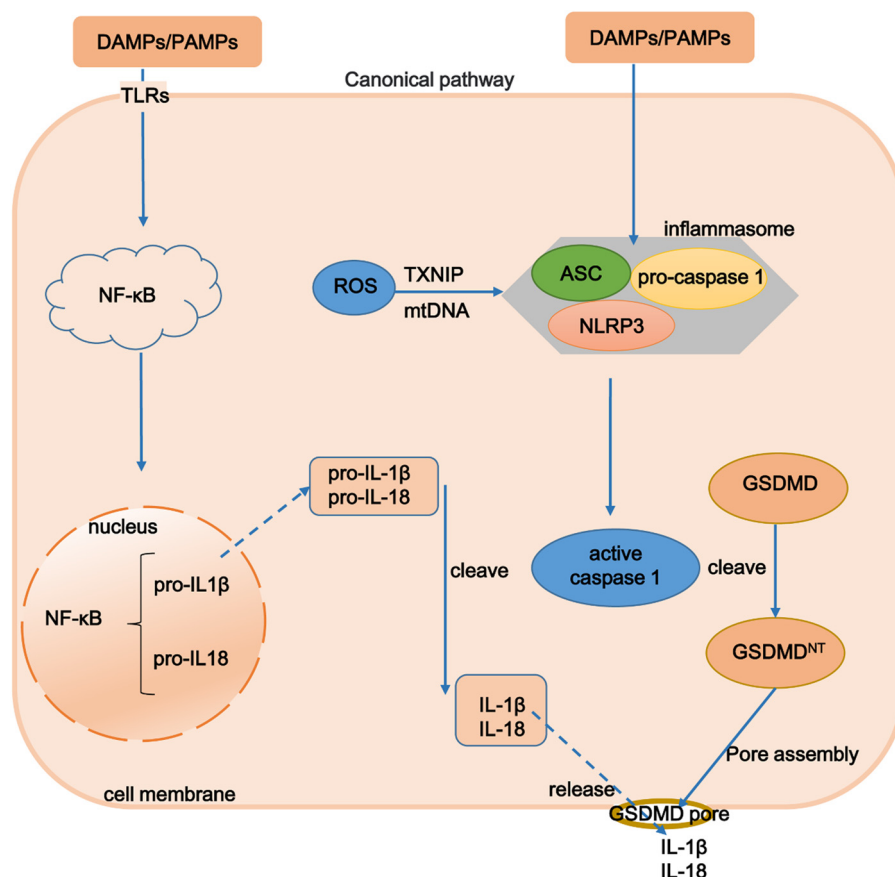


Figure 1: Canonical pathway of pyroptosis. In the canonical pathway, inflammasomes are regulated by PRRs, including various DAMPs, PAMPs, and ROS, to activate caspase-1 and then cleaved the executor protein GSDMD into GSDMD-N fragments that form “pores” on the cell membrane to allow for the release of proinflammatory cytokines such as interleukin (IL)-1 β and IL-18. PRRs, pattern recognition receptors; DAMPs, damage-associated molecular patterns; GSDMD, gasdermin D; PAMPs, pathogen-associated molecular patterns; ROS, reactive oxygen species.

pathogen-associated molecular patterns (PAMPs), to activate IL-1 β and IL-18 to generate and release proinflammatory cytokines [10]. The canonical pathway involves two signaling pathways. First, DAMPs and PAMPs are recognized by PRRs on the cell membrane surface, which triggers the downstream MyD88-NF- κ B signaling pathway to produce pro-IL-1 β and pro-IL-18 (Figure 1) [11]. Second, caspase-1 is the only caspase that exists in the canonical pathway and can be activated by inflammasomes [12]. As shown in Figure 1, DAMPs and PAMPs enter cells and activate the inflammasomes to form multiprotein complexes and subsequently activate caspase-1. Then, active caspase-1 cleaves the executor protein GSDMD into 22 and 31 kDa active N-terminal and C-terminal fragments. GSDMD-N fragments cleave phosphatidylinositol/cardioidlipid-containing liposomes from cell membranes and “punch” holes in the cell membrane [13]. Meanwhile, caspase-1 completes the cleavage and maturation of pro-IL-1 β and pro-IL-18 to form active proinflammatory factors IL-1 β and IL-18 [14]. IL-1 β and IL-18 are secreted outside the cell through the

“pores” formed by GSDMD-N in the cell membrane, inducing an inflammatory response called pyroptosis [10,13].

In addition, an imbalance between mitochondrial homeostasis and reactive oxygen species (ROS) production is associated with pyroptosis. ROS are mainly produced by mitochondria and mediate various mitochondrial dysfunctions. Nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2)-derived ROS can activate NLRs in NLRP3 inflammasomes in macrophages [15,16]; however, whether NOX2 is involved in NLRP3 activation is controversial. Currently, two main pathways of ROS-induced cellular pyroptosis are known (Figure 1). First, mitochondrial ROS (mtROS) inhibit the synthesis of related protein subunits responsible for encoding mtDNA, potentially disrupting mitochondrial oxidative phosphorylation, releasing more mtROS, and continuously damaging mtDNA, creating a vicious cycle of bioenergetic disruption and ultimately leading to pyroptosis [16]. Second, with the increase in ROS, thioredoxin separates from thioredoxin-interacting protein (TXNIP) and binds to NLRP3, leading to NLRP3 activation [17].

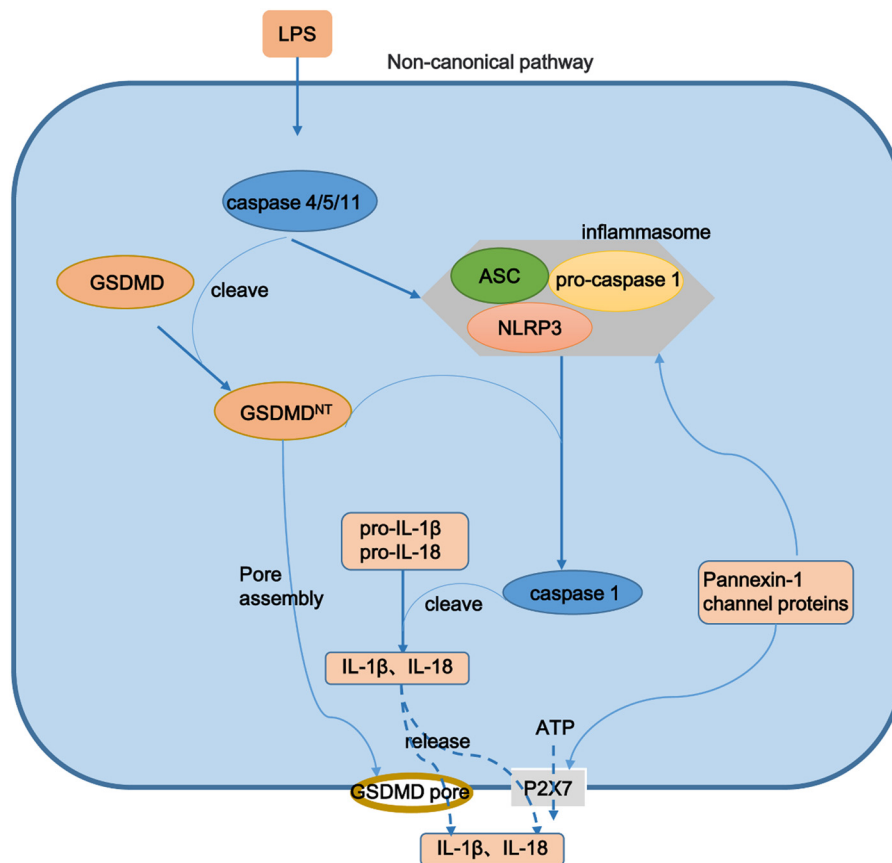


Figure 2: Non-canonical pathway of pyroptosis. In the non-canonical pathway, LPS binds to caspases 4 and 5 (human) or caspase-11 (mouse) and initiates pyroptosis, which is very similar to that induced via the canonical pathway. LPS, lipopolysaccharide.

2.2 Non-canonical pathway

Unlike caspase-1 dependence in the classical pathway, in the non-canonical pathway, other PRRs such as lipopolysaccharide (LPS) can directly bind to caspases 4, 5, and 11 to induce pyroptosis (Figure 2). Notably, caspases 4, 5, and 11 cannot cleave pro-IL-1 β /pro-IL-18 but can cleave the GSDMD [18]. Caspase-11 is mainly present in mice, whereas caspases 4 and 5 are mainly present in humans [19]. Activated caspases 4, 5, and 11 cleave GSDMD to biologically active GSDMD-NT, which further activates the downstream factor caspase-1 by binding to NLRP3 inflammasomes and ultimately secretes mature IL-1 β and IL-18 outside cells [20,21]. As shown in Figure 2, Pannexin-1 channel proteins can open P2X7 cell membrane channels, release ATP under the action of caspase-11, and then form “holes” in the cell membrane, inducing pyroptosis [22]. Moreover, the activation of pannexin-1 channel protein promotes the release of intracellular K⁺ ions and activates NLRP3, which also promotes the release of IL-1 β and IL-18 [23].

2.3 Other mechanism pathways of pyroptosis

Some studies have confirmed some mechanisms of focal death independent of classical and nonclassical mechanisms; however, the mechanisms are not fully defined yet. In 2020, granzyme B was found to activate caspase-3 to cleave gasdermin family protein E (GSDME), resulting in extensive pyroptosis [24]. Moreover, granzyme A was found to cleave the GSDMB at non-aspartic acid sites, which causes pyroptosis [25]. Thus, the granzyme-mediated pathway is another mechanism of pyroptosis. Second, recent studies have shown that GSDME plays a role in

mediating pyroptosis [26]. Unlike GSDMD, GSDME can be cleaved at specific sites by caspase-3, a key factor in apoptosis, and the cleaved GSDME-N fragment can penetrate cell membranes. Caspase-3 is activated by tumor necrosis factor- α and induces apoptosis; however, if cells can express GSDME, the mode of cell death shifts rapidly to pyroptosis or even direct pyroptosis [26]. Notably, the addition of caspase inhibitors to cells or GSDME knockdown will prevent pyroptosis [27]. *In vivo* tests showed the same effect, with chemotherapeutic drugs producing significantly fewer side effects in GSDME-knockout mice [28]. Thus, the GSDME-mediated pathway is another mechanism of pyroptosis. Third, the caspase-3/8-mediated pathway may also play a role in pyroptosis. Although it was previously thought that apoptosis-related caspases (e.g., caspases 3 and 8) could not stimulate GSDMD-induced pyroptosis, recent studies have found that chemotherapeutic agents can induce caspase-3-mediated cleavage of highly expressed GSDME, leading to tumor cell pyroptosis [27,28]. In addition, the YopJ protein can suppress transforming growth factor-beta (TGF- β)-activated kinase 1 and induce caspase-8-related cleavage of GSDMD, resulting in pyroptosis [29,30]. Thus, another pathway is the caspase-3- or caspase-8-mediated pyroptosis pathway. Interestingly, caspase-3 is generally considered one of the important markers for apoptosis, and this finding links two regulated cell death processes, namely, apoptosis and pyroptosis, and is important to further explore the mechanism of pyroptosis.

3 Pyroptosis and liver cirrhosis

As shown in Figure 3, cirrhosis is the final stage of several liver diseases. Liver fibrosis is a prevalent pathological process associated with various chronic liver diseases,

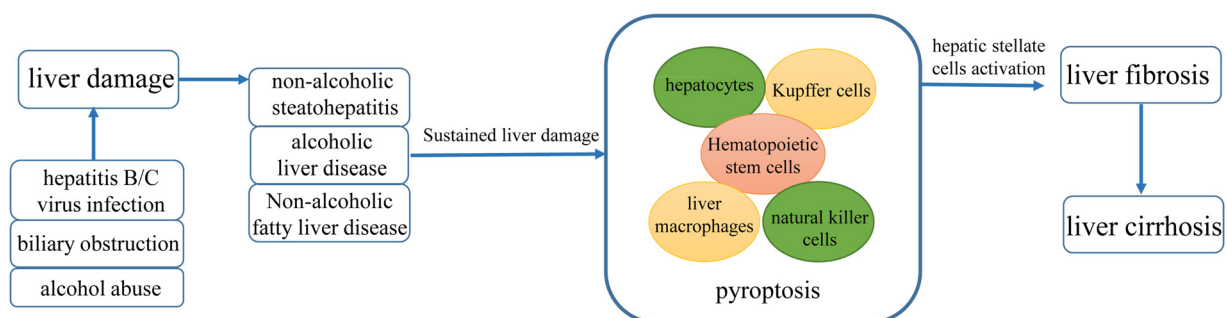


Figure 3: Relationship between pyroptosis and cirrhosis. HBV or HCV infection, biliary obstruction, and alcohol abuse could cause liver damage, which progresses to different liver diseases. In the early stages of liver disease-related inflammation, the activation of inflammasomes in hepatocytes and Kupffer cells induces the release of a plethora of proinflammatory compounds, which will activate HSCs and evoke a state of fibrosis, degenerating to end-stage cirrhosis.

which is primarily driven by hepatocellular damage [3]. Liver fibrosis is characterized by the activation and transformation of HSCs into myofibroblasts, which synthesize collagen fibers. This process results in the progressive accumulation of the extracellular matrix, fibrous scar formation, and disruption of the physiological structure of the liver. Increasing studies have shown that pyroptosis is a strong trigger for HSC activation, fiber formation, fibrosis, and even cirrhosis. For example, in clinical studies, patients with cirrhosis have shown elevated levels of circulating GSDMD, IL-1 β , and IL-18 [31]. Excessive activation of NLRP3 inflammasomes in mice can lead to hepatocyte pyroptosis and cause severe liver inflammation and fibrosis, and pyroptosis products IL-1 β and IL-18 regulate the activation of HSCs and promote liver fibrosis *in vitro* [32]. NLRP3 inflammasome activation is required for liver inflammation and fibrosis in mouse models of NAFLD and non-alcoholic steatohepatitis (NASH) [33]. Moreover, pyroptosis of various cells is crucial in cirrhosis development. For example, pyroptosis of hepatocytes and release of inflammasome particles stimulate the activation of HSCs, leading to liver fibrosis [8]. Ursolic acid mitigates Kupffer cell pyroptosis in liver fibrosis by modulating the NOX2/NLRP3 inflammasome signaling pathway [34]. The activation of inflammasomes in natural killer (NK) cells promotes HSC apoptosis and mitigates the progression of liver fibrosis via tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-dependent degranulation [35]. Soluble egg antigens of *Schistosoma japonicum* trigger HSC pyroptosis, thereby intensifying liver damage [36]. In summary, pyroptosis is an important cause of liver fibrosis and even cirrhosis.

4 Pyroptosis markers that can be used as drug targets

To date, no treatment with sustained effectiveness has been approved for the management of liver fibrosis, highlighting the need to explore specific therapeutic targets. Different forms of pyroptosis are closely associated with cirrhosis. Researchers are currently trying to improve the therapeutic efficacy of liver fibrosis/cirrhosis through pyroptosis. Pyroptosis can be primarily inhibited in two main ways: by blocking the activation of NLRP3 inflammasomes and inhibiting the GSDM family signaling pathway. Herein, we summarize the role of inhibitors of the pyroptosis pathway, natural plant compounds, and other effective approaches in the anti-pyroptosis process to provide data for the development of clinical treatment of liver fibrosis/cirrhosis.

4.1 Inflammasome-related therapy

Inflammasomes, multiprotein complexes, are an important component of pyroptosis, which are composed of a sensor molecule, apoptosis-associated speck-like protein (ASC), and pro-caspase-1 (Figure 1) [37]. Inflammasomes can be divided into two types according to their receptors: NLR family (NLRP1/2/3/6, NLRC4, and NLRP12) and the pyrin and hematopoietic interferon-inducible nuclear protein (HIN) domain family including absent in melanoma 2 (AIM2) and pyrin [38]. Inflammasomes play a crucial role in recognizing cellular stress to activate caspases that induce pyroptosis [39]. NLRC4 depletion provides protection against hepatocyte pyroptosis in mice [40]. Therefore, inflammasome inhibition may be a promising treatment strategy in liver fibrosis/cirrhosis.

A large number of small molecule inhibitors can be targeted to inhibit the activation of NLRP3 inflammasomes,

Table 1: Inhibitor drugs for pyroptosis

Drug	Target
NLRP3/AIM2-IN-3 (compound 59)	NLRP3/AIM2
MCC950	NLRP3
A438079	P2X7/NLRP3
CY-09	NLRP3
JC2-11	Inflammasomes
NLRP3-IN-13	NLRP3
NLRP3-IN-9	NLRP3
Dapansutrole	NLRP3
Stavudine (d4T)	NLRP3
Muscione	NF- κ B/NLRP3
Emlenoflast (MCC7840) sodium	NLRP3 inflammasomes
Licochalcone B	NEK7-NLRP3
Ruscogenin	TXNIP/NLRP3
Arglabin ((+)-Arglabin)	NLRP3 inflammasomes
CORM-3	NLRP3 inflammasomes
YQ128	NLRP3
Soyasaponin II	YB-1 and NLRP3
NLRP3-IN-10	NLRP3
NLRP3-IN-NBC6	NLRP3
INF4E	NLRP3
Emlenoflast (MCC7840)	NLRP3 inflammasomes
Disulfiram (tetraethylthiuram disulfide)	ALDH1/GSDMD
LDC7559	GSDMD
Ac-FLTD-CMK	GSDMD
2-Bromohexadecanoic acid (2-bromopalmitic acid)	BAK/BAX-baspase
Ac-FEID-CMK TFA	3-GSDME
Ac-FEID-CMK	GSDMEb, caspy2
Pep19-2.5	GSDMEb, caspy2
Vx-166	PRRs
Emricasan	Caspases
Ac-YVAD	Caspases

as shown in Table 1. MCC950, originally known as a cytokine release inhibitor, specifically inhibits NLRP3 inflammasome activity in canonical and non-canonical pathways [41]. In a mouse model of cholestatic liver injury, MCC950 application significantly reduces the production of proinflammatory cytokines and incidence of hepatocyte death and attenuated cholestatic liver injury and liver fibrosis by inhibiting NLRP3 activation and assembly [42]. Compound 59, which targets NLRP3/AIM2-IN-3, can inhibit NLRP3/AIM2 to form inflammasomes that block pyroptosis [43]. P2X7 activation triggers NLRP3 inflammasomes. A438079, a specific inhibitor of P2X7 that acts as a trigger for NLRP3 inflammasomes, attenuates CCL4-induced hepatic fibrosis in mice by downregulating smooth muscle α -actin and TGF- β 1 expression and reducing hepatic collagen formation [23]. These studies suggest that small-molecule inhibitors targeting NLRP3 inflammasomes (Table 1) may have the potential to improve cirrhosis. However, the lack of animal and clinical trials has hindered the understanding of the efficacy of these inhibitors in patients with cirrhosis.

Most of the drugs shown in Table 1 are known to inhibit pyroptosis and thus demonstrate therapeutic effects in various diseases. However, the effectiveness of only a few inhibitors in liver cirrhosis is supported by the literature.

4.2 Caspase-related therapy

The caspase family is a class of cysteine proteolytic enzymes that recognize the tetrapeptide sequence of the substrate and cleave it after aspartic acid (D) residues to activate the substrate protein [44]. In the absence of upstream signals, the caspase family remains in the cytoplasm as inactive proenzymes. Substrate recognition and cleavage can only occur when the caspase undergoes self-cleavage and is activated in response to an upstream signal. Currently, a total of 13 caspases have been discovered, and caspases 1, 4, 5, 11, and 12 are related to the pyroptosis signaling pathway [37]. Among them, GSDMD can be cleaved by caspases 1, 4, and 5 in humans and caspase 11 in mice [45]. Some pyroptosis inhibitors based on caspase family members have also been developed. For instance, VX-166 and Emricasan, as caspase inhibitors, show beneficial effects on liver inflammation and fibrosis in NASH mice by decreasing IL-1 β and IL-18 expression and inactivating HSCs [46,47]. Ac-YVAD, a caspase-1 specific inhibitor, could block hepatic steatosis and fibrosis in high-fat-diet-fed mice [48]. Caspase-11 deficiency ameliorates liver inflammation and fibrosis by inducing hepatocyte pyroptosis

in NALFD mice in *in vitro* experiments, but no specific inhibitor of caspase-11 is available [49]. Although these inhibitors have shown good results in experimental models, it remains unclear whether these inhibitors can improve liver inflammation and fibrosis in patients with cirrhosis in clinical treatment.

4.3 Executioner protein GSDM-related therapy

In 2015, GSDMD was confirmed as the executor of pyroptosis [20,50]. The N-terminal of cleaved GSDMD inserts into the plasma membrane of cells and forms stable pores, which enables the release of proinflammatory factors and plays an important role in pyroptosis [13,51]. Butyrate-led inhibition of GSDMD-mediated pyroptosis could ameliorate AFLD [52]. In humans, six genes are related to the GSDM family, namely, *GSDMA*, *GSDMB*, *GSDMC*, *GSDMD*, *GSDME* (also known as *DFNA5*), and *PJVK* (also known as *DFNB59*) [53]. GSDMD cleavage is the most studied process, and GSDMD inhibitor is also currently the most developed inhibitor (Table 1), including disulfiram, LDC7559, Ac-FLTD-CMK, Ac-FEID-CMK, and Ac-FEID-CMK TFA. However, the efficacy of these inhibitors in liver fibrosis/cirrhosis remains to be determined. For example, disulfiram, a dithiocarbamate family member, is widely used in clinical practice as an anti-alcoholic drug, which can inhibit GSDMD expression by covalently modifying cysteine 192 of GSDMD, thereby inhibiting plasma membrane pore formation and pyroptosis [54]. Disulfiram can also inhibit NLRP3 activity and IL-1 β production in the downstream pathway by reducing ROS production [55]. However, despite the multitudes of studies on GSDMD, no studies on small-molecule drugs targeting GSDMD for the treatment of cirrhosis can be retrieved from PubMed.

4.4 Therapeutic effects of natural plant compounds based on pyroptosis

Traditional Chinese medicines are based on the combination of natural plants, animals, or minerals that are characterized by “multicomponent and multitarget” nature, and their effectiveness in treating various liver diseases has been proven. Although the exact single drug target cannot be known because of the complexity of herbal formulations, emerging studies have demonstrated that pyroptosis is an active target of natural medicines for the treatment of fibrosis/cirrhosis (Table 2).

Table 2: Therapeutic effects of natural plant compounds based on pyroptosis in liver fibrosis/cirrhosis

Natural plant compounds	Targets
Jiangzhi Ligan Decoction	GSDMD
Quercetin	PGC-1α/NLRP3 inflammasomes
Mangostin	AMPK/NLRP3
Ursolic acid	NOX2/NLRP3 inflammasomes
Berberine	ROS/TXNIP/NLRP3
Dihydromyricetin	GSDMD
Nobiletin	SIRT1
Naringenin	NF-κB/NLRP3
Cannabidiol	NF-κB/NLRP3
Salidroside	TXNIP/NLRP3
Dieckol	NLRP3 inflammasomes
Antcin A	NLRP3 inflammasome assembly
Oleic acid	Endoplasmic reticulum stress/NLRP3-GSDMD
Taurine	Autophagy
Sestrin2	NLRP3
Peroxisredoxin	NLRP3
Curcumin	JAK2/NLRP3

Jiangzhi Ligan Decoction, a classical Chinese herbal formula, has demonstrated therapeutic effects on high-fat-diet-induced NAFLD and is dependent on the inhibition of the GSDMD-mediated canonical/non-canonical pyroptosis pathway [56] or inflammasome signaling pathway [57].

Quercetin is a dietary phytochemical found in a variety of fruits and vegetables. Owing to its ion chelation and iron stabilization, quercetin has the ability to scavenge ROS and reduce lipid peroxidation [58]. PGC-1α, a key mitochondrial biogenesis regulator, modulates NLRP3 inflammasomes and attenuates pyroptosis in ALD [59]. Quercetin reduced hepatocyte pyroptosis in L02 cells by scavenging mitROS and promoting PGC-1α-mediated mitochondrial dynamics to protect against ethanol-induced hepatocyte pyroptosis. Specifically, quercetin reduces NLRP3 inflammasomes, pro-caspase1/ASC, and GSDMD activation, decreases IL-1β and IL-18 secretion from L02 cells, and alleviates ALD hepatocyte pyroptosis [60].

Mangostin, a naturally occurring carbon glycoside molecule, is abundant in the leaves of the tropical medicinal plant mango. Mangiferin significantly reduces serum triglyceride and free fatty acid levels and improves lipid levels in patients who are overweight and hyperlipidemic [61]. Adenosine monophosphate-activated protein kinase (AMPK) is a key regulatory enzyme of hepatic tissue cell energy homeostasis, which is related to hepatocyte glucolipid metabolism and is a potential target for NAFLD therapy. Mangiferin activates AMPK and significantly downregulates NLRP3, caspase-1, and IL-1β expression and inhibits NLRP3 inflammasome activation-mediated GSDMD cleavage and pyroptosis.

Ursolic acid is a natural triterpene that can be extracted from a variety of plants and has a variety of biological functions, such as antioxidant, anti-inflammatory, hepatoprotective, and immunomodulatory [62]. Ursolic acid inhibits KC pyroptosis in liver fibrosis *in vitro* and *in vivo* by suppressing the protein expression of pyroptosis-related indicators (NLRP3, pro-caspase-1, cleaved caspase-1, GSDMD, GSDMD-N, and IL-1β) in the NOX2/NLRP3 inflammasome signaling pathway [34].

Berberine is an isoquinoline alkaloid derived from certain herbs, including yellow lily, and is used for treating diarrhea and intestinal infections [63]. Berberine improves mitochondrial function, attenuates oxidative stress, lowers serum cholesterol levels, and shows strong beneficial effects on NAFLD [64]. Berberine inhibits NLRP3 inflammasome activation and downstream signaling factor expression via the ROS/TXNIP pathway or NF-κB signaling pathway, ultimately inhibiting hepatocyte pyroptosis and attenuating NAFLD and liver fibrosis [64].

Dihydromyricetin is the most abundant natural flavonoid in vine grapes and demonstrates various pharmacological effects [65]. Dihydromyricetin inhibits CCl4-induced pyroptosis by reducing GSDMD and IL-18 levels [66].

Nobiletin, a herb thought to have antioxidant and anti-tumor properties, is a polymethoxyflavonoid present in citrus peel. Nobiletin inhibited NLRP3 inflammasome activation and the expression of its downstream pathway factors by increasing the expression of SIRT1 and effectively protects AML-12 cells from palmitic acid-induced steatotoxicity [67].

Naringenin is a flavonoid with antioxidant, antifibrotic, anti-inflammatory, and anticancer properties and could prevent liver damage caused by different drugs. Naringenin attenuates NAFLD by reducing the expression levels of NF-κB, NLRP3, IL-1β, and IL-18 in the NF-κB/NLRP3 pathway [68].

Cannabidiol is a nonpsychotropic cannabis-derived compound with a wide range of pharmacological properties, including cardioprotective, antioxidant, and anti-inflammatory abilities [69]. Cannabidiol can attenuate NAFLD and NASH by inhibiting the expression of various factors in the NF-κB/NLRP3 pathway [70,71].

Salidroside, a phenylpropanoid glycoside compound, is the main active ingredient of *Rhodiola rosea*, which grows at high altitudes and has various positive biological activities [72]. Treatment with salidroside improves dyslipidemia and inhibits hepatic lipid deposition and attenuates NAFLD by modulating oxidative stress and inhibiting the TXNIP/NLRP3 pathway [73].

Dieckol is a natural phenolic compound found in kelp. It can decrease the expression of NLRP3, ASC, caspase-1, GSDMD, and cleaved GSDMD to improve NAFLD *in vivo* [74].

Antcin A is a steroidal phytochemical and has potent anti-inflammatory and anti-tumor effects. It can bind to NLRP3 and then inhibit NLRP3 inflammasome assembly and activation, suppressing the inflammatory response in mouse liver tissues and reducing lipid deposition and inflammatory factor levels [75].

Oleic acid is a typical monounsaturated fatty acid and is the predominant component in olive oil (70–80%). It inhibits NLRP3/GSDMD expression by suppressing palmitic acid-induced endoplasmic reticulum (ER) stress, ultimately inhibiting HepG2 cell pyroptosis and reducing hepatic lipotoxicity in NASH rats [76].

Taurine is a sulfur-containing beta-amino acid found in free cells in many tissues of humans and animals. Taurine inhibits arsenic-induced inflammation and pyroptosis through the autophagic-CTSB-NLRP3 inflammasomal pathway, ultimately alleviating NASH [77].

Sestrin is a highly conserved family consisting of Sestrin1, Sestrin2, and Sestrin3 in mammals. Sestrin2 deficiency promotes liver ER stress during cholestasis and exacerbates cholestasis-induced liver fibrosis [78]. Cholestasis-induced Sestrin2 attenuates ER stress via the AMPK/mammalian target of rapamycin complex 1 (mTORC1)-dependent pathway. In cholestatic liver injury, Sestrin2 inhibits NLRP3 activation to suppress pyroptosis, benefiting patients [79].

Peroxisiredoxin is a family of thiol peroxidases that scavenge peroxides from cells. Among the six mammalian peroxiredoxins, peroxiredoxin 3 is specifically localized in the mitochondria. Peroxiredoxin 3 eliminates large amounts of hydrogen peroxide and is a major target of peroxynitrite in the mitochondria. Notably, peroxiredoxin 3 could reduce hepatotoxicity through inhibiting the NLRP3 inflammasome signaling pathway by targeting mitochondrial ROS to inhibit pyroptosis [80].

Curcumin, a diketone compound, belongs to polyphenol and is isolated from *Curcuma longa*. Cui *et al.* demonstrated that curcumin could mitigate liver fibrosis in ducks through inhibiting JAK2/NLRP3-mediated pyroptosis [81].

4.5 Biomaterials inhibit liver cirrhosis based on pyroptosis

With the development of science and technology, bioengineering materials have played an irreplaceable role in the medical field. In recent years, the application of biomaterials in liver fibrosis based on the pyroptosis pathway has been gradually discovered.

Stem cells (SCs) have the capacity for self-renewal, multispectral differentiation, and immunomodulation [82]. SC replacement therapy has broad application prospects in liver cirrhosis. For example, SCs from human exfoliated deciduous teeth (SHEDs) have angiogenic differentiation and proliferative potential and are resistant to apoptosis. SHEDs were found to attenuate liver fibrosis by differentiating into hepatocyte-like cells *in vivo*, and SHED-derived hepatocyte transplantation mitigates liver fibrosis [83]. Importantly, SHEDs improve liver cirrhosis by inhibiting the pyroptosis pathway through the suppression of NLRP3 inflammasome-activated GSDMD [83]. Human umbilical cord mesenchymal SCs improve acute liver failure by suppressing inflammation, pyroptosis, and apoptosis [84]. Mesenchymal SCs have also been reported to have possible therapeutic potential in cirrhosis through pyroptosis [85]. However, stem cell therapy for cirrhosis has certain limitations. Currently, there are no unified standards to determine which type of SCs to use, the optimal cell dosage, and the delivery route [86]. Furthermore, the long-term effects and potential side effects of SC therapy require more clinical research for validation. These challenges limit the widespread application of SC therapy in the treatment of liver cirrhosis.

Exosomes, vesicles measuring 30–150 nm in diameter, are secreted by cells and contain functional nucleic acids, proteins, lipids, and cytokines. They have emerged as a promising advanced cell-free therapy in various diseases such as fibrosis/cirrhosis [87]. For instance, exosomes derived from bone marrow mesenchymal SCs mitigate liver fibrosis in cirrhosis rat models by inhibiting PCNA/NLRP3/caspase 1/GSDMD-mediated pyroptosis [88]. Milk-derived exosomes encapsulated with forsythiaside A specifically targeting CD44 could attenuate liver fibrosis by NLRP3-mediated pyroptosis [89]. These studies have indicated that pyroptosis-based exosomes are effective in cells and animals; therefore, they have great potential in the treatment of liver fibrosis. Although exosomes show some potential in the treatment of cirrhosis, there are still some limitations [90,91]. First, the distribution and duration of action of exosomes within the body are still not clear, which limits their clinical application. Second, the technical challenges associated with the production, purification, and large-scale application of exosomes are major barriers to their clinical use. Finally, the safety and long-term effects of exosome therapy require further validation through more clinical research. Furthermore, research on exosome-based nanomaterials for the treatment of liver fibrosis is still in the preclinical trial stage. Before clinical application, rational nanomaterials must be designed, and

their hepatotoxicity, pharmacokinetics, and targeted metabolic pathways evaluated systematically.

4.6 Clinical therapy in liver cirrhosis

In clinical practice, drug development is an arduous process, in which solid preclinical biology and pharmacology of drugs are important factors for clinical success [92]. Liu et al. discovered that Yaq-001 could significantly reduce liver injury in acute-on-chronic liver failure animals, and Yaq-001 has met the safety and tolerability criteria in clinical trials, providing theoretical evidence for the clinical transformation of Yaq-001 in patients with cirrhosis [93]. The treatment of liver cirrhosis involves the administration of various medications, including antiviral, liver-protecting, and antibacterial drugs, and cell therapy [94–96]. Wong et al. found that entecavir reduced the risk of hepatic events and death in patients with chronic hepatitis B and liver cirrhosis [97]. Zeng et al. reported that low-dose rifaximin reduced complications and boosted survival in patients with decompensated liver cirrhosis [98]. Brennan et al. confirmed the safety and potential efficacy of autologous macrophage therapy in the treatment of liver cirrhosis through a Phase II randomized controlled trial [99]. Rinella et al. conducted a randomized trial in patients with NASH and compensated cirrhosis, showing that 3 mg of aldafermin significantly reduced enhanced liver fibrosis scores [100]. Currently, research on the clinical application of pyroptosis in liver cirrhosis is still in the developmental stage; however, existing studies have provided important scientific evidence for a deeper understanding of the pathological mechanisms of liver cirrhosis and the development of new treatment methods. With more studies on the mechanisms of pyroptosis, more drugs targeting this pathway may be clinically applied in the future.

4.7 Limitations and challenges in the clinical application of pyroptosis-related therapies

Pyroptosis-related therapies face a series of limitations and challenges in clinical applications. First, these therapies have difficulty in specificity. How to precisely target the pyroptosis pathway without affecting other cellular processes is an urgent issue to be resolved. Additionally, modulating pyroptosis may interfere with the immune system, leading to immunosuppression and increased risk of

infection. Drug delivery is also a challenge. Ensuring that the therapeutic agent effectively reaches the site of disease and achieves an effective concentration is crucial for the therapeutic outcome. Finally, the complexity of diseases means that a single therapy targeting pyroptosis may not comprehensively cover the multifactorial mechanisms of the disease.

5 Prospectives

Undoubtedly, pyroptosis plays an important role in liver fibrosis and even cirrhosis; thus, therapy targeting the pyroptosis signaling pathway has promising therapeutic prospects. However, clinical research on small-molecule drug inhibitors or natural plant compounds or nanocarriers for pyroptosis is limited. Therefore, more in-depth basic research and clinical trials are urgently needed. In addition, the molecular mechanisms of pyroptosis mediated by natural plant compounds in liver cirrhosis still have a broad scope for research, and certain molecular mechanisms of pyroptosis may be unrecognized. Finally, to advance the progress of clinical trials, liver organoid simulation of cirrhosis requires in-depth investigation as a pathological model that can maximally recapitulate the pathological and molecular changes of cirrhosis in humans. Specifically, organoid libraries may provide a reliable technology for screening drugs for the pyroptosis-based treatment of cirrhosis.

6 Conclusions

As an inflammatory programmed death mode, increasing evidence suggests the important role of pyroptosis in liver fibrosis/cirrhosis; however, there are still some issues that need to be urgently addressed, such as how to continuously improve and translate the basic research on pyroptosis and cirrhosis into clinical practice. This study summarizes approaches that mitigate liver fibrosis/cirrhosis through the anti-pyroptosis pathway, including inhibitors targeting NLRP3, GSDMD, and caspases in the pyroptosis pathway, natural plant compounds and biomaterials (SCs and exosomes). These approaches can be effectively targeted to inhibit the pyroptosis pathway in cellular and animal models; however, the specific mechanisms and value in clinical applications must be further investigated. This study provides a reference and a drug list to understand the treatment of liver fibrosis/cirrhosis from a pyroptosis perspective.

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