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Review article

Exploring the potential of treating chronic liver disease targeting the PI3K/Akt pathway and polarization mechanism of macrophages

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ABSTRACT

Chronic liver disease is a significant public health issue that can lead to considerable morbidity and mortality, imposing an enormous burden on healthcare resources. Understanding the mechanisms underlying chronic liver disease pathogenesis and developing effective treatment strategies are urgently needed. In this regard, the activation of liver resident macrophages, namely Kupffer cells, plays a vital role in liver inflammation and fibrosis. Macrophages display remarkable plasticity and can polarize into different phenotypes according to diverse microenvironmental stimuli. The polarization of macrophages into M1 pro-inflammatory or M2 anti-inflammatory phenotypes is regulated by complex signaling pathways such as the PI3K/Akt pathway. This review focuses on investigating the potential of using plant chemicals targeting the PI3K/Akt pathway for treating chronic liver disease while elucidating the polarization mechanism of macrophages under different microenvironments. Studies have demonstrated that inhibiting M1-type macrophage polarization or promoting M2-type polarization can effectively combat chronic liver diseases such as alcoholic liver disease, non-alcoholic fatty liver disease, and liver fibrosis. The PI3K/Akt pathway acts as a pivotal modulator of macrophage survival, migration, proliferation, and their responses to metabolism and inflammatory signals. Activating the PI3K/Akt pathway induces anti-inflammatory cytokine expression, resulting in the promotion of M2-like phenotype to facilitate tissue repair and resolution of inflammation. Conversely, inhibiting PI3K/Akt signaling could enhance the M1-like phenotype, which exacerbates liver damage. Targeting the PI3K/Akt pathway has tremendous potential as a therapeutic strategy for regulating macrophage polarization and activity to treat chronic liver diseases with plant chemicals, providing new avenues for liver disease treatment.

1. Introduction

Chronic liver disease (CLD), which includes chronic viral hepatitis, alcoholic liver disease, nonalcoholic steatohepatitis, cirrhosis, liver cancer, and other conditions, is a major global health issue [1]. More than 1.5 billion people globally suffer from CLD, which

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results in approximately 2 million deaths each year: 1 million from complications of cirrhosis and 1 million from viral hepatitis and hepatocellular carcinoma (HCC) [2,3]. There are multiple causes of CLD, with the primary causes being chronic hepatitis B virus, chronic hepatitis C virus, non-alcoholic fatty liver disease, and alcoholic liver disease. The most common reasons are viral hepatitis and non-alcoholic fatty liver disease [4]. In the past 20 years, the incidence rate of CLD has increased rapidly, not only becoming one of the main causes of premature death but also a global health concern [5]. The Global Burden of Liver Disease report in 2023 indicates that every 25 deaths globally involves one related to liver disease. As the 11th leading cause of death, liver disease disproportionately impacts the 25–49 age group, which represents the segment with the most potential workforce productivity. In 2020, 1.1 million people died from diseases related to hepatitis B and C, yet there are minimal resources globally to control and eliminate viral hepatitis [6]. HCC has a high mortality rate, being the fourth leading cause of cancer-associated deaths. Cirrhosis is an important risk factor for HCC, representing the 15th leading life years lost due to disability worldwide. Furthermore, patients with cirrhosis require enormous healthcare costs [6,7]. Compared to other chronic diseases, most CLDs can be prevented, treated, and/or cured if diagnosed early [8]. Thus, understanding the mechanisms underlying CLD pathogenesis and developing effective treatment strategies are urgently needed. Macrophages are the first line of defense against infections [9]. Under physiological conditions, they are present in almost all tissues and play a crucial role in immunity, repair, and maintenance of tissue homeostasis [10]. Depending on their location in the body, macrophages have different names, such as alveolar macrophages, kupffer cells (KCs) in the liver, microglia in the central nervous system, etc. [11,12]. Liver macrophages include both resident KCs and recruited macrophages derived from monocytes. KCs are the largest population of macrophages residing around the sinusoids of the liver, with high phagocytic activity and functions in clearing apoptotic cells and particulate matter in the portal circulation and microbes. Studies have shown that liver macrophages play an important role in maintaining liver homeostasis and are closely associated with various CLDs [13,14]. The phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway is one of the most important intracellular signaling pathways [15]. It plays a crucial role in regulating macrophage survival, migration, proliferation, and orchestrating responses to various metabolic and inflammatory signals [16]. The PI3K/Akt pathway is also a focus of research for many diseases, including renal cell carcinoma [17], metastatic prostate cancer [18], metastatic urothelial carcinoma [19], and others. In this review, we summarize the interplay between macrophage polarization, the PI3K/Akt signaling pathway, and CLDs, as well as potential therapies for CLD by controlling macrophage polarization through the PI3K/Akt pathway.

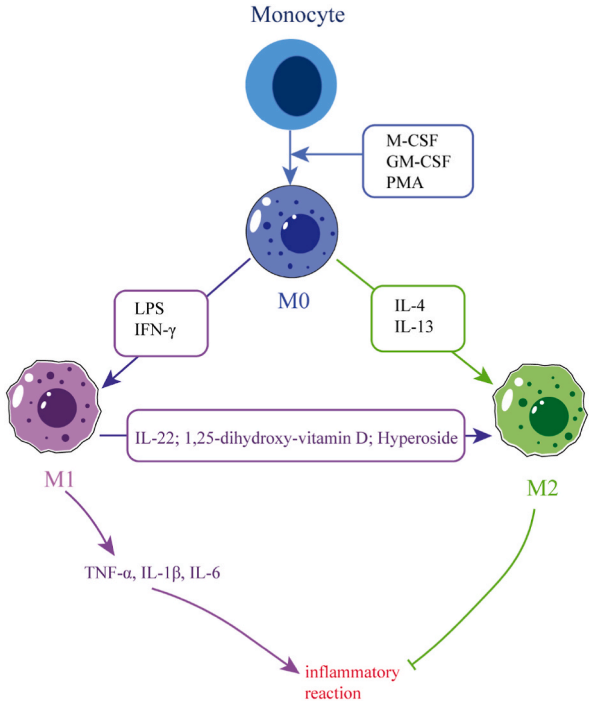

Fig. 1. Macrophage polarization. This figure illustrates the process of macrophage polarization. Monocytes mature into macrophages under certain stimulation, which can be further differentiated into M1 or M2 types based on the changes in the microenvironment. M1 macrophages secrete pro-inflammatory cytokines and promote inflammatory responses, whereas M2 macrophages have the opposite effect. Additionally, M1 macrophages can also be polarized into M2 macrophages under certain factors.→ indicates promotion, and ⊣ indicates inhibition. The abbreviations used in the figure are: GM-CSF (Granulocyte-macrophage Colony Stimulating Factor), IFNγ (Interferon-γ), LPS (Lipopolysaccharide), TNF-α (Tumor Necrosis Factor-α), M-CSF (Macrophage colony-stimulating factor), IL-1β (interleukin-1β), PAM (phorbol ester), IL-4 (Interleukin-4), IL-22 (Interleukin-22), and IL-13 (Interleukin-13).

2. Macrophage polarization in chronic liver disease

2.1. Macrophage polarization

Macrophage polarization refers to the activation of macrophages under the stimulation of pathogenic microorganisms, inflammatory reactions, cytokines or some physical and chemical factors. Macrophages differentiate into different phenotypes based on the prevailing conditions and changes in the microenvironment (as shown in Fig. 1). These differentiated macrophages possess unique properties that enable them to effectively combat pathogens or repair damage caused by inflammation [20]. There are three ways to control macrophage polarization. The first way involves using epigenetics and cell survival mechanisms to prolong or shorten the time for macrophage development and survival. The second way is by manipulating the normal tissue microenvironment. Finally, the third way is by being influenced by exogenous factors, such as cytokine release due to inflammation [21,22]. Macrophages possess a high degree of plasticity and can be polarized into two main phenotypes, namely classically activated (M1) and alternatively activated (M2) macrophages [23]. M1 polarization is characterized by the promotion of inflammatory responses. This type of polarization is driven by factors such as granulocyte-macrophage colony-stimulating factor, lipopolysaccharide (LPS), or other pathogen-associated molecular patterns [24]. The secretion of cytokines such as interleukin-1β(IL-1β), tumor necrosis factor-a (TNF-a), and interleukin-12 (IL-12) by M1 macrophages boosts pro-inflammatory T helper type 1 (Th1) responses. Furthermore, chemokines such as CXC chemokine ligand 9 (CXCL9) and CXC chemokine ligand 10 (CXCL10) are secreted by these macrophages to enhance the recruitment of Th1 cells to inflammatory sites [25]. Interleukin-4 (IL-4) and interleukin-13 (IL-13) can activate M2 macrophages [26]. These types of macrophages are involved in anti-inflammation, immune regulation, tissue remodeling, parasitic infection prevention, and participate in processes such as angiogenesis, immune regulation, and tumorigenesis [27]. M2 macrophages produce anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). Based on various activation stimuli, M2 macrophages can be further subdivided into M2a, M2b, and M2c subtypes. The most immunosuppressive of these subsets is M2c [28,29]. M2-polarized macrophages typically emerge after M1 polarization as a means to restore homeostasis when an infection or inflammation is severe enough to affect an organ. Such macrophages function to counterbalance the inflammatory response and promote tissue repair [30].

2.2. Macrophage polarization and chronic liver disease

Alcoholic liver disease (ALD) is a leading cause of CLD worldwide, responsible for 0.9% of all deaths globally [31,32]. It occurs due to prolonged and excessive alcohol consumption and is characterized by the activation of KCs and recruitment of inflammatory monocytes/macrophages [33,34]. KCs in ALD patients exhibit increased levels of reticulon 4B (Nogo-B), which correlates with disease severity. Nogo-B has been found to promote M1 polarization of KCs in ethanol-fed mice and inhibit M2 polarization, thereby aggravating liver injury in human and mouse ALD [35]. Similarly, inhibiting M1 polarization while promoting M2 polarization could be a potential therapeutic strategy for ALD. For instance, studies have found that inulin can reduce the inflammatory response of ALD in female C57BL/6j mice by inhibiting M1 macrophage polarization while activating M2 macrophages via the production of short-chain fatty acids [36,37]. Through this intervention, the proportion of liver M1 macrophages was reduced, and that of M2 macrophages was increased, ultimately leading to a reduction in inflammation in mice with ALD.

Nonalcoholic steatohepatitis (NASH) is commonly defined as the advanced stage of nonalcoholic fatty liver disease (NAFLD), characterized by the accumulation of fat, inflammation, and progressive fibrosis in the liver [38,39]. NASH often lacks apparent clinical symptoms in the early stages. However, if left untreated, it can progress to cirrhosis, end-stage liver disease, or require liver transplantation over time [40]. Studies have revealed that the overexpression of M1 markers in the liver is associated with increased inflammation in methionine-choline-deficient (MCD)-induced NASH C57BL/6 mice [41]. Therefore, targeting the inhibition of M1 macrophage polarization might represent an effective approach for treating NASH. In wild-type mice, growth hormone secretagogue receptor 1a (GHSR1a) was detected in KCs. Ghrelin, a 28-amino acid gastric hormone, has been found to inhibit M1 polarization of KCs mediated by GHSR1a and subsequently block the progression of lipopolysaccharide-induced NASH [42]. Furthermore, inhibiting M1 macrophage polarization or activating M2 macrophage polarization can both be beneficial for treating NASH. Tong et al. demonstrated that curcumin can inhibit the activation of M1 macrophages both in vitro and in vivo, reduce the expression of IL-1β and TNF-α, thus reducing liver damage and inflammatory response in NASH [43]. Similarly, honokiol (HNK) reduced the expression of M1 marker genes (such as TNFα and monocyte chemoattractant protein-1 (MCP-1) and increased the expression of M2 marker genes (such as IL-10 and IL-13) in the livers of mice fed with a high cholesterol and high-fat (CL) diet. HNK alleviates CL diet-induced NASH by activating peroxisome proliferator-activated receptor γ (PPARγ) to regulate macrophage polarization towards the M2 phenotype. Moreover, it was observed that treatment with 10 μM HNK induced M2 macrophage polarization in mouse peritoneal cells, RAW264.7 cells, and ANA-1 cells [44].

Hepatic fibrosis is an excessive healing response to prolonged liver injury in CLD. The progressive accumulation of fibrotic tissue can lead to cirrhosis, which can further develop into HCC in severe cases and even result in liver failure in some patients with liver fibrosis. Hepatic macrophages have been found to play a crucial role in initiating inflammatory responses to liver injury, promoting fibrosis progression, and the formation of fibrosis [45]. Su et al. discovered that the level of interleukin-22 (IL-22) was positively correlated with the number of M2-KCs during liver fibrosis development. IL-22 can regulate the signal transducer and activator of transcription 3 (STAT3)/extracellular signal-regulated kinase (Erk)/Akt pathways to increase the ratio of M2/M1 KCs, thus slowing down the progression of liver fibrosis [46]. Similarly, inhibiting M1 macrophage polarization can also play a role in the treatment of liver fibrosis. Xu et al. found that Yiguanjian (YGJ) has an anti-hepatic fibrosis effect. In rats with liver fibrosis induced by 2-acetylaminofluorene (2-AAF)/carbon tetrachloride (CCl4) and RAW264.7 cells, YGJ treatment significantly decreased the expression levels of

signal transducer and activator of transcription 1 (STAT1), interferon regulatory factor 3 (IRF3), interferon regulatory factor 5 (IRF5), and suppressor of cytokine signaling 3 (SOCS3) in M1 macrophages [47].

Liver cirrhosis is a chronic disease caused by liver inflammation and fibrosis. It has been revealed that advanced fibrosis and even cirrhosis can be reversed by treating the underlying cause, with a liver biopsy being the gold standard for diagnosing cirrhosis [48]. Liver cirrhosis is closely related to KCs polarization. Zhang et al. discovered that angiopoietin-like 4 (ANGPTL4), an important regulator of KCs, can regulate KCs polarization and hepatic stellate cell activation, thereby reducing hepatitis B virus-induced cirrhosis in mice. The mechanism may be related to the activation of Toll-like receptor 4 (TLR4)/nuclear factor kappaB (NF-κB) signaling pathway [49]. Relevant studies have found that inhibiting M1 macrophages and promoting M2 macrophages can also play a role in the treatment of cirrhosis. YGJ can improve the therapeutic effect of fetal liver stem/progenitor cells (FLSPCs) on 2-AAF/CCl4-induced liver cirrhosis in rats by regulating macrophage activation (significantly reducing TNF-α and CD68 expression levels, while significantly increasing CD163 expression levels). Moreover, the results of in vitro experiments were consistent with those of in vivo experiments [50].

HCC is the most common primary liver cancer and is considered to be the leading cause of death in patients with cirrhosis [51]. Studies have discovered that M2 KCs polarization is the primary cause of HCC in Akt (myr-Akt) and NRas (NRas-V12) oncogenes (Akt/Ras) mice. This phenotype can be recapitulated in vivo by hydrodynamically transfecting activated forms of Akt/Ras into the mouse liver. MicroRNA-206 drives the M1 polarization of KCs, which promotes the recruitment of $CD8^+$ T cells and prevents HCC [52]. Furthermore, HCC has been found to be closely associated with both M1 and M2 macrophages [53,54]. Lu et al. discovered that cantharidin (NCTD) may play an anti-HCC role by regulating macrophage polarization through miR-214. The addition of NCTD-treated RAW264.7 or tumor-associated macrophages (TAMs) enhanced M1 polarization by increasing microRNA-214 (miR-214) expression [55]. Min et al. found that astragaloside IV (AS-IV) reduced the expression of macrophage markers CD206, CD209 and TGF-β. AS-IV may inhibit macrophage M2 polarization through the TLR4/NF-κB/STAT3 signaling pathway and inhibit the proliferation, invasion, and migration of HCC [59]. The above passage illustrates that CLD is closely related to macrophage polarization. Table 1 summarizes the therapeutic effects of traditional Chinese medicine targeting macrophage polarization in the treatment of CLD.

Table 1
Overview of Chinese medicine targeting macrophage polarization in chronic liver disease.

Disease	Chinese medicine and active ingredients	In vitro/in vivo	Mechanisms	M1	M2	Reference
Alcoholic liver disease	Inulin	In vitro and in vivo	Single-chain fatty acids↑	↓	↑	[37]
	Cannabinoid CB2 Receptors	In vitro and in vivo	HO-1↑	↓	↑	[36]
Nonalcoholic steatohepatitis	Honokiol	In vivo	PPAR γ↑	-	↑	[44]
	Nobiletin	In vitro and in vivo	KLF4↑	↓	↑	[56]
	Jiangzhi Granule	In vivo	TNF/NFκB signaling↓	↓	–	[57]
	Myricetin	In vitro and in vivo	TREM-1-TLR2/4-MyD88 signaling molecules↓	↓	↑	[58]
	Curcumin	In vitro and in vivo	IL-1βand TNF-α↓	↓	–	[43]
Non-alcoholic fatty liver disease	artemether	In vitro and in vivo	TGF-β/SMAD pathway↓	–	↑	[60]
	Hyperoside	In vivo	Nr4A1↑	–	↑	[61]
	DWJ504	In vivo	TLR4↓	↓	↑	[62]
Liver fibrosis	Yiguanjian decoction	In vivo	Non-canonical Wnt signaling pathway↓	↓	-	[47]
	Resveratrol	In vitro and in vivo	IL-10↑	↓	↑	[63]
	Curcumin	In vitro	ERK1/2 and p38 pathways↑	↓	–	[64]
Liver cirrhosis	Yiguanjian decoction	In vitro and in vivo	Fetal liver stem/progenitor cell↑	↓	↑	[50]
Hepatocellular carcinoma	Cantharidin	In vitro and in vivo	miR - 214↑	↑	-	[55]
	Astragaloside IV	In vitro	TLR4/NF-κB/STAT3 signaling pathway↓	-	↓	[59]
	Astragalus polysacharin	In vitro	–	↑	↓	[65]
	Ganoderma lucidum polysaccharid	In vitro	MAPK/NF-κB signaling pathway↑	↑	–	[66]
	Emodin	In vitro and in vivo	miR-26/TGF-β1/Akt axis↑ insulin-like growth factor-1 secretion↓	↓	↑	[67]

Abbreviation: HO-1, Heme oxygenase-1; PPARγ, peroxisome proliferator-activated receptor γ; KLF4, Kruppel like factor 4; TNF/NFκB, tumor necrosis factor/nuclear factor kappa-B; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β; DWJ504, extract of Opuntia ficus indica seed; Nr4A1, the orphan nuclear hormone receptor nuclear receptor subfamily 4, group a, member 1; TLR4, Toll-like Receptor 4; IL-10, interleukin-10; ERK1/2, extracellular signal-regulated kinases 1/2; STAT3, signal transducer and activator of transcription3; MAPK, mitogen activated protein kinase; TGF-β, transforming growth factor-β1; Akt, protein kinase B.
The symbol ↑ represents an increase, while the symbol ↓ represents a decrease.

3. PI3K/Akt signaling pathway in chronic liver disease

3.1. PI3K/Akt signaling pathway

The PI3K/Akt pathway is a crucial signaling pathway that controls cellular processes such as cell division, autophagy, survival and differentiation [68]. Recent research has identified the role of this pathway in regulating macrophage survival, migration, proliferation and response to various metabolic and inflammatory signals [16]. The primary proteins involved in the PI3K/Akt pathway are phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) [15]. Based on their primary structure, regulation and lipid substrate specificity, the PI3K family is divided into three categories: class I, class II and class III. Class I includes two subgroups, IA and IB, which are coupled to different receptors. Class II catalyzes the conversion of PI to PI(3)P and PI(3,4)P2 while class III is composed of a regulatory and catalytic subunit heterodimer [69]. Akt is the primary downstream target of PI3K and belongs to the AGC kinase family of serine/threonine kinases that regulate cell cycle, transcription, translation, apoptosis, and differentiation. There are three subtypes of Akt: Akt1, Akt2, and Akt3. Akt1 is present in all tissues and regulates multiple cellular processes, Akt2 is mostly found in muscle tissue and adipocytes, and Akt3 is mostly found in the brain [68,70]. Activation of receptor tyrosine kinases and growth factors initiates the formation of heterodimers of class Ia lipid kinases composed of catalytic and regulatory subunits, which generate transient lipid second messengers PIP2 and PIP3. The latter activates T308 and S473 residues of Akt. T308 phosphorylation is both necessary and sufficient for inducing Akt signaling, while S473 phosphorylation is required for maximum kinase activation. However, phosphatase and tensin homolog (PTEN) normally quickly metabolizes PIP3 by removing the 30-phosphate from it, terminating PI3K signaling [16,71]. There are two main mechanisms that inhibit the PI3K/Akt pathway. Firstly, PTEN converts PI (3,4,5) P3 to phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2), thus removing it from the pathway. Secondly, Akt inactivation is primarily accomplished by the PH domain leucine-rich repeat protein phosphatase (PHLPP) family, which inhibits Akt signaling by directly dephosphorylating Akt [72].

The PI3K/Akt pathway is activated by TLR4 and other pathogen recognition receptors, cytokines and chemokines, and Fc receptors to regulate downstream signals that control cytokine production [73–75]. IL-1 receptor-associated kinase M (IRAK-M) is a negative regulator of Toll-like receptor (TLR) signaling and plays a crucial role in maintaining the homeostasis of innate immunity [76]. It has been discovered that the PI3K/Akt1 axis up-regulates IRAK-M and suppresses TLR4 signaling by deactivating tumor necrosis factor receptor-associated factor 6 (TRAF6) [16]. Insulin-like growth factor binding protein-related protein 1 (IGFBP-rP1) has been found to inhibit the M2 polarization of TAMs through the PI3K/Akt pathway, reversing the process of endometrial carcinoma (EC) cells inducing naive macrophages (M0) to differentiate into M2 macrophages [77]. Conversely, Zhang et al. found that alpha-fetoprotein (AFP) promotes the polarization of macrophages to M2 macrophages and inhibits the phagocytosis of M1 macrophages to liver cancer cells, possibly by activating the PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway [78]. However, a single PI3K and Akt subtype can also cause M1 or M2 macrophage polarization. Inhibition of PI3K enhances NF-κB activation and inducible nitric oxide synthase (iNOS) synthesis, promoting M1 macrophage polarization. Inhibition of PI3K negative regulators leads to decreased secretion of pro-inflammatory cytokines in macrophages, inducing the synthesis of M2 macrophage surface markers and changing macrophage phenotype to M2 type [16]. Additionally, studies have shown that Akt1 and Akt2 have different effects on macrophage polarization. The absence of Akt1 promotes M2 macrophage polarization, while the absence of Akt2 promotes M1 macrophage polarization [71].

3.2. PI3K/Akt signaling pathway and chronic liver disease

An increasing number of studies have found that the PI3K/Akt signaling pathway is closely related to CLD, such as ALD, liver fibrosis, HCC, and more [79,80]. Therefore, targeting the PI3K/Akt pathway may be an effective way to treat CLD. Wu et al. showed that quercetin could reduce liver fibrosis in bile duct ligation or CCl4 mice by inhibiting autophagy through the transforming growth factor-β1 (TGF-β1)/Smads signaling pathway and activating the PI3K/Akt signaling pathway, regulating matrix metalloproteinase (MMPs)-9 and tissue inhibitor of metalloproteinase (TIMP)-1, and preventing liver fibrosis [81]. Similarly, dihydroartemisinin has been found to prevent liver fibrosis in bile duct ligated rats by inhibiting the PI3K/Akt pathway, inducing caspase-related mitochondrial apoptosis in hepatic stellate cells (HSCs), and giving cytotoxic effects [82]. Additionally, dihydroartemisinin has also demonstrated potential in treating ALD and inhibiting the activation of endoplasmic reticulum stress-c-Jun N -terminal binase (JNK)/C/EBP homologous protein (CHOP)–mitochondrial cascade in ethanol-treated hepatocytes, showing promise for reducing hepatocyte lipid apoptosis by regulating the PI3K/Akt pathway [83]. In terms of treating HCC, targeting the PI3K/Akt pathway has demonstrated effectiveness. Sun et al. found that the matrine derivative WM622 (a matrine derivatives named WM622) exhibited anti-proliferative properties by inducing apoptosis and G0/G1 phase cell cycle arrest in vitro and inhibiting tumor growth in vivo via the PI3K/Akt pathway [84]. Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease with an unknown cause. It has been discovered that cellular communication network factor 1 (CCN1) can induce the production of interleukin 6 (IL-6) through the a6b1/PI3K/Akt/NF-κB pathway, leading to an increased inflammatory response in autoimmune hepatitis [85]. Consequently, inhibiting this pathway may prevent further development of AIH. In animal experiments, Wang et al. discovered that celastrol significantly reduced AIH by inhibiting the PI3K/Akt pathway [86]. Similarly, scoparone has also been found to inhibit the activation of PI3K/Akt/mTOR pathway in mice with nonalcoholic steatohepatitis, improving liver inflammation and autophagy. Furthermore, it enhances autophagic flux and regulates autophagy by inhibiting reactive oxygen species (ROS)/P38/nuclear factor erythroid-2 related factor 2 (Nrf2) axis and PI3K/Akt/mTOR pathway in LPS-induced macrophages, thereby inhibiting inflammatory response [87]. Therefore, modulation of the PI3K/Akt signaling pathway could potentially serve as an effective therapeutic strategy for the

management of chronic liver disease (CLD) [88–91] (Fig. 2).

4. PI3K/Akt signaling pathway regulates macrophage polarization in chronic liver disease

Recent studies have shown that the PI3K/Akt pathway also plays a crucial role in innate immunity and macrophage activation [92, 93]. Fibrosis-induced M1 and M2 macrophage markers increased, indicating that both M1 and M2 macrophages were triggered by CCl4 treatment. Conversely, regression of hepatic fibrosis led to a decrease in M1 and M2 hepatic macrophages. These findings further demonstrate the significant impact of activated hepatic macrophages on hepatic fibrosis development and recovery [94,95]. PTEN, the primary negative regulator of the PI3K/Akt pathway, is an upstream regulator of hepatic macrophage polarization and function. PTEN

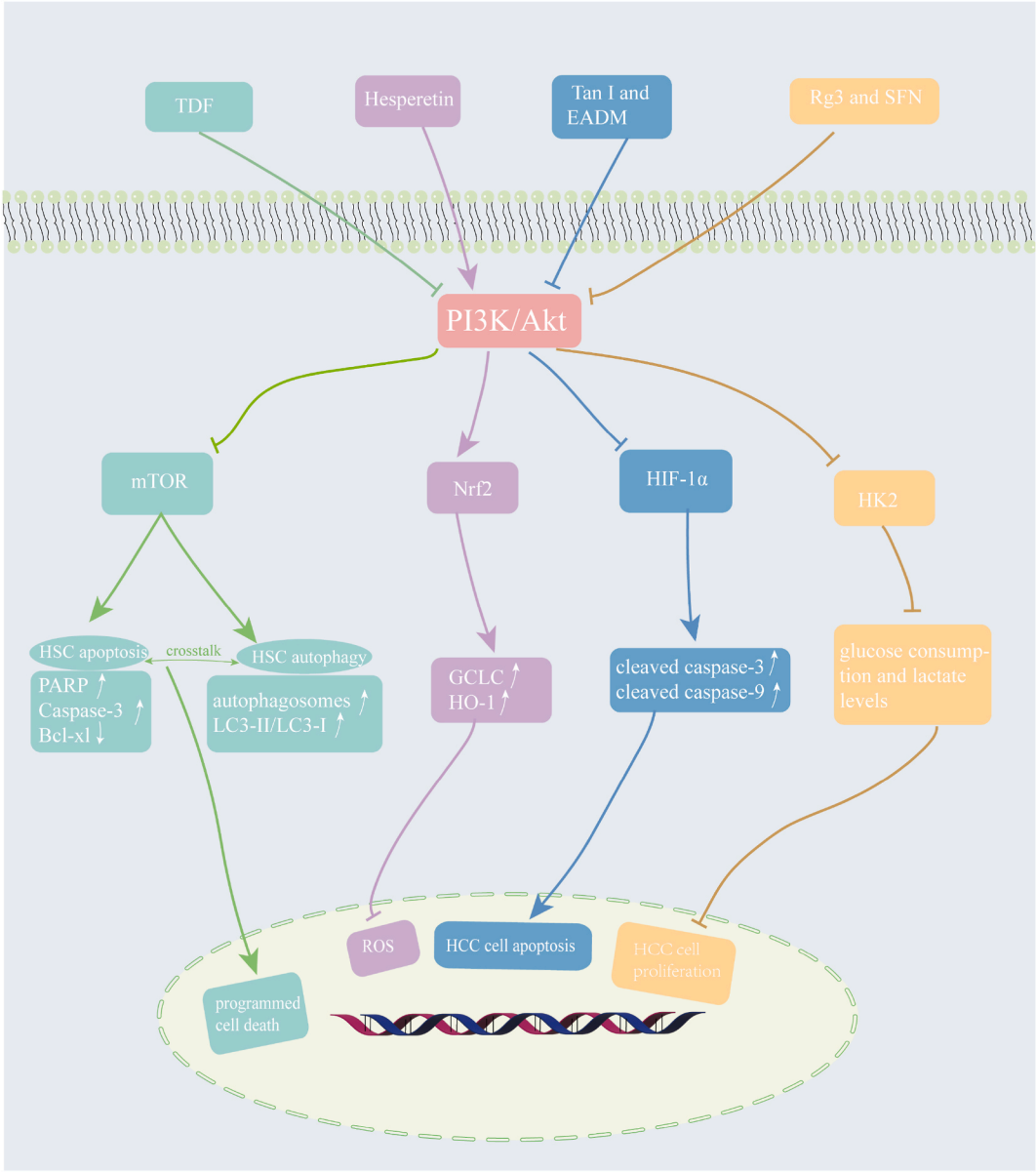

Fig. 2. Medications targeting the PI3K/Akt signaling pathway are used for treating CLD. Green and purple arrows indicate promotion of liver fibrosis and nonalcoholic fatty liver disease, respectively, while blue and orange arrows represent inhibition of HCC development (Fig. 2). The abbreviations used in the figure are: HCC (hepatocellular carcinoma), TDF (Tenofovir disoproxil fumarate), PARP (poly ADP-ribose polymerase), Bcl-xl (B-cell lymphoma-extra large), ROS (reactive oxygen species), LC3I (microtubule-associated protein light chain 3I), LC3II (microtubule-associated protein light chain 3II), HO-1 (heme oxygenase-1), GCLC (glutamate-L-cysteine ligase catalytic subunit), Nrf2 (Nuclear factor erythroid-2-related factor 2), EADM (Epirubicin), Tan I (Tanshinone I), HIF-1α (hypoxia-inducible factor-1α), Rg3 (ginsenoside Rg3), and SFN (sorafenib). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

collaborates with PI3K/Akt/signal transducer and activator of transcription 6 (STAT6) to regulate IL-4-induced murine M2 macrophages [94]. Chen et al. found that triggering receptor-1 expressed on low-expressed myeloid cells may regulate the transformation of M2 macrophages to M1 macrophages through the PI3K/Akt pathway, leading to inhibited migration and invasion of HepG2 and MHCC97H cells when the signaling pathway was blocked [96]. P. amarus has been found to inhibit Myeloid differentiation factor SS (MyD88)-dependent signaling pathways and suppress inflammatory responses in LPS-induced U937 (ATCC ® CRL-1593.2) macrophages through its ethanol extract, which may be related to its inhibitory effects on pro-inflammatory mediators. Thus, the ethanol extract of P. amarus has promising anti-inflammatory activities by blocking the NF-κB, mitogen activated protein kinase (MAPK), and PI3K-Akt signaling pathways [97]. Song et al. found that Ganoderma lucidum spore polysaccharide can promote the polarization of primary macrophages to M1 type, up-regulate the expression of cytokines such as TNF-α, IL-1β, IL-6 and transforming growth factor-β1 (TGF-β1), block H22 tumor cells in G2/M phase, and activate PI3K/Akt pathway to affect mitochondrial apoptosis pathway and promote tumor cell apoptosis [98]. Acetaminophen-induced liver injury is the most common medicine-induced liver injury in CLD patients [99]. Studies have found that styrene maleic acid copolymer (SMA) micelle encapsulating CO releasing molecule (SMA/-CORM2) regulates macrophage reprogramming to an M2 phenotype by inhibiting HIF-1α and activating the PI3K/Akt/mTOR pathway, promoting hepatocyte proliferation, and aiding hepatic protection against inflammatory damage [100]. Interleukin-33 (IL-33) enhances M2 polarization via the PI3K/Akt pathway while activating AMP-activated protein kinase (AMPK)α/mTOR signaling pathways to promote protective hepatocyte autophagy in male C57BL/6 N mice with Acetaminophen (APAP)-induced liver injury [101]. Hyperglycemia promotes liver macrophage pro-inflammatory responses through the AMPK/PI3K/Akt-mediated oxidative stress pathway, aggravating APAP-induced acute liver injury [102]. The codelivery of HBx-siRNA and Plasmid Encoding IL-12 (siRNA/pIL-12) exhibits good potential in preventing viral hepatitis type B (HBV)-induced HCC by inhibiting the PI3K/Akt and ERK pathways. Transfecting siRNA/pIL-12 complexes mediates pIL-12 in immune cells (J774A.1 macrophages), successfully regulating the immune response and increasing cytokine secretion [103]. In conclusion, regulating macrophage polarization through the PI3K/Akt signaling pathway may be an effective approach to treating CLD (Table 2).

5. Conclusions and perspectives

Macrophages can polarize into M1 or M2 types under different microenvironmental stimuli, and regulating this polarization through the PI3K/Akt signaling pathway is a new avenue for treating chronic liver disease. While inhibiting M1 polarization or promoting M2 polarization has shown promise in treating various chronic liver diseases, additional research is needed to determine the best methods for targeting and administering therapies, appropriate dosages, and potential technical challenges. Further exploration of cellular and molecular mechanisms through advanced technologies such as gene editing, proteomics, metabolomics, single-cell RNA sequencing, and bioinformatics may lead to the development of more personalized and precise treatment strategies for chronic liver diseases.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Table 2
Overview of the research on regulating macrophage polarization through PI3K/Akt signaling pathway in the treatment of chronic liver disease.

Disease	Regulation Factor	Research objects	The administration of modeling and dose	Duration	Macrophage polarization	Mechanisms	Reference
Liver fibrosis	↓PTEN	Mice and cell	CCL4(0.02 mL/g/mouse),; LPS (1000 ng/mL), IL-4 (20 ng/mL)	8weeks; 24 h	M2↑	*p*-Akt↑, p-STAT6↑	[94]
Drug-induced liver injury	SMA/CORM2	Mice and cell	APAP (300 mg/kg)	–	M1↓M2↑	p-Pi3k↑, *p*-Akt↑, *p*-mTOR↑, PCNA↑	[100]
Viral hepatitis type B	siRNA/pIL-12@lipo	Cell	–	–	Mø→M1	p-PI3K↓, *p*-Akt↓, *p*-ERK↓, Bcl-2↓, p53↑	[103]
HCC	↓TREM1	Cell and patients and specimens	–	–	M2→M1	p-PI3K/PI3K↓, *p*-Akt/Akt↓, *p*-mTOR/mTOR↓	[96]
	GLSP	Mouse and cell	GLSP (800,400,200 μg/mL)	24 h	Mø→M1	PI3K↓, *p*-Akt↓, BAX↑, BCC-2↓, CASD-9↑	[98]
	AFP	Cell	LPS(50 ng/mL)+IFN-γ(20 ng/mL); IL-4 (20 ng/mL) +IL-13 (20 ng/mL)	24 h; 72 h	M1phagocytic ability↓	PI3K/Akt↑	[78]

Abbreviation: PTEN, phosphatase and tensin homolog; CCl4, carbon tetrachloride; LPS, lipopolysaccharide; IL-4, Interleukin-4; KCs, Kupffer cells; SMA/CORM2, styrene maleic acid copolymer (SMA) micelle encapsulating CO releasing molecule; siRNA/pIL-12@lipo, Codelivery of HBx-siRNA and Plasmid Encoding IL-12; HCC, Hepatocellular carcinoma; TREM1, Triggering receptor expressed on myeloid cells 1; THP-1, The human leukemia monocytic cell line; Mø, primary macrophage; GLSP, Ganoderma lucidum Spore Polysaccharide; AFP: alpha-fetoprotein.
The symbols ↑, ↓, and → represent an increase, decrease, and or polarization, respectively.

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Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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