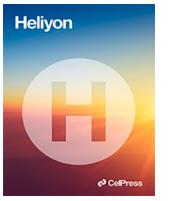
Heliyon 10 (2024) e39176

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Chinese medicine in the treatment of chronic hepatitis B: The mechanisms of signal pathway regulation

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ARTICLE INFO

Keywords:
Chinese medicine
Chronic hepatitis B
The regulation mechanism
Signal pathway
Immunology
Pharmacology

ABSTRACT

Chronic hepatitis B (CHB) is a chronic inflammatory disease of the liver caused by infection with the hepatitis B virus (HBV), which in later stages can lead to the development of end-stage liver diseases such as cirrhosis and hepatocellular carcinoma in severe cases, jeopardizing long-term quality of life, with a poor prognosis, and placing a serious financial burden on many families around the world. The pathogenesis of the disease is complex and closely related to the immune function of the body, which has not yet been fully elucidated. The development of chronic hepatitis B is closely related to the involvement of various signaling pathways, such as JAK/STAT, PI3K/Akt, Toll-like receptor, NF-κB and MAPK signaling pathways. A large number of studies have shown that Chinese medicine has obvious advantages in anti-hepatitis B virus, and it can effectively treat the disease by modulating relevant signaling pathways, strengthening immune resistance and defense, and inhibiting inflammatory responses, and certain research progress has been made, but there is still a lack of a comprehensive review on the modulation of relevant signaling pathways in Chinese medicine for the treatment of CHB. Therefore, this article systematically combed and elaborated the relevant literature on the modulation of relevant signaling pathways by traditional Chinese medicine in recent years, with a view to providing new ideas for the treatment of CHB and further drug development.

1. Introduction

Chronic hepatitis B(CHB) is a chronic inflammatory disease of the liver caused by infection with hepatitis B virus (HBV). HBV is a hepatophilic DNA virus that causes the body to develop acute or chronic hepatitis B. HBV infection is also one of the leading causes of

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https://doi.org/10.1016/j.heliyon.2024.e39176
Received 6 October 2024; Accepted 8 October 2024
Available online 12 October 2024

Abbreviations

CHB	Chronic hepatitis B
HBV	Hepatitis B virus
TCR	T cell receptor
NAs	Nnucleos(t)ide analogues
PEG-IFN	Pegylated interferon
TYK2	TyrosineKinase2
IFN	Interferon
ISG	Interferon-stimulated gene
OSM	OncostatinM
IFITM1	IFN-induced transmembrane protein1
EGCG	Epigallocatechin gallate
LS	Lipophilic constituents in Salvia miltiorrhiza
NAFLD	Non-alcoholic fatty liver disease
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis B e antigen
RIP	Radix Isatidis polysaccharide
XCHD	Xiao chai hu Decoction
RTK	Receptor tyrosine kinase
GPCR	G-protein-coupled receptor
HBcAg	Hepatitis B core antigen
LA	Lithospermic acid
HBx	HBV X protei
YCHD	Yinchenhao Decoction
YGL	Yiganling
TLR	Toll-like receptor
PAMPs	Pathogen-associated molecular patterns
DAMPs	Damage-associated molecular patterns
LRR	LLeucine-rich repeat sequence
LPS	Lipopolysaccharides
MyD88	Myeloid differentiation factor 88
MD-2	Myeloid differentiation factor-2
TIRAP	Toll-interleukin 1 receptor domain containing adaptor protein
IRAK	Interleukin-1 receptor-associated kinase
TRAF6	TNF receptor associated factor 6
IRF5	Interferon regulatory factor 5
TAK1	Transforming growth factor beta-activated kinase 1
TAB1	TAK1-binding protein 1
TAB2	TAK1-binding protein 2
ERK	Extracellular signal-regulated kinase
JNK	c-Jun N-terminal kinase
IRF3	Interferon regulatory factor 3
TRIF	TIR-domain containing adaptor inducing interferon-β
TRAF3	Tumor necrosis factor receptor-associated factor 3
SGPL1	Sphingosine-1-phosphate lyase 1
ESPS	Eupolyphaga sinensis Walker polysaccharide
APS	Astragalus polysaccharides
ASH	Artemisiae scopariae Herba
IκB	NF-κB inhibitor
IKK	IκB kinase
NIK	NF-κB-inducible kinase
TNFR	Tumor necrosis factor receptor
HBx	Hepatitis B virus protein X
ECH	Echinacoside
HK-2	cell line Renal tubular epithelial cells
HRP	Hippophae rhamnoides L
SNS	Sini-San
GPCRs	G protein-coupled receptors
RTKs	Receptor tyrosine kinases

UA	Ursolic acid
PCA	Protocatechuic acid
EHNB	Ent-13-Hydroxykaur-16-ene-19-N-butylureide
GXZY	Gexia-Zhuyu formula
YZHG	Yinzhihuang granules

chronic liver disease worldwide, and as the virus continues to replicate in the liver, this leads to further liver failure and cirrhosis, among other things, and is also capable of increasing the incidence of liver cancer [1–3]. A related study found that 50 % of liver cancer patients are caused by HBV infection, which places a huge burden on society [4]. Epidemiologic research studies have shown that HBV infection is now a worldwide pandemic [5–7]. According to relevant research statistics [8], less than 300 million people worldwide are infected with HBV, and about 1 million people die of HBV-related end-stage liver disease every year, while in China, more than 300, 000 people die of chronic liver disease caused by HBV infection every year. Today, HBV is transmitted through three routes: blood, mother-to-child and sexual contact. In China, HBV is mainly transmitted from mother to child, accounting for about half of the total number of new infections, and most of them occur in the perinatal period and are transmitted through the body fluids or blood of HBV-positive mothers [9]. In adults, HBV is mainly transmitted through sexual contact and blood, such as unprotected sex and transfusion of blood and blood products that have not been rigorously tested and screened, and it can also be transmitted through broken mucous membranes or skin [10,11]. In today's society, hepatitis B vaccination is the most effective measure to prevent HBV infection, and care should be taken to cut off the transmission route of the virus to effectively prevent further transmission.

The pathogenesis of chronic HBV infection is complex and has not yet been fully elucidated. Hepatitis B has traditionally been divided into four immune phases: immune-tolerant phase, immune-active phase, inactive CHB phase, and immune reactivation phase, reflecting the dynamic correlation between the replication and evolution of hepatitis B virus and the host immune response [11]. And the body's immune cells play a crucial role, such as dendritic cells are responsible for capturing foreign antigens and presenting these antigens to other immune cells, which effectively activate the body's immune response under the regulatory effect of IFN-γ [12]. CD40 and CD40L were able to significantly affect T cell activation, while a complex network of interactions was established between antiviral CD4 T cells and antiviral CD8 T cells [13] under the modulatory effect of IL-2 to jointly participate in the process of regulating the immune response, and the T cell receptor (TCR) on these two T cells could recognize the antigens presented on MHC-I and MHC-II molecules and ensures an effective immune response by regulating cell surface molecules such as CD28, CD4, and CD8. At the same time, IL-12 also promotes the differentiation of CD4 T cells to Th1 cells, which enhances the cellular immune response, and IFN-alpha/beta is produced in response to viral infection, which activates the antiviral immune response. Together, these key immune cytokines are involved in the antiviral immune response, and in their interactions work together to regulate and strengthen the immune system's ability to respond to viruses (Fig. 1).

HBV does not directly damage hepatocytes, but the immune response induced by HBV is the key mechanism leading to hepatocyte damage or inflammatory necrosis, and because of the recurrence or persistence of inflammatory necrosis, patients with CHB develop cirrhosis or even HCC, which is ultimately life-threatening (Fig. 2). For the treatment of CHB patients, modern medicine mostly uses antiviral drugs such as nucleos(t)ide analogues (NAs) [14,15] and pegylated interferon (PEG-IFN) [16],hepatoprotective drugs or immunomodulators. Although clinical practice has confirmed their ability to inhibit HBV replication efficiently and have a good safety

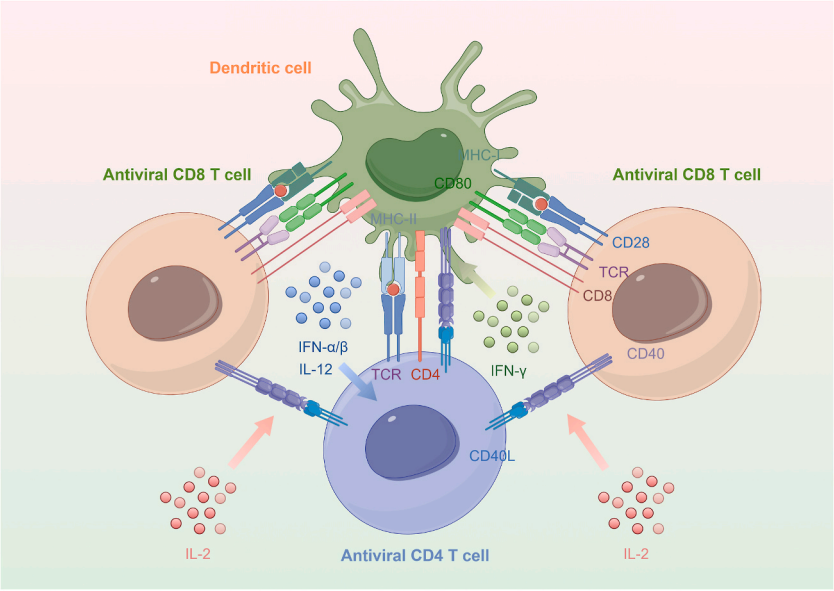

Fig. 1. Mechanisms of immune cell interactions.

profile, other studies have found that these antivirals do not achieve a complete virologic response in a timely manner, that there is a certain incidence of poor response, and that the rate of HBsAg clearance is extremely low, and that the incidence of HCC is still very high [11,17–20]. Therefore, there is an urgent need to develop some novel anti-hepatitis B virus drugs for current treatment. Nowadays, traditional Chinese medicine and its active ingredients play a key role in the treatment of CHB patients with their unique antiviral and hepatoprotective advantages, which have a very broad application prospect. Relevant studies [21–24] have found that Chinese medicine can exert positive therapeutic effects on CHB patients through various aspects such as antiviral and immunomodulation.

In recent years, the research on Chinese medicine for the treatment of CHB and its related signaling pathways has progressed rapidly. In this study, by searching relevant databases such as Web of Science and PubMed, we found a large number of studies on the effects of Chinese medicine on CHB and its related signaling pathways by modulating relevant signaling pathways, such as JAK/STAT, PI3K/Akt, Toll-like receptor, NF-κB, MAPK and other related signaling pathways (Table 1), which have positive therapeutic effects on CHB patients. This article systematically summarizes the specific regulatory effects of Chinese medicine on CHB-related signaling pathways, and it is believed that with the in-depth elucidation of these signaling pathways and their regulatory mechanisms, it will certainly provide new insights into the mechanisms of CHB occurrence, and then further discover safe and effective Chinese medicine treatments that can protect and control, or even achieve clinical cure (Fig. 3).

2. JAK/STAT signaling pathway

2.1. JAK/STAT signaling pathway and chronic hepatitis B

JAK/STAT signaling pathway is composed of JAK, STAT and tyrosine kinase-associated receptor, which can be involved in a variety of biological processes such as cell differentiation, proliferation, apoptosis, and immune regulation, and it is one of the most common “star pathways” in immune system diseases [25,26,33]. As a complex and conserved pleiotropic cellular cascade pathway, the JAK/STAT signaling pathway also has dual roles as a signal transducer and gene transcription activator protein [34]. JAK is a non-receptor-type tyrosine kinase located in the cytoplasm of the cell, which mainly exists between the tissues of the organism, and contains a total of four different isoforms, JAK1, JAK2, JAK3, and TyrosineKinase 2 (TYK2), whereas JAK3 is expressed predominantly in hematopoietic cells, especially myeloid and lymphoid cells [35,36]. Moreover, the JAK family has a role in exerting cytokine-receptor binding and mediating inter-signal transduction, and is able to intervene in the expression of a wide range of growth factors and cytokines [37]. STAT, a protein with transcriptional activation and signal transduction functions, is a downstream target of JAK, mainly including seven family members, STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6, which are involved in protein-protein interactions and enhance transcriptional activity [38]. And among them, STAT5A and STAT5B are two proteins with the same amino acids encoded by different genes.

The JAK/STAT signaling pathway promotes cytokine-mediated cellular activation by binding to specific surface receptors, which further activates specific JAKs and phosphorylates the corresponding STATs, resulting in conformational changes of inactive cytoplasmic STAT monomers, leading to the formation of reactive homodimers as well as heterodimers, which then translocate to the

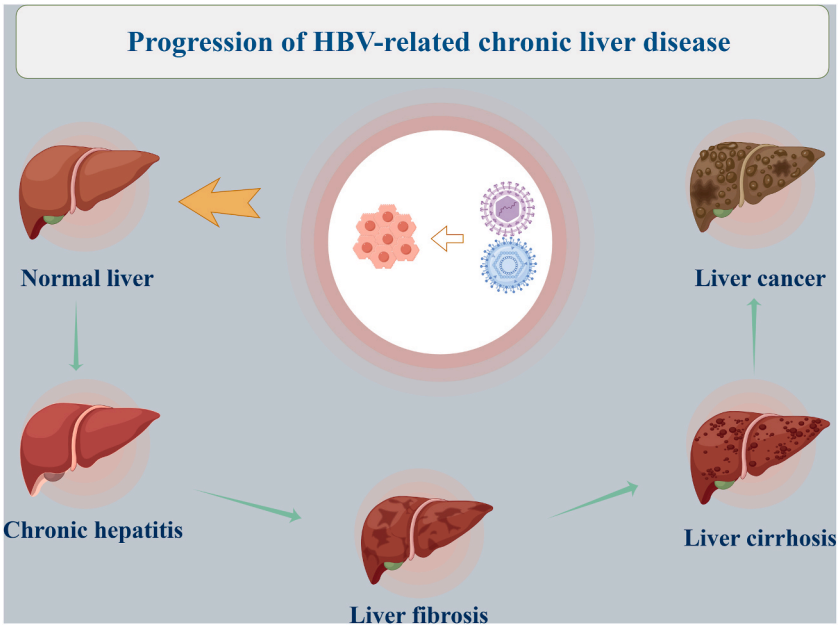

Fig. 2. Progression of HBV-related chronic liver disease.

Table 1
Research on the mechanism of related signaling pathways

No.	Name	Entry	Disease	Key Findings	References
1	JAK/STAT	map04630	CHB	JAK/STAT signalling pathway is involved in a variety of biological processes, including cell differentiation and immune regulation, and is one of the most common pathways in immune system diseases.	Xin et al. (2020) [25]; Hu et al. (2023) [26]
2	PI3K/Akt	map04151	CHB	PI3K/Akt signalling pathway can participate in and regulate a variety of cell cycle processes, and is closely related to cell growth, proliferation and other life activities.	Karar et al. (2011) [27]; Fruman et al. (2017) [28]
3	Toll-like receptor	map04620	CHB	TLR is a type I transmembrane receptor in natural immunity, and as a pattern recognition receptor and inflammatory signalling gateway protein, it can effectively regulate immune function and inflammatory response.	Cui et al. (2024) [29]; Sun et al. (2024) [30]
4	NF-κB	map04064	CHB	NF-κB family of transcription factors are key regulators of immune response, immune development, inflammation, and cancer, and play an important role in disease development.	Liu et al. (2017) [31]
5	MAPK	map04010	CHB	MAPK signalling pathway can participate in the regulation of cell growth, differentiation and other biological processes, and is of key significance for the regulation of growth signals.	Kim et al. (2010) [32]

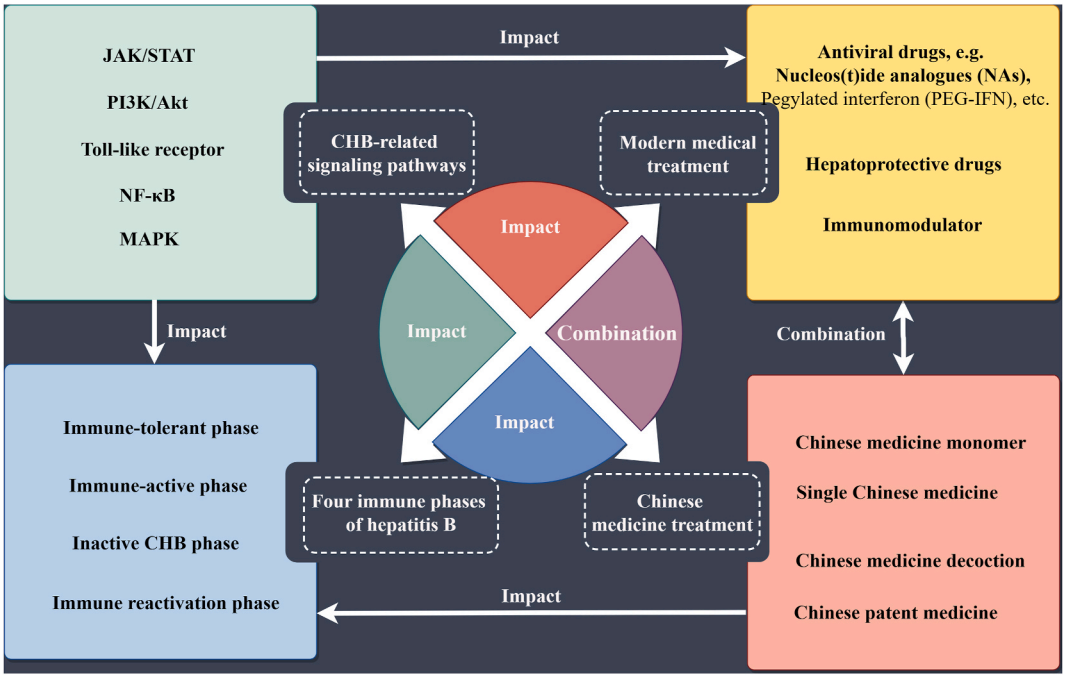

Fig. 3. CHB and its associated factors.

nucleus and bind to DNA regulatory elements to participate in related gene transcription and mediate specific cellular signaling [39]. Nowadays, the JAK/STAT signaling pathway has been recognized as a central communication node in the regulation of immune inflammation, and related cytokines such as IL-6 and interferon (IFN)-γ can activate the JAK/STAT signaling pathway to mediate intracellular signals and promote the expression of a variety of inflammatory factors, resulting in the formation of a series of inflammatory cascade responses and the regulation of the human immune system [40–42].

JAK-STAT signaling pathway also plays a key role in HBV infection and immune response. IFN has been used in the treatment of HBV for many years as one of the most critical cytokines in the immune system to protect against viral infection, and IFN activates the expression of antiviral genes, which play a key role in each stage of HBV replication [43,44]. Critically, START is able to regulate IFN-mediated antiviral activity against hepatitis B virus by modulating the JAK-START signaling pathway and the expression of interferon-stimulated gene (ISG), which establishes an important line of defense for the body to fight against viral infection and maintain immune homeostasis [45,46]. Recent studies [47] have also found that oncostatinM (OSM), the most potent cytokine in the IL-6 family of cytokines for inhibiting HBV replication, is able to inhibit HBV replication through activation of the JAK/STAT signaling pathway, and at the same time, OSM increases the expression of a variety of genes known to be functional in adaptive immunity and

innate immunity, which ultimately remodels the immune response against HBV and thus exerts potent anti-HBV activity. Also, OSM activation increased the expression of antiviral effectors and IFN-induced transmembrane protein1 (IFITM1), which is essential for immune clearance of HBV. In addition to that, several studies [48–51] have confirmed the close relationship between the JAK/STAT signaling pathway and CHB. In summary, the JAK-STAT signaling pathway not only occupies an important position in immunological research in basic biology, but also plays a great potential in the treatment of many liver diseases, including hepatitis B. An in-depth study of the relationship between the JAK-STAT signaling pathway and CHB will help us gain a deeper understanding of the molecular mechanisms of HBV infection and provide a theoretical basis for the development of new antiviral treatment strategies.

2.2. Chinese medicine treatment of the chronic hepatitis B and JAK/STAT signaling pathway

Baicalin is a natural active ingredient derived from the Chinese medicine *Scutellaria baicalensis*, which has anti-inflammatory, anticancer, antibacterial and hepatoprotective effects, and is able to prevent liver damage caused by a variety of liver diseases, including viral hepatitis [52,53]. Fan and his research team [54] explored the main mechanism of Baicalin's anti-HBV action and found that long-term use of baicalin could activate the JAK/STAT signaling pathway. And after knockdown of ISGs such as TRIM25, there was a significant recovery of baicalin-mediated HBV inhibition in HepG2 cells, confirming the importance of ISGs in the antiviral defense process. A novel study [55] also found that the antiviral capacity and bioavailability of baicalin could be significantly improved by constructing liver-targeted baicalin liposomes, which could more effectively inhibit HBV transcription and replication. Amygdalin is commonly found in the Rosaceae family, and most commonly in seeds of apricot almonds. As a natural aromatic cyanogenic ingredient, it has now been shown to have anti-inflammatory, anti-fibrotic and immunomodulatory properties [56]. However, it is of concern that high dose exposure to amygdalin may result in some cyanide toxicity, so the dose should be controlled for clinical use [57]. Wang et al. [58] conducted an in-depth study of cellular immune responses and found that the phosphorylation levels of JAK2 and STAT3 in HBV-T cells were high, while the phosphorylation levels were significantly reduced after amygdalin treatment, confirming that amygdalin can promote T-cell activity by regulating the JAK2/STAT3 signaling pathway, and ultimately inhibit the further development of HBV-associated hepatocellular carcinoma. Epigallocatechin gallate (EGCG) is a key polyphenol in green tea that possesses significant anti-tumor and antioxidant properties, as well as some immunomodulatory effects [59,60]. In addition, EGCG was able to inhibit macrophages inflammasome activation, which further ameliorated HBV-induced liver fibrosis and liver injury [61]. Relevant researchers [62] found that in HepG2.2.15 cells, EGCG was able to significantly down-regulate ERK1/2-mediated HNF4α, and also further activate the JAK2/STAT3 signaling pathway, and ultimately EGCG dose-dependently inhibited the activity of the HBV core promoter and HBV replication.

The Chinese medicine *Salvia miltiorrhiza* has a history of more than 2000 years and is ranked as the highest grade in Shennong's Classic of Materia Medica [63]. It is one of the most common medicines used clinically for the treatment of cardiovascular and cerebrovascular diseases and liver diseases, and is known for its remarkable blood-boosting effects. Other researchers [64] have found that key active ingredients in *Salvia miltiorrhiza* are able to exert significant anti-HBV activity by modulating autophagy. Tang et al. [65] found that Lipophilic ingredients in *Salvia miltiorrhiza* (LS) had a significant therapeutic effect on HBV-associated liver fibrosis, and LS was able to significantly down-regulate the JAK1/STAT3 signaling pathway, as well as inhibit hepatic stellate cell activation, promote apoptosis, inhibit cell viability, and decrease liver fibrosis marker expression. Betaine [66,67] is a natural ingredient isolated from Lycium barbarum and other herbs with biological properties such as anti-inflammatory and anti-diabetic. Several other studies have found that betaine has a significant regulatory effect on chronic liver diseases such as non-alcoholic fatty liver disease (NAFLD) [68] and hepatitis B [69]. Zhang et al. [70] found that betaine significantly reduced the secretion of HBV DNA, hepatitis B surface antigen (HBsAg), and hepatitis B e antigen (HBeAg) in HepG2.2.15 cells through in vitro and in vivo experiments and that betaine exerted its therapeutic effects through its actions on the JAK/STAT signaling pathway to exert therapeutic effects, thus ultimately improving the anti-HBV effect of IFN-α. Radix Isatidis polysaccharide (RIP) [71], which is mainly derived from the Chinese medicine Radix isatidis, has been shown to have significant immunomodulatory effects in vivo and in vitro, as well as some antiviral effects. Some experimental studies [72] have found that RIP can significantly reduce the levels of HBV DNA, HBeAg and HBsAg in HepG2.2.15 cells, and the degree of reduction is closely related to the time and dose. In addition, RIP can further enhance the production of IFN-α in cells by effectively activating the JAK/STAT signaling pathway and inducing the expression of anti-HBV proteins, and ultimately exert a significant inhibitory effect on HBV.

Ginseng, also known as the king of herbs, has been widely used by clinicians for thousands of years since ancient times. Ginsenosides, as a group of triterpenoid saponins, are the key ingredients of the Chinese medicine Ginseng, with significant antidiabetic [73] and anti-HBV [74] properties. Zhang and many other scholars [75] have found that ginseng and its saponins and extracts, etc. are able to regulate the body's immune response through the modulation of the JAK/STAT signaling pathway, thus exerting an anti-HBV effect, providing a key scientific basis for the use of ginseng as an adjuvant therapeutic medicine. Xiaochaihu Decoction (XCHD) from Shanghan Lun is composed of a variety of Chinese medicines, including Chaihu, Bianxia, and Ginseng, and is commonly used in the treatment of various chronic liver diseases, with remarkable efficacy in clinical practice. A network pharmacology study [76] found that XCHD modulates viral infections and also regulates the body's immunity and metabolism, providing a preventive and therapeutic effect against CHB. Chen and some other researchers [77] conducted relevant clinical trials and cellular assays and detected the protein and mRNA expression levels of JAK2 and STAT3, and found that modified XCHD could significantly inhibit HBV replication. In addition, intervention of cells with serum containing modified XCHD effectively regulated the expression of STAT3 and promoted the proliferation of HepG2.2.15 cells. In summary, herbal monomers or traditional herbal formulations were able to regulate the immune response of the body through the modulation of the JAK/STAT signaling pathway, which ultimately exerted anti-HBV effects and effectively prevented the occurrence and exacerbation of end-stage liver disease.

3. PI3K/Akt signaling pathway

3.1. PI3K/Akt signaling pathway and chronic hepatitis B

PI3K/Akt signaling pathway participates in and regulates a variety of cell cycle processes, and is closely related to cell growth, proliferation, migration, apoptosis, and metabolism, and other life activities, and exists in a wide range of organisms, mainly composed of PI3K, Akt and its downstream molecules [27,28,78]. PI3K, as a key regulator of many cellular processes, is a heterodimeric lipid kinase formed by the p85 regulatory subunit and the p110 catalytic subunit (p110α, p110β, and p110δ), which possesses the dual activities of a serine/threonine protein kinase and a phosphatidylinositol kinase.According to the different structures and substrate specificities, PI3K is classified into three types, namely, PI3KI(PI3K α, β, γ, δ), PI3KII (PI2KC21α, β, γ), and PI3KIII three types [79–81]. In addition, the most widely studied is PI3K I, which can be activated by cell surface receptors. PI3K class I is further divided into class IA (PI3Kα, β, and δ), which is activated by the growth factor receptor tyrosine kinase (RTK), and class IB (PI3Kγ), which is activated by the G-protein-coupled receptor (GPCR), according to its activation mode [82,83]. In membrane lipid metabolism, PI3K with phosphatidylinositol kinase activity catalyzes the generation of PIP2 from PIP, which in turn catalyzes the generation of the second messenger PIP3, which enters the cell and binds specifically to the PH domain of the downstream signaling molecule Akt and activates the phosphorylation of Akt by the PDK1 kinase, which regulates multiple downstream effectors and further signaling. phosphorylated Akt regulates multiple downstream effectors and further signaling, targeting and regulating important physiological and pathological processes such as protein synthesis, apoptosis and metabolism [27,84,85].

Akt, a major downstream effector molecule of PI3K, also known as PKB, is an evolutionarily conserved serine threonine kinase that signals downstream of and is regulated by PI3K and is capable of influencing cell growth, metabolism, and proliferation, with three distinct isoforms, Akt1 (PKBα), Akt2 (PKBβ), and Akt3 (PKBγ) [86]. Akt1, Akt2, and Akt33 isoforms are highly homologous and structurally similar, and consist of a catalytic domain, a regulatory domain, and a PH domain. Akt1 is widely found in cells of various tissues and is involved in biological processes such as cell growth and inflammatory responses, Akt2 is found in adipose and muscle tissues and is mainly involved in insulin effector tissues for glucose homeostasis. Akt3 is found in the brain and testes and contributes to neuronal processing and development [87]. The three Akt isoforms share homologous amino acid sequences, including the kinase-catalyzed structural domain, C-terminal regulatory and N-terminal regulatory regions, and the Ser473 site in its C-terminal regulatory domain and the Thr308 site in its kinase-catalyzed structural domain are the core of Akt activation [88]. The central node Akt is a positive regulator of multiple signaling pathways and plays an irreplaceable role in cell growth, proliferation and metabolism in several species [89,90]. In addition, Akt is capable of directly regulating and phosphorylating a variety of proteins, such as mTOR and Nrf2 complex.

HBV replication may be regulated by a variety of cell signaling pathways, including the PI3K/Akt signaling pathway, which also plays an important role in the development of CHB, and research targeting the PI3K/Akt signaling pathway may provide new ideas for the treatment of CHB. Relevant studies [91] have found that AKT appears phosphorylated during natural HBV infection suggesting that the AKT signaling pathway may be activated during HBV entry into the human body. Moreover, long-term treatment with inhibitors of the PI3K/AKT/mTOR pathway significantly promoted HBV replication in both the natural HBV infection model and the replication model, and thus the PI3K/AKT/mTOR pathway also became a negative regulator of HBV replication. In addition, scholars [92] have also thoroughly investigated the major regulatory mechanisms of the PI3K/AKT signaling pathway on HBV replication, and confirmed that the expression of constitutively active Akt1 can inhibit the transcription of HBV RNA to a certain extent, thus further reducing the replication of HBV DNA in HepG2 cells. Moreover, activation of the PI3K/AKT signaling pathway is one of the main reasons for eliminating HBV replication in tumor cells during the development of HBV-associated hepatocellular carcinoma. On the contrary there are some studies [93] that found its close relationship with the immune system, hepatitis B core antigen (HBcAg) significantly induces AKT phosphorylation, while PI3K/AKT inhibitors significantly reduce HBcAg-induced PD-1 up-regulation on CD4 (+) T-cells, and in this way, the progression of CHB can be effectively controlled and reduce the number of associated complications. Among patients infected with HBV, HBV has a complex relationship with the PI3K/AKT signaling pathway, which can also be jointly involved in the development of HBV-associated end-stage liver disease. Hepatitis B virus HBx protein-induced AFP expression can promote malignant transformation of hepatocytes by activating the PI3K/mTOR signaling pathway [94]. Chen et al. [95] also found that hepatitis B virus infection-associated PDzk1 protein is also able to regulate fatty acid metabolism and PI3K/AKT signaling pathway ultimately oncogenic effects. Importantly, PI3K/Akt signaling pathway has a complex regulatory network in the physiological and pathological processes of hepatocytes, and the specific regulatory mechanisms have not been fully elucidated. Therefore, therapeutic strategies targeting this pathway need to comprehensively take into account the impacts of multiple factors and validate their efficacy and safety through clinical trials.

3.2. Chinese medicine treatment of chronic hepatitis B and PI3K/Akt signaling pathway

The Chinese medicine *Salvia miltiorrhiza* is a perennial herb with slender, cylindrical roots and a vermillion-red rind, with pharmacological properties such as anti-tumor, anti-inflammatory, anti-fibrotic and anti-diabetic, and is often used in the treatment of cardiovascular and liver diseases [96,97]. Lithospermic acid (LA) is a key component in *Salvia miltiorrhiza* and its antitumor [98] activity is widely recognized in the clinic. Zhu and his research team [64] demonstrated the significant anti-HBV activity of LA, which effectively inhibited HBV DNA replication in pHBV-transfected HepG2 cells and HepG2.2.15 cells, and also suppressed HBeAg and HBsAg levels in HepG2.2.15 cells, with the therapeutic effect being dose- and time-dependent. In addition, they found that LA inhibited HBV-induced activation of AKT and mTOR and induced autophagy by blocking the PI3K/AKT/mTOR signaling pathway, which

ultimately exerted significant anti-HBV effects. Matrine, as a herbal monomer and a natural hepatoprotective agent, has been found to alleviate obesity in mice by inducing adipose thermogenesis, thereby improving lipid accumulation [99]. In addition, both matrine [100] and oxymatrine [101] had significant anti-HBV effects. Sun et al. [102] found that a matrine derivatives could effectively inhibit the proliferation of HBV and other related hepatocellular carcinomas in vitro and in vivo while inducing apoptosis in tumor cells, and that their antitumor properties exerted their therapeutic effects precisely by inhibiting the PI3K/AKT signaling pathway. The Chinese medicine Cordyceps sinensis, a fungus of the ergot family with a sweet taste, has been widely used in clinical practice since ancient times. Some studies [103] have found that cordyceps sinensis has enhanced humoral immune function in humans, and its aqueous extract also has good adaptive immunomodulatory function. He and other researcher [104] found that HBV X protein (HBx) first activates the PI3K/Akt signaling pathway and also triggers apoptosis in HK-2 cells, whereas cordyceps sinensis significantly reduced the effects of HBx and exerted its anti-HBV effects by inhibiting the PI3K/Akt signaling pathway.

Yinchenhao Decoction (YCHD) has been used as a traditional Chinese herbal formula for about 2000 years and is often applied in the clinical treatment of chronic liver diseases. A related study [105] found that YCHD was able to regulate the immune response of largemouth bass, reducing the RNA levels of pro-inflammatory genes by modulating its immune response and autophagy, etc., which ultimately alleviated the level of inflammation and necroptosis of largemouth bass. Cai and other researchers [106] found that YCHD can exert a therapeutic effect on HBV and other related liver fibrosis by regulating apoptosis-related signaling pathways, such as PI3K/Akt, which can effectively reduce apoptosis of hepatic parenchymal cells, and at the same time alleviate the clinical symptoms of liver fibrosis, according to a network pharmacological study and in vivo experiments. Yiganling (YGL) capsule is a kind of Chinese patent medicine with hepatoprotective effect, which is commonly used in the treatment of acute and chronic hepatitis and prolonged hepatitis. It is a capsule preparation with the content of light yellow to brown granules or powder. By constructing a network diagram of the mechanism of action of YGL in the treatment of hepatitis B, Lu et al. [107] found that many key targets are involved in the immune process of hepatitis B, such as PIK3CA, NFKB1, and IKBKB, etc. These key targets are able to act on the relevant pathways, such as PI3K/Akt, and are involved in the process of inflammatory response, innate immunity, and secondary immunity, which ultimately exerted significant anti-HBV The effect of anti-HBV is significant. In summary, Chinese medicine monomers, combinations and Chinese patent medicines can exert significant anti-HBV effects by modulating the PI3K/Akt signaling pathway. And nowadays, the development and study of anti-HBV medicines by precisely targeted molecular pathways of Chinese medicine monomers has become the mainstream direction of future development. Compared with single Chinese medicine and Chinese medicine monomers, Chinese medicine combinations and Chinese patent medicines are able to exert the synergistic effect of Chinese medicines and enhance the regulation of PI3K/Akt signaling pathway and immune modulation mechanism, so as to improve the clinical effect of the treatment of CHB patients, but due to the existence of synergistic and crosstalk mechanisms between the medicines, it also increases the relative complexity of the study of the mechanism of action, and we need to carry out an in-depth study of the mechanism in the future.

4. Toll-like receptor signaling pathway

4.1. Toll-like receptor signaling pathway and chronic hepatitis B

Toll-like receptor (TLR), a type I transmembrane receptor in natural immunity, plays an important role in the regulation of inflammatory response and immune function as a pattern recognition receptor and inflammatory signaling portal protein [29,30]. Also TLR recognizes pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which are important bridges between specific and nonspecific immunity [108,109]. Moreover, TLR was first discovered during Drosophila embryonic development and can be widely expressed in Drosophila and mammals [108]. Nowadays, we have identified 13 TLRs family members [110], 12 of which are in mice and only 10 in humans [111]. TLRs are mainly classified into two major groups based on their specific ligands and cellular localization, the first of which is capable of recognizing membrane components of microorganisms and is mainly expressed on the cell surface, as in the case of lipids and lipoproteins, which mainly include TLR2 and TLR4, among others. And another class of microbial-recognizable nucleic acids is expressed mainly on the surface of intracellular such as endoplasmic reticulum, lysosomes and other vesicles, such as TLR3, TLR7 and TLR9 [112]. TLR4, as one of the major members of TLRs, is also the most widely studied and first identified pattern recognition receptor. TLR4 is mainly composed of a structural domain consisting of a leucine-rich repeat sequence (LRR), an intracellularly conserved Toll/IL-1 receptor structural domain, and a transmembrane structural domain [113], whereas the TLR4 receptor system recognizes lipopolysaccharides (LPS) on the surface of Gram-negative bacteria and ligands such as heat-shock proteins, PAMPs, DAMPs, etc., and forms a receptor dimerization at the cell membrane to produce interferons and pro-inflammatory cytokines, thus being able to mediate the inflammatory response [109,114].

The TLR4 signaling pathway is mainly transmitted through two different signaling pathways, the myeloid differentiation factor 88 (MyD88)-dependent and MyD88-independent signaling pathways [115]. The MyD88-dependent pathway is the most classical pathway in TLR4 and plays a key role in the production of pro-inflammatory factors [116].

TLR4 first binds to myeloid differentiation factor-2 (MD-2) to form the TLR4-MD-2 complex, which recruits the cytoplasmic toll-interleukin 1 receptor domain containing adaptor protein (TIRAP) and MyD88, phosphorylates the interleukin-1 receptor-associated kinase (IRAK) family of protein kinases and interacts with TNF receptor associated factor 6 (TRAF6) to form the IRAK-TRAF6 complex.) interacts to form the IRAK-TRAF6 complex. TRAF6 directly produces pro-inflammatory cytokines through activation of interferon regulatory factor 5 (IRF5). and also through transforming growth factor beta-activated kinase 1 (TAK1), TAK1-binding protein 1 (TAB1), and TAK1-binding protein 2 (TAB2) kinase complexes; one part of the TAK1 pathway activates the IKK complex, which leads to the activation of NF-κB, causing the release of proinflammatory factors [117]; the other part of the TAK1 pathway is the activation of MAPKs, involving p38, extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK). MAPKs induce nuclear

translocation of the transcription factor complex AP-1, initiating intranuclear signaling and triggering a massive release of downstream inflammatory factors [118,119]. While the MyD88-independent pathway mainly leads to the delayed activation of NF-κB and interferon regulatory factor 3 (IRF3). TIR-domain containing adaptor inducing interferon-β (TRIF) is indirectly recruited by the TRIF-associated articulator molecule TRAM, which binds to TRAF6. On the one hand, the N-terminal end of TRIF can activate tumor necrosis factor receptor-associated factor 3 (TRAF3), which in turn activates IRF3, which produces interferon and causes it to release cytokines such as TNF-α, thereby mediating the inflammatory response. On the other hand, TRIF can activate TRAF6, which leads to IKK activation, NF-κB activation and release into the nucleus, driving the production of pro-inflammatory cytokines and creating various inflammatory responses [120,121]. After binding to the corresponding ligands, TLRs activate signaling pathways through signaling cascade reactions and ultimately mediate inflammatory responses, which are able to influence the development of a variety of chronic liver diseases such as hepatitis B.

During chronic HBV infection, both the expression and specific function of TLRs are impaired, and nowadays TLR ligands have become one of the new therapies for the treatment of chronic HBV infection [122]. The expression of TLR4, TLR9, etc. was significantly reduced in immune cells during the immune escape phase of HBV infection [123–125]. And TLRs can initiate downstream signaling pathways through MYD88-dependent or non-dependent pathways, thus promoting the secretion of cytokines by the body's immune cells, and ultimately exerting anti-HBV effects [126]. In addition, HBV is also able to block intracellular signaling pathways in TLRs. HBV rapidly inhibits TLR9-mediated IFN-α secretion, and HBsAg specifically inhibits TLR9-mediated IFN-α production by inhibiting IRF expression and nuclear translocation [127]. At the same time, HBcAg can ultimately play a role in suppressing HBV-specific T-cell responses by activating the TLR2 pathway, thereby promoting the production of cytokines such as IL-10 [128,129]. HBeAg was also able to inhibit IL-1-mediated activation of NF-κB in hepatocytes by interfering with homotypic TIR interactions, and it was also able to inhibit TLR2-mediated activation of the NF-κB and IFN-α promoters [130,131]. And HBV polymerase was also able to inhibit NF-κB signaling induced by TLR4 and TNF-α by inhibiting the activity of IKKs [132]. In summary, these all reflect a very close link between HBV and TLRs, HBV infection can lead to changes in the expression level and function of immune cells, taking into account the inhibitory effect of different HBVs on the natural immune system, such as TLRs, an in-depth understanding of the immune mechanisms induced by different components of HBV is expected to provide new directions for the development of immunization strategies targeting the intrinsic immune response to HBV, as well as for the immunotherapeutic treatment of HBV [133].

4.2. Chinese medicine treatment of chronic hepatitis B and toll-like receptor signaling pathway

Ginsenoside Rg1, which is also derived from the traditional tonic Chinese medicine Ginseng, can be used in the treatment of hepatic impairment in liver diseases induced by different causes, and has shown good multi-targeting effects in the treatment [134]. In addition, ginsenoside Rg1 was able to exert significant anti-apoptotic effects against NAFLD by down-regulating the expression of sphingosine-1-phosphate lyase 1 (SGPL1) [135]. Importantly, Yuan et al. [136] found that ginsenoside Rg1 could help stimulate the expression of IgG, cell surface marker TLR4, and cytokine IFN-γ in HBsAg-immunized mice in a mouse assay, and in addition, the TLR4 signaling pathway was involved in the adjuvant activity of ginsenoside Rg1, confirming that ginsenoside Rg1 was able to enhance the immune response to hepatitis B surface antigen in mice by acting on the TLR4 signaling pathway. *Eupolyphaga sinensis* Walker as a medicinal insect, the dried female body is a traditional animal medicine, clinically used in the treatment of immune diseases and cancer [137]. Moreover, the active peptide extracted from Eupolyphaga sinensis Walker was able to effectively alleviate hyperlipidemia in rats by modulating the gut microbiota and biomarkers [138]. Relevant studies [139] have found that Eupolyphaga sinensis Walker polysaccharide (ESPS) can enhance the activity of lymphocytes in vitro, which further promotes the proliferation of lymphocytes, and ultimately exerts the effect of inhibiting the growth of hepatocellular carcinoma cells. Zhang and his research team [140] thoroughly investigated the antiviral effects of ESPS on HBV, and found that ESPS is able to enhance the body's innate immune function by activating the TLR4 pathway, which ultimately exerts significant anti-HBV effects. In addition, in vivo studies in transgenic mice revealed that ESPS was also able to significantly reduce the levels of HBeAg, HBsAg and HBV DNA in mouse serum, as well as the levels of HBV RNA and HBV DNA in mouse liver.

The Chinese medicine Astragalus membranaceus is a perennial herb of the family Leguminosae, genus Astragalus, with a height of 50–100 cm. It has a wide range of pharmacological effects, such as immunomodulation, anti-apoptosis and hepatoprotection [141]. Astragalus polysaccharides (APS) is extracted from the roots of Astragalus membranaceus, and related studies have revealed its ability to exert immunomodulatory effects in vivo and in vitro through the TLR4-mediated MyD88-dependent signaling pathway [142–144]. And nowadays, with the further deepening of APS pharmacological research, the nanocrystals and moderate structural modification can effectively improve the bioavailability of APS, thus further expanding the application scope of APS [145]. Du and other researchers [146] investigated the potential adjuvant effect of APS on cellular and humoral immune responses to hepatitis B subunit vaccine and found that the expression of TLR4 was significantly increased after APS intervention, which ultimately confirmed that APS enhances the body's cellular and humoral immune responses by activating the TLR4 signaling pathway, and also effectively suppresses the Treg cell number and TGF-β expression. Oxymatrine is extracted from the herb Sophora alopecuraides L., and as a matrine-type alkaloids, it is beneficial to human health, especially in the treatment of liver, gastrointestinal and other diseases, and plays an active role [147]. A Meta-analysis [148] found that oral oxymatrine preparation had a statistically significant effect on the clearance of HBV DNA, HBeAg, and HBsAg and was beneficial in alleviating liver injury. Yao et al. [127] conducted a clinical trial and found a synergistic effect of oxymatrine and TLR9 ligands on antiviral cytokine secretion in vitro. Relevant data showed that oxymatrine was able to directly induce peripheral lymphocytes to secrete antiviral cytokines, which not only activated the TLR9 signaling function, but also further enhanced the expression of TLR9 signaling molecules, which ultimately confirmed the mechanism of oxymatrine in vitro anti-hepatitis B virus immunomodulation.

Artemisiae scopariae Herba (ASH) is a commonly used herb for the treatment of liver diseases with pharmacological activities such as antifibrotic, anti-inflammatory and hepatoprotective [149]. Some studies [150] have also found significant antitumor effects, improving the current use of ASH in tumor therapy. He et al. [151] conducted a network pharmacology study and found that ASH exerts its anti-HBV effect mainly by acting on TLR and hepatitis B signaling pathways. While the core therapeutic targets include AKT1, FOS, CCL2, CXCL8, and CXCL10, the final molecular docking results further confirmed the strong binding activity between the key ingredient quercetin and AKT1. In summary, Chinese medicine ingredients or single Chinese medicine were able to regulate the TLR signaling pathway, thus exerting immunomodulatory effects, effectively inhibiting viral replication, exerting anti-HBV effects, and ultimately preventing or delaying the occurrence of end-stage liver diseases such as cirrhosis or hepatocellular carcinoma, which provides a new way of thinking about the clinical use of medicines in patients with CHB in the future.

5. NF-κB signaling pathway

5.1. NF-κB signaling pathway and chronic hepatitis B

The NF-κB family of transcription factors is a major regulator of immune response, immune development, inflammation and cancer [31]. NF-κB transcription factors consist of five members, including NF-κB1 (p50), NF-κB2 (p52), RelB, c-Rel, and p65 (RelA), in which the NF-κB1 and NF-κB2 proteins are able to be used to synthesize the precursor proteins, p105 and p100, and further processed into the active NF-κB subunits, p50 and p52. Moreover, these five transcription factors N-terminally share the Rel homology structural domain [152]. The NF-κB signaling system consists mainly of interactions between NF-κB dimers, NF-κB inhibitor (IκB), and IκB kinase (IKK) complexes [153]. In the physiological state, NF-κB dimer and IκB can synergize with each other in order to maintain the inflammatory level of the body and further promote cell growth, proliferation and apoptosis [154,155]. Based on the components of the signaling cascade, the NF-κB signaling pathway is divided into canonical and non-canonical pathways, represented by the p50/RelA and p52/RelB transcription protein complexes, respectively [156].

First, the canonical NF-κB pathway mediates activation of only three transcription factors, RelA, p50, and c-Rel [157]. The classical pathway is triggered by microbial products and further by pro-inflammatory cytokines such as IL-6, TNF-α, etc. When the classical NF-κB pathway is activated, p50 and RelA bind to form a dimer responsible for the transcription of the target gene, and IKK signaling induces the phosphorylation of the IκB molecule, which leads to the release of NF-κB dimers from the cytoplasm, which are then rapidly translocated to the nucleus, to driving the transcription of target genes, it is rapidly activated in adaptive and innate immune cells [158]. The activated canonical NF-κB pathway is involved in a variety of physiological and pathological processes, including immunity, inflammation, cell proliferation and differentiation, and deserves further in-depth exploration in the future [159]. The core component of the NF-κB pathway of the non-canonical pathway is the NF-κB-inducible kinase (NIK) [160], which is primarily activated by ligand-selective activation of a subgroup of tumor necrosis factor receptor (TNFR) superfamily members. In contrast, NIK serves as the main signaling component for activation of the atypical NF-κB pathway by activating the kinase IKKα in order to induce p100 phosphorylation. p100 is both a precursor protein for p52 and functions as an IκB-like molecule, mediating nuclear translocation of RelB, p52 dimers and acting as an IκB-like NF-κB inhibitor. Under the stimulation of external signals, NIK induces p100 phosphorylation through activation of IKKα. p100 protein hydrolysis releases RelB and generates p52, forming a RelB/p52 dimer, which is then translocated to the nucleus, ultimately activating the NF-κB signaling pathway [161]. In contrast to the rapid activation of the canonical NF-κB pathway, the activation of the non-canonical NF-κB pathway is characteristically slow and persistent, and plays a key role in immune regulation and inflammatory response processes [162–164].

Recent studies [165,166] have also found that activation of NF-κB signaling pathway can be involved in the progression of multiple liver diseases, and plays an irreplaceable role in the development of chronic liver diseases such as hepatitis B, autoimmune liver disease, NAFLD and hepatocellular carcinoma. Previously, we talked about that NF-κB, as a transcription factor, is involved in regulating biological processes such as immune response and inflammatory response of cells. More importantly, there is a great correlation between HBV infection and the NF-κB signaling pathway. In HBV infection, activation of the NF-κB signaling pathway is closely related to viral replication and the inflammatory response of the body [167,168]. HBV infection induces an inflammatory response in host cells. Inflammatory cells release inflammatory factors, such as cytokines and chemokines, which in turn activate the NF-κB signaling pathway. activation of NF-κB leads to an increase in the transcription of inflammatory genes and may be involved in the regulation of the transcription of HBV genes and viral replication, thereby exacerbating liver inflammation and injury [169,170]. Some researchers [171] have found that hepatitis B virus protein X (HBx) is able to induce relevant chemokines, such as IL-32, which exacerbates the inflammatory response after HBV infection, and that NF-κB inhibitors are effective in blocking this process. Importantly, the NF-κB signaling pathway also plays a key role in the regulation of immune response and can regulate the activation of immune cells. And the activation of NF-κB signaling pathway can affect the function of immune cells, such as B cells and T cells, and regulate the host immune response [172,173]. In addition, the NF-κB signaling pathway is capable of modulating the antiviral immune response and influencing host clearance and control of viruses [174,175]. Taken together, the NF-κB signaling pathway plays an important role in the inflammatory response and immune regulation of HBV infection. An in-depth study of the key regulatory roles of the NF-κB signaling pathway in HBV infection can help to better explore the pathogenic mechanism of HBV and provide a theoretical basis for the development of relevant immunotherapeutic strategies.

5.2. Chinese medicine treatment of chronic hepatitis B and NF-κB signaling pathway

Echinacoside (ECH) is a natural phenylethanol glycoside extracted from Cistanche spp. It has significant anticancer and

neuroprotective activities [176], in addition to some antidepressant effects [177]. Relevant studies [178–180] have also found that ECH has been widely used in the prevention and treatment of many chronic liver diseases with remarkable efficacy. Zhang and his research team [181] delved into the specific relationship between Hepatitis B virus X (HBX) and ECH, and found that ECH was able to disrupt the function of HBX in human renal tubular epithelial cells (RTECs; HK-2 cell line), exerting a significant inhibitory effect on HBX. In addition, this study revealed that NF-κB is involved in the HBX/TREM2 signaling pathway and exerts a negative regulatory effect on TREM2 expression in RTECs. The Chinese medicine Liriope platyphylla is a plant of the genus Mountain Maitake in the family Asparagaceae, with slender roots and many branches, mostly distributed in China and Japan, and it is advisable to choose a sunny, well-drained and well-aerated sandy soil with a thick layer of fertile and loose soil for planting. There was also an earlier study that found that aqueous extract of Liriope platyphylla had significant immunomodulatory activity and was effective in reducing the hyper-immune response during macrophage activation by lipopolysaccharide [182]. The ingredient LPRP-Et-97543 isolated from Liriope platyphylla roots had significant anti-HBV effects. Huang et al. [183] found that LPRP-Et-97543 effectively attenuated the nuclear expression of the p65/p50 NF-κB member proteins during anti-HBV treatment and increased the cytoplasmic IκBα protein levels. Importantly, the expression of these proteins in untransfected HBV cells was not affected in any way. LPRP-Et-97543 was able to interfere with the NF-κB signaling pathway and affect the feedback regulation of viral gene expression and viral DNA replication by HBV viral proteins, which ultimately exerted anti-HBV effects. Curcumin is a natural phenolic antioxidant extracted from the rhizomes of turmeric, and tulip tree in the ginger family, with significant immunomodulatory, anti-inflammatory, and anti-tumor effects [184, 185]. As a natural ingredient, curcumin is also mostly used in the treatment of CHB patients in the clinic. Hesari and other related researchers [186] found that curcumin can inhibit the replication of HBV virus by regulating the signaling pathways such as NF-κB, Wnt/β-catenin, and so on, and thus produce a significant therapeutic effect on CHB patients.

NC-8 (ent-16-oxobeyeran-19-N-methylureido) is an isosteviol-derived analogue with significant anti-inflammatory, antibacterial, and antiviral biological activities [187]. Relevant studies [188] have already found that NC-8 is able to inhibit the TLR2/NF-κB signaling pathway, thus exerting significant anti-HBV effects. Huang and other researchers [189], through further studies, also found that NC-8 was able to significantly inhibit the TLR2/NF-κB signaling pathway, and was also able to interfere with HBV replication and gene expression, ultimately exerting significant anti-HBV effects. Hippophae rhamnoides L. (HRP) has a long history of medicinal use in China. The roots, stems, fruits, and other parts of the plant can be used as medicine, and the fruits, in particular, are rich in nutrients and biologically active substances, with high vitamin content, which allow them to survive on salinized land, and thus they have also been widely used for soil and water conservation. Pharmacological studies [190,191] have shown that key extracts or ingredients of HRP have a wide range of benefits such as hepatoprotective, anti-inflammatory, anticancer, hypolipidemic, hypoglycemic, and antioxidant, and are also mostly used in the treatment of skin diseases. Zou et al. [192] found that HRP effectively inhibited NF-κB signaling and further regulated the cAMP/PKA/CREB/CYP2D6 signaling pathway, and also increased CYP2D6 expression in the liver, restoring the metabolic function of the liver. More importantly, this study highlights the critical role of HRP in the treatment of immune-related liver diseases, such as hepatitis B, and provides a new reference for the development of new anti-HBV drugs in the future clinic.

The traditional formula Qizhu decoction is often used in the treatment of chronic liver disease with remarkable clinical efficacy, mainly composed of Astragalus, Atractylodis Macrocephalae, and many other herbs. Wan et al. [193] conducted in vivo and in vitro experimental studies and found that Qizhu decoction extract was able to inhibit NF-κB signaling, as well as reduce the levels of inflammatory factors, such as TNF-α and IL-1β, and had a significant inhibitory effect on HBV-induced hepatitis, as well as diethylnitrosamine-induced hepatocellular carcinoma. The traditional Chinese herbal formula Sini-San (SNS), which has a long history and is derived from “Shanghan Lun”, consists of four herbs: Licorice, Chai Hu, Hovenia and Paeonia lactiflora, and is mainly used to treat the symptoms of distension and pain in the chest and chest wounds, as well as depression and irritability. Moreover, SNS is effective in the treatment of chronic liver diseases such as NAFLD, liver fibrosis and viral hepatitis [194]. Lin et al. [195] also found that SNS was able to further inhibit MMP-9 transcription by suppressing NF-κB activity. In addition, SNS was able to inhibit HBx-induced NF-κB activation, which ultimately alleviated HBx-induced hepatocellular carcinoma cell metastasis and invasion. Xiaochaihu decoction (XCHD), also from “Shanghan Lun”, has been shown to have good therapeutic effects on liver diseases such as liver fibrosis and NAFLD [196,197]. Modern pharmacological studies [198,199] have also found that XCHD also has anti-influenza virus and anti-inflammatory properties. Zeng and other scholars [76] conducted a network pharmacology study and screened 87 active components of XCHD and 155 key anti-HBV targets, and analyzed them in depth, and found that XCHD was able to exert anti-HBV effects by modulating pathways related to immunity, viral infection and metabolism. In addition, the results of GO analysis also revealed that Glycyrrhizae Radix, a key Chinese medicine for XCHD, was able to modulate the I-κB/NF-κB complex, resulting in a positive regulatory effect. All of the above studies have shown that HBV replication can be significantly inhibited after intervention with herbal monomers or herbal combinations, and that inhibition of the NF-κB signaling pathway is a potential therapeutic strategy for anti-HBV, which is even more worthy of deeper exploration in the future.

6. MAPK signaling pathway

6.1. MAPK signaling pathway and chronic hepatitis B

MAPK signaling pathway is a class of phosphorylation-mediated tertiary cascade signaling, which is of great significance in the regulation of growth signaling, and can participate in the regulation of cell growth, differentiation, proliferation, stress response and apoptosis and other biological processes [200,32]. The MAPK signaling pathway contains three main cascade kinases, namely MAPKKK, MAPKK, and finally MAPK [201,202]. Importantly, MAPKKK is at the most upstream part of the pathway and can be

responsible for receiving signals from external stimuli and passing them further downstream, and its activation further phosphorylates and activates MAPKK downstream [203,204]. MAPKK, as an intermediate node of the MAPK signaling pathway, is mainly responsible for receiving signals from MAPKK and transmitting them to the downstream MAPK, which activates downstream MAPK through phosphorylation, while MAPK receives signals from MAPKK and ultimately regulates intracellular biological effects and signal transduction through a series of phosphorylation reactions [205–207]. These three different kinases are in a cascade relationship in the MAPK signaling pathway, activating and transmitting signals sequentially, and ultimately affecting downstream cellular biological processes. The main difference between the three is the difference in their functions and positions in the signaling pathway, as well as the difference in their regulatory effects on downstream molecules [208]. When the receptors on the cell membrane and external stimuli bind, it triggers the activation of G protein-coupled receptors (GPCRs), receptor tyrosine kinases (RTKs), ion channel receptors, and cytosolic receptors, etc., and then the activated receptors transmit the signals to the signaling molecules inside the cell through transmembrane conductance, which initiates the cascade response of the MAPK signaling pathway [209,210]. The MAPK family in mammals consists mainly of ERK, p38MAPK and JNK [208].

There are five different isoforms in the ERK family, namely ERK1, ERK2, ERK3, ERK5 and ERK6, among which ERK1/2 is the most classical and the most intensively researched, which is capable of inducing cell growth and differentiation [211]. As the first pathway in the MAPK family to be elucidated, the main mode of activation of ERK1/2 is phosphorylation, and the signaling process is roughly Ras, Raf, MEK1/2, ERK [212,213]. This pathway is involved in the regulation of many cellular processes, including immune responses, cell proliferation, apoptosis, and RNA processing and synthesis [214]. p38MAPK is another MAPK pathway, an evolutionarily highly conserved serine/threonine protein kinase. p38MAPK, another MAPK pathway, is an evolutionarily highly conserved serine/threonine protein kinase. This protein family consists of members encoded by four different genes: p38α, p38β, p38γ, and p38δ [215]. p38MAPK controls a wide range of biological functions in cells by phosphorylating a large number of protein substrates in the nucleus and cytoplasm, and plays a central role in cellular adaptation to environmental changes as well as in immune responses, inflammation, tissue regeneration, and tumor formation [216]. JNK was discovered as a specific phosphorylation of an intranuclear transcription factor: c-Jun kinase, hence the name. The JNK family consists of three isoforms, JNK1, JNK2, and JNK3 [217]. In contrast, the JNK signaling pathway plays an irreplaceable role in the regulation of eukaryotic cells in response to a variety of stresses and is further involved in the regulation of the entire physiological processes of the organism through its effects on cytoskeletal protein dynamics, gene expression and cell survival pathways, among others [218]. JNK signaling pathway is highly sensitive to a variety of cellular stimuli such as viral infection, growth factors, inflammatory factors, etc., and can participate in the regulation of a variety of different cellular processes, including cell proliferation, differentiation, survival, as well as cellular senescence and apoptosis, etc., as well as being closely related to the inflammatory response and metabolic processes of the organism [219,220].

MAPK signaling pathway also plays a critical role in the onset and progression of HBV infection. Relevant studies have found that HBV infection can effectively activate the p38MAPK signaling pathway and that HBsAg-induced hepatitis can be blocked by p38MAPK signaling pathway inhibitors [93,221,222]. Moreover, the hepatitis B core antigen with strong immunogenicity is one of the key core proteins of HBV, which is positively correlated with the degree of inflammation in the liver, and it is able to promote the production of inflammatory factors such as IL-6 by hepatocytes through the activation of the p38MAPK signaling pathway, which can further lead to the occurrence or exacerbation of hepatitis [223]. In addition, some studies have found that recombinant HBV C antigen upregulates B7-H1 expression in monocyte-dendritic cells through activation of p38MAPK and ERK signaling pathways, thereby exacerbating liver inflammation [224]. In summary, the p38MAPK signaling pathway is closely related to HBV replication, and activation of this pathway may be positively correlated with HBV activity. In addition, in the MAPK signaling pathway, ERK, p38MAPK and so on also play important roles in the development of HBV infection-associated end-stage liver disease [225,226]. Therefore, we can conclude that aberrant activation of the MAPK signaling pathway plays an irreplaceable role in the developmental process of HBV infection and HBV-associated liver disease.

6.2. Chinese medicine treatment of chronic hepatitis B and MAPK signaling pathway

The natural product Ursolic acid (UA) has a wide range of pharmacological activities, such as anti-inflammatory [227], hepatoprotective [228] and anti-tumor [229], and has been widely used in clinical practice. Wu and associated investigators [230] found that UA has a potential effect on HBx-mediated tumorigenic activity in vivo and in vitro and was able to completely block the HBx-mediated effects. Using immunoblotting and specific MAPK inhibitors, these investigators also found that UA was able to selectively activate MAPK signaling in some of the tested cells, significantly inhibiting HBx-mediated tumor activity and ultimately exerting hepatoprotective effects. The polyphenol ingredient Protocatechuic acid (PCA), which is widely found in herbal medicines and our daily diet, has been shown to have significant mitigating effects on liver damage [231]. Dai et al. [232] conducted an in-depth study on the anti-HBV mechanism of PCA and found that PCA could exert its anti-HBV activity by activating the ERK1/2 pathway, thereby further inhibiting the expression of HNF1α and HNF4α in HepG2.2.15 cells. In addition, some studies have also found that the herbal monomer Cucurbitacin IIa can ultimately exert hepatoprotective and anti-HBV properties through the regulation of signaling pathways such as ERBB-MAPK and JAK2/STAT3, as well as the modulation of survivin, autophagy-associated cytokines and kinases, and apoptosis.

Matrine is an alkaloid extracted from the Sophora family of traditional Chinese medicine, which is widely used in the fields of agronomy and pharmaceutics and possesses a variety of biological activities [233]. As a Chinese medicine monomer to enhance autoimmunity, Zhou et al. found that Matrine could rapidly mediate the activation of the MAPK signaling pathway, regulate MAPK/ATF2 signaling and further inhibit HBV replication in patients with chronic HBV infection, in addition to the promising effects of Matrine to enhance human immunity [234]. Fucoidan is rich in sulfated polysaccharides of fucoidan, which have potent

anti-inflammatory and immunomodulatory effects and are often used in clinical therapy [235]. Some researchers [236] established a mouse model of HBV by hydrodynamic injection of HBV replicant plasmid. fucoidan or saline were used to intervene mice respectively, and it was found that fucoidan could significantly inhibit the secretion of HBsAg, HBeAg and HBV DNA in cells. fucoidan can also activate the ERK pathway to produce type I interferon, which can inhibit HBV replication, while the use of specific inhibitors of the ERK pathway can reduce this therapeutic effect. Ent-13-Hydroxykaur-16-ene-19-N-butylureide (EHNB), one of the 33 synthesized c -4-substituted steviol derivatives, was found to have a significant effect on HBV surface antigen secretion. Lin et al. [237] found that EHNB was able to exert anti-HBV effects by regulating the MAPK and NF-κB signaling pathways, and in Huh7 cells that had been transfected with HBV, EHNB significantly reduced the levels of ERK/MAPK and NF-κB signaling-related proteins and inhibited their phosphorylation. Importantly, the use of MAPK-specific activators was also able to impede the inhibitory effect of EHNB on viral DNA replication.

The Chinese medicine formula Gexia-Zhuyu formula (GXZY) has been mostly applied in the treatment of chronic liver diseases, such as viral hepatitis and cirrhosis of the liver, since ancient times, and its efficacy is more prominent. Cao and other researchers [238] found that GXZY can play a therapeutic role in the fibrotic lesions of liver tissue caused by the repeated progression of chronic hepatitis, involving key genes such as MYC, AR, CASP3, and JUN, etc., and functioning through the regulation of MAPK, hepatitis B, and the TNF signaling pathway, etc., through a network of pharmacological studies. Meanwhile, ex vivo and in vivo studies confirmed that GXZY was able to reduce the expression of MMP9 to regulate cell migration and proliferation, and ultimately inhibit the development of cirrhosis. Yinzhihuang granules (YZHG) is also a Chinese medicinal preparation commonly used in the treatment of chronic hepatitis, which has a good effect of clearing heat and detoxifying toxins, as well as being effective in treating neonatal jaundice [239]. Zhang et al. [240] identified a total of 13 potential YZHG anti-HBV targets through network construction, and molecular docking results revealed that TP53, CDK2, BRCA1, and CDK6 are closely related to hepatitis B treatment. It is also worth our attention that HBV can activate the MAPK signaling pathway, and YZHG can significantly inhibit this series of effects, ultimately exerting a significant antiviral effect. Nowadays, the application of Chinese medicine monomers and Chinese medicine complexes in the prevention and treatment of hepatitis B virus infection through the modulation of MAPK signaling pathway shows a broad application prospect. Based on the inheritance of traditional Chinese medicine theories, multidisciplinary in-depth integration research should be carried out and the close integration and synergistic development of basic research and clinical application should be promoted, so as to lay a solid foundation for the excavation of low-toxicity and high-efficiency new anti-hepatitis B viral drugs from traditional Chinese medicine.

7. Perspectives and conclusions

Nowadays, CHB is one of the most common factors affecting the development of end-stage liver disease, and the development of CHB is regulated by a number of signaling pathways, including YAP/TAZ signaling pathway [241], Notch signaling pathway [242] and so on, in addition to the five related signaling pathways mentioned above, but there are fewer related studies in the present, which are worthy of more in-depth exploration in the future. At present, the clinical treatment of CHB patients mostly uses antiviral drugs, generally clinical antiviral drugs can only reduce viral replication rather than a complete cure, while Chinese medicine has a strong potential in anti-HBV, through the use of traditional Chinese medicine monomers, traditional Chinese medicine combinations and proprietary Chinese medicines, etc., through the modulation of the relevant signaling pathways, thereby regulating the body's immune function and inhibiting viral replication. At the same time, acupuncture and other Chinese medicine specialties also have unique advantages in the treatment of CHB patients.

However, in this process, this study found that there are still some problems in Chinese medicine in the anti-HBV: firstly, in the process of Chinese medicine treatment, most of the Chinese medicine monomers and their extracts, Chinese medicine ingredients to regulate the relevant signaling pathway in order to play a role, and there is also a study confirming that acupuncture regulates the relevant signaling pathway to prevent and control the occurrence of CHB, which has its own merits, but there are fewer literature on the relevant acupuncture treatment in the early stage of the process, which needs to be increased to further research. Secondly, although the research on the anti-HBV of Chinese medicine has been deepening in recent years, most of the experiments are still conducted by animal experiments, and there is a lack of strong clinical data to prove whether this method is scientific and effective, so this is a problem that needs to be solved urgently in the future. Finally, there is a lack of standardized quality standards for traditional Chinese medicines, and the different duration of hepatitis B disease results in large differences in the efficacy of traditional Chinese medicines, and the characteristics of traditional Chinese medicines with multiple components, multiple targets and multiple pathways add difficulties to the study of the targets and mechanisms of anti-HBV Chinese medicines.

In conclusion, there are still some limitations in the current treatment of CHB patients with Chinese medicine, which are reflected in the unclear regulatory mechanism of Chinese medicine on the relevant signaling pathways and insufficient research and development of relevant drugs, but overall Chinese medicine anti-HBV has a high research value. The limitations of Chinese medicine based on the study of related signaling pathways can be further addressed in future research by means of modern technology with new plans such as spatial transcriptome, single-cell technology, etc. We can also gradually explore the potential application of Chinese medicine against HBV, develop related Chinese medicinal preparations, and strengthen the research of acupuncture and other characteristic therapies for the prevention and treatment of chronic liver diseases. This not only provides new strategies and methods for the prevention and treatment of CHB, but also provides a good guarantee to promote the vigorous development of Chinese medicine.

CRediT authorship contribution statement

Shihao Zheng: Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing. **Wenying Qi:** Data curation, Methodology, Writing – review & editing. **Tianyu Xue:** Data curation, Formal analysis, Supervision, Validation, Writing – review & editing. **Xiaobin Zao:** Supervision, Writing – review & editing. **Jinchi Xie:** Data curation, Project administration. **Peng Zhang:** Data curation, Supervision, Validation. **Xiaoke Li:** Data curation, Validation. **Yongan Ye:** Data curation, Funding acquisition, Writing – review & editing. **Aimin Liu:** Data curation, Formal analysis, Funding acquisition, Resources, Supervision, Writing – review & editing.

Data availability statement

Data will be made available on request.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No.82104810), Science, Technology and Innovation Specialization 2023 (Grant No.DZMKJCX-2023-014) and Changjiang Scholars Special Posting Programme (Grant No: ZYS-2021CJ01).

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.

Acknowledgments

The material in all the pictures of this article was provided friendly by Figdraw.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39176.

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