The protective effects and mechanism of myricetin in liver diseases (Review)

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Abstract. Liver diseases have become one of the significant threats to global health. However, there is a lack of effective targeted therapeutic drugs in this field and the existing drugs used for liver disease treatment usually have side-effects. Traditional Chinese medicine (TCM) has the distinctive advantages of multi-target and low side-effects. As a flavonoid with various pharmacological activities such as anti-tumour, anti-oxidant, anti-inflammatory and anti-bacterial, the TCM myricetin has been widely used in liver disease research. The present work focuses on the role and molecular mechanism of myricetin in liver diseases such as acute liver injury, fatty liver, liver fibrosis and hepatocellular carcinoma. It is a promising reference for further research and application of myricetin in the treatment of liver diseases.

Contents

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1. Introduction

As the metabolic center of the body, the liver plays a vital role in glucose metabolism, lipid metabolism, bile secretion and vitamin storage hormone synthesis (1,2). Consequently, this leads to its constant exposure to potentially pathogenic molecules or endotoxins produced by digestive products and gut microbiota. Moreover, the liver is the target of most hepatotoxic drugs and hepatitis viruses (3), which makes it highly susceptible to damage that can induce different types of liver diseases. Epidemiological reports indicate that >2 million individuals die annually worldwide from liver diseases (4). Although medicines are already available for the treatment of various common liver diseases such as acute liver injury, fatty liver, liver fibrosis and hepatocellular carcinoma (HCC), they usually induce serious adverse effects during treatment. For instance, obeticholic acid, a drug for treating liver fibrosis, can cause itching, while sorafenib, a drug for treating liver cancer, can cause diarrhea (5,6). Therefore, it is urgent to explore safer medicines with fewer side-effects for the treatment of liver diseases.

Traditional Chinese medicine (TCM) has received increasing attention from researchers in the treatment of liver diseases due to its high efficiency, multi-targeting and low side effects. As a monomer of TCM, myricetin (3,3',4',5,5',7-hexahydroxyflavone) is a natural polyhydroxy flavonoid extracted from various plants (7). It has a good safety profile for consumption, as well as being an important ingredient in food and juice drinks (8,9). The US Food and Drug Administration has approved myricetin as being a healthy product (10). Recent studies have revealed that myricetin plays a vital role in the treatment of liver diseases (11,12). Given its edible safety and low side-effects, myricetin is probably a promising candidate for the treatment of liver diseases. However, a review of the efficacy and mechanism of myricetin in the treatment of various liver diseases has not been made, to the best of the authors' knowledge. In view of this, the present study summarized the progress of research on myricetin in the treatment of liver diseases to provide a direction and basis for further exploration of the potential of myricetin in the clinical treatment of liver diseases.

2. Sources and characteristics of myricetin

Myricetin, initially extracted from the bark of *Myrica nagi* by Perkin and Hummel, is widely present in a variety of plants, such as *Rosa canina* L. (Rose Hip), *Urtica dioica* L. (Nettle) and *Portulaca oleracea* L. (Purslane) (13,14). The structural formula of myricetin is shown in Fig. 1. Its relative molecular mass is 318.24 and its melting point is within the range of 324.0-325.5˚C. It is soluble in methanol, ethanol and ethyl acetate, slightly soluble in water and insoluble in chloroform and petroleum ether (15). It has been found that berries, vegetables and tea also contain myricetin and there are two main methods to obtain myricetin, namely plant extraction and chemical synthesis (16,17). Moreover, myricetin possesses multiple biological characteristics such as anti-bacterial, anti-inflammatory, anti-oxidant, anti-tumour and immunomodulatory effects (18-20). In view of this, the present study focused on the efficacy and mechanism of myricetin in liver diseases.

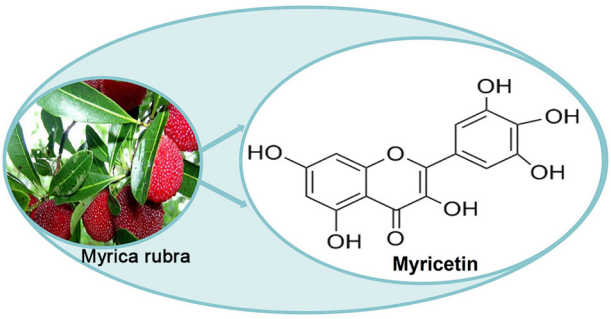

Figure 1. The source and molecular structure of myricetin.

3. Role of myricetin in acute liver injury

Acute liver injury is a liver dysfunction disease with rapid onset, complex causative factors and significant clinical symptoms. As the major component of the outer membrane of Gram-negative bacteria, lipopolysaccharide (LPS) is an important virulence factor inducing acute liver injury (21). It can be recognized and bound by the Toll-like receptor (TLR) 4, which activates the NF-κB signalling pathway to induce an inflammatory response (22). Inactive NF-κB will bind to IκB and remain in the cytoplasm, but when NF-κB in the conjugate is activated, the two become phosphorylated and separate (23). Subsequently, phosphorylated (p-)NF-κB is translocated to the nucleus, thereby inducing the expression of immune-associated factors such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), IL-6, TNF-α and IL-1β (24). Notably, Berköz *et al* (25) found that myricetin inhibits the expression of p-NF-κB and p-IκB, as well as the inflammation-associated factors COX-2, iNOS, IL-6, TNF-α and IL-1β in a rat model of LPS-induced acute liver injury (Fig. 2). As members of the MAPK cascade system family, ERK, JNK and P38 play essential roles in acute liver injury (26). D-galactosamine (D-GalN), a chemical hepatotoxic agent, is often combined with LPS for the study of acute liver injury. Unexpectedly, Lv *et al* (27) found that myricetin inhibits the expression of TLR4, p-IκB and MAPK members (p-ERK, p-JNK and p-P38) in LPS/D-GalN-induced acute liver injury, thereby attenuating inflammation-induced liver injury (Fig. 2).

In addition, LPS/D-GalN disrupts the mitochondrial structure of hepatocytes and generates large amounts of reactive oxygen species (ROS), thereby inducing oxidative stress (28). Nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) is an important regulatory pathway for liver oxidative stress, in which HO-1 degrades heme and releases biliverdin, CO and ferrous ions to alleviate liver oxidative stress (29). Excessive ROS in hepatocytes induces Nrf2 into the nucleus, promoting the expression of the downstream anti-oxidant gene HO-1 (30). In acute liver injury, myricetin with strong anti-oxidant and free radical scavenging ability promotes the expression of Nrf2 and Ho-1 to alleviate liver oxidative stress injury (Fig. 2) (20,27). Excessive ROS induces the expression and phosphorylation of P53 in hepatocytes (31). P53 promotes the expression of Bax (a pro-apoptotic gene) and inhibits the expression of Bcl-2 (an anti-apoptotic gene), which induces an increase in mitochondrial membrane permeability, resulting in the release of pro-apoptotic factors, such as cytochrome *c*, from the mitochondria into the cytoplasm (32). In the cytoplasm, cytochrome *c* forms an apoptotic complex with apoptotic protease-activating factor-1, which activates caspase-9 and caspase-3, thereby triggering the mitochondrial apoptotic pathway and leading to aberrant apoptosis in hepatocytes (33). Lv *et al* (27) found that myricetin reduces the protein expression of activated caspase-3 (cleaved caspase-3) and caspase-9 (cleaved caspase-9) to inhibit aberrant apoptosis in acute liver injury (Fig. 2). In addition, caspase-3 activates endonucleases in apoptosis, cleaving nuclear DNA and inducing DNA damage (34). STAT3 is involved in DNA damage repair and its phosphorylation (p-STAT3) promotes the expression of FOXM1, which initiates the expression of proteins involved in the regulation of the DNA damage repair system (35). Significantly, Matić *et al* (36) found that myricetin promotes the expression of p-STAT3 and p-Akt to inhibit DNA damage in pyrogallol-induced acute liver injury (Fig. 2).

4. Role of myricetin in fatty liver disease

Fatty liver disease is a metabolic disease characterized by hepatocellular steatosis, which mainly consists of non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD). With the change of the lifestyle and dietary structure of an individual, the incidence of fatty liver disease has shown a significant growing trend and has become a major threat to health in recent years. It has been found that myricetin not only relieves acute liver injury but also plays a vital role in treating AFLD and NAFLD (37,38).

AFLD. AFLD is a chronic liver disease caused by prolonged and heavy alcohol consumption. Studies have shown that disorders of lipid metabolism, oxidative stress and inflammatory responses are all associated with the development of AFLD (39,40).

In the liver, alcohol is first converted to acetaldehyde by alcohol dehydrogenase (ADH), then to acetic acid by acetaldehyde dehydrogenase (ALDH) and then enters the tricarboxylic acid cycle as acetyl-CoA, which is eventually converted to CO_2

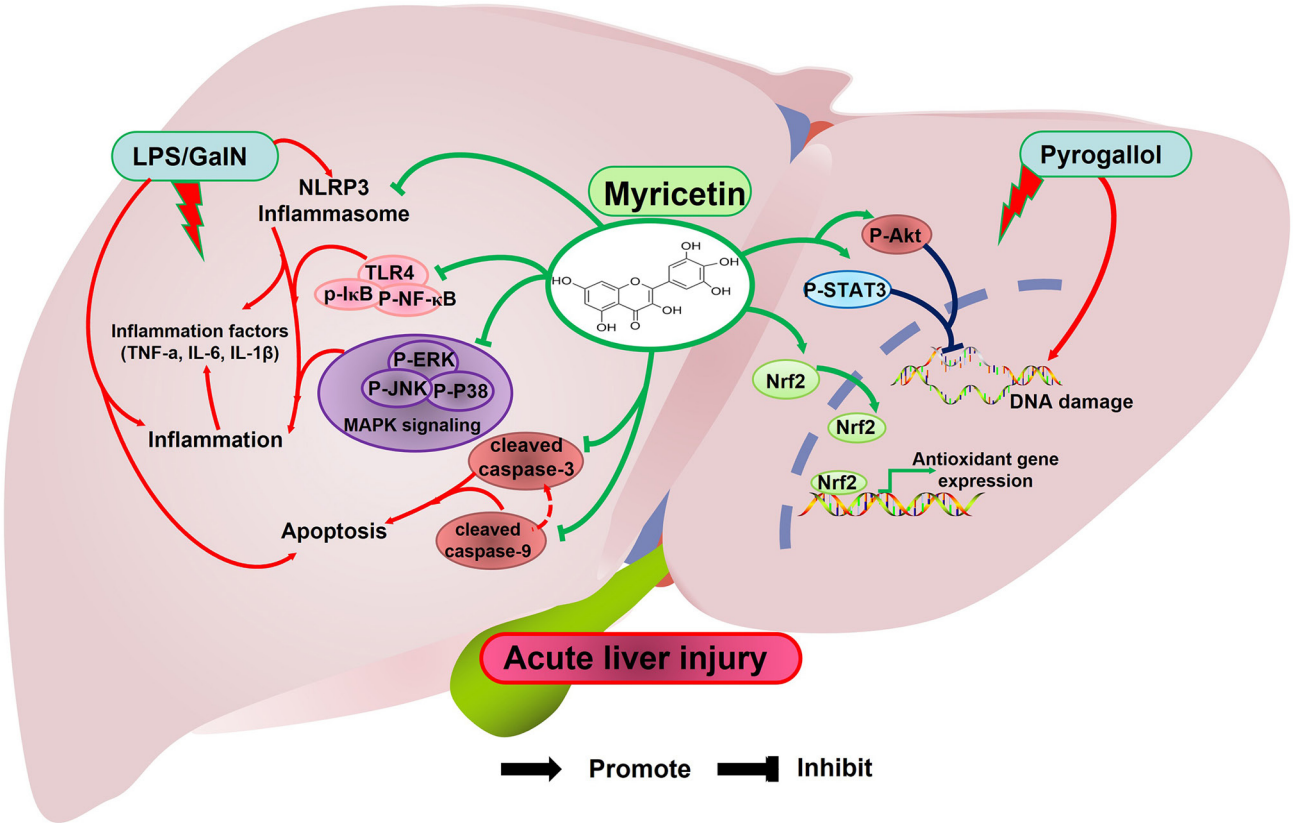

Figure 2. The molecular mechanism of myricetin in alleviating acute liver injury by regulating inflammatory response, apoptosis, DNA damage and anti-oxidant. LPS, lipopolysaccharide; p-, phosphorylated; GaIN, galactosamine; NLRP3, Nod-like receptor family pyrin domain containing 3; Nrf2, nuclear factor erythroid 2-related factor 2.

and H_2O (41). In addition, cytochrome P450 2E1 (CYP2E1) in the liver can be activated by ethanol to oxidize ethanol into acetaldehyde and produce large amounts of ROS, which can induce mitochondrial dysfunction, inhibit fatty acid β-oxidation and exacerbate the formation of FLD (42). Myricetin attenuates ROS-induced ALFD by decreasing ADH and CYP2E1 activities and alcohol-induced oxidative damage in the liver by decreasing ROS and MDA levels (Fig. 3) (38,43).

Dysregulation of lipid metabolism due to aberrant expression of metabolic enzymes is another key factor in the pathogenesis of AFLD. Acetyl coenzyme A carboxylase, the rate-limiting enzyme for *de novo* synthesis of fatty acids and carnitine palmitoyltransferase 1 (CPT1), the rate-limiting enzyme for fatty acid oxidation, work together to maintain lipid homeostasis (44). AMP-activated protein kinase (AMPK) can promote lipid metabolism in the liver by inactivating acetyl coenzyme A carboxylase through phosphorylation and promoting the expression of CPT1; moreover, p-AMPK can reduce fatty acid synthesis by decreasing the expression of Srebp-1 (45). Guo *et al* (38) found that myricetin promotes the expression of phosphorylated AMPKa and reduces ethanol-induced lipid synthesis and accumulation in the liver (Fig. 3).

NAFLD. First proposed by Ludwig *et al* (46) in 1980, NAFLD is a liver disease caused by steatosis in the absence of alcohol intake. It is currently the most common liver disease worldwide and a significant risk factor for the development of HCC. Similar to AFLD, disorders of lipid metabolism, oxidative stress, inflammatory response and apoptosis are also the pathogenic mechanisms in NAFLD (47).

The accumulation of triglycerides in hepatocytes is known as steatosis, which is the initial stage in the development of NAFLD. As a member of the ligand-activated nuclear receptor superfamily, peroxisome proliferator-activated receptor gamma (PPAR-γ) plays a vital role in the development of NAFLD. It has been found that PPARγ upregulates the expression of CD36, which promotes fatty acid transmembrane transport and exacerbates liver lipid accumulation (48). It also upregulates the expression of Srebp-1, which promotes liver lipid synthesis and exacerbates the development of NAFLD (49). Myricetin was found to inhibit the expression of PPARγ and CD36 and alleviate high-fat diet-induced liver steatosis, as well as inhibit the expression of Srebp-1 and reduce liver fat content in *ob/ob* mice (Fig. 3) (50,51). Nrf2 protects the liver by regulating the expression of anti-oxidant enzymes nicotinamide adenine dinucleotide phosphate: quinone oxidoreductase 1 (NQO1) and HO-1 to scavenge ROS (52). In NAFLD, myricetin promotes the expression of NRF2 and its downstream genes NQO1 and HO-1, thereby alleviating liver oxidative stress (Fig. 3) (53).

The imbalance of intestinal flora structure is another crucial factor in the occurrence and development of NAFLD. It will affect the levels of metabolites such as short-chain fatty acids, bile acids and inflammatory factors (54). Acetic acid, propionic acid and butyric acid are the majority of short-chain fatty acids produced in the intestinal environment

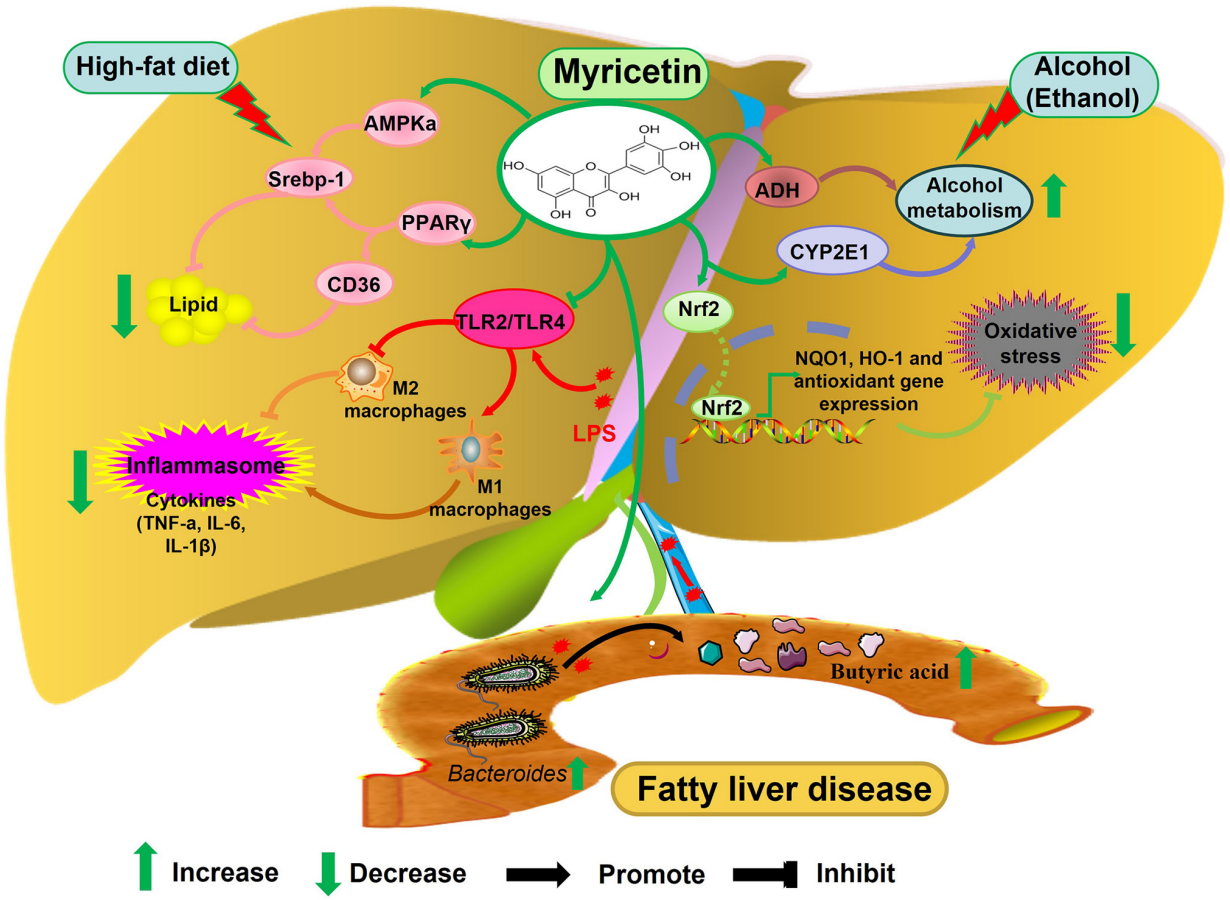

Figure 3. The molecular mechanism of myricetin in alleviating fatty liver disease by regulating inflammatory response, lipid metabolism, oxidative stress, alcohol metabolism and intestinal flora. AMPK, 5' AMP-activated protein kinase; PPARγ, peroxisome proliferator-activated receptor gamma; TLR, Toll-like receptor; ADH, alcohol dehydrogenase; CYP2E1, cytochrome P450 2E1; NQO1, NADPH quinone oxidoreductase 1; HO-1, heme oxygenase 1; Nrf2, nuclear factor erythroid 2-related factor 2.

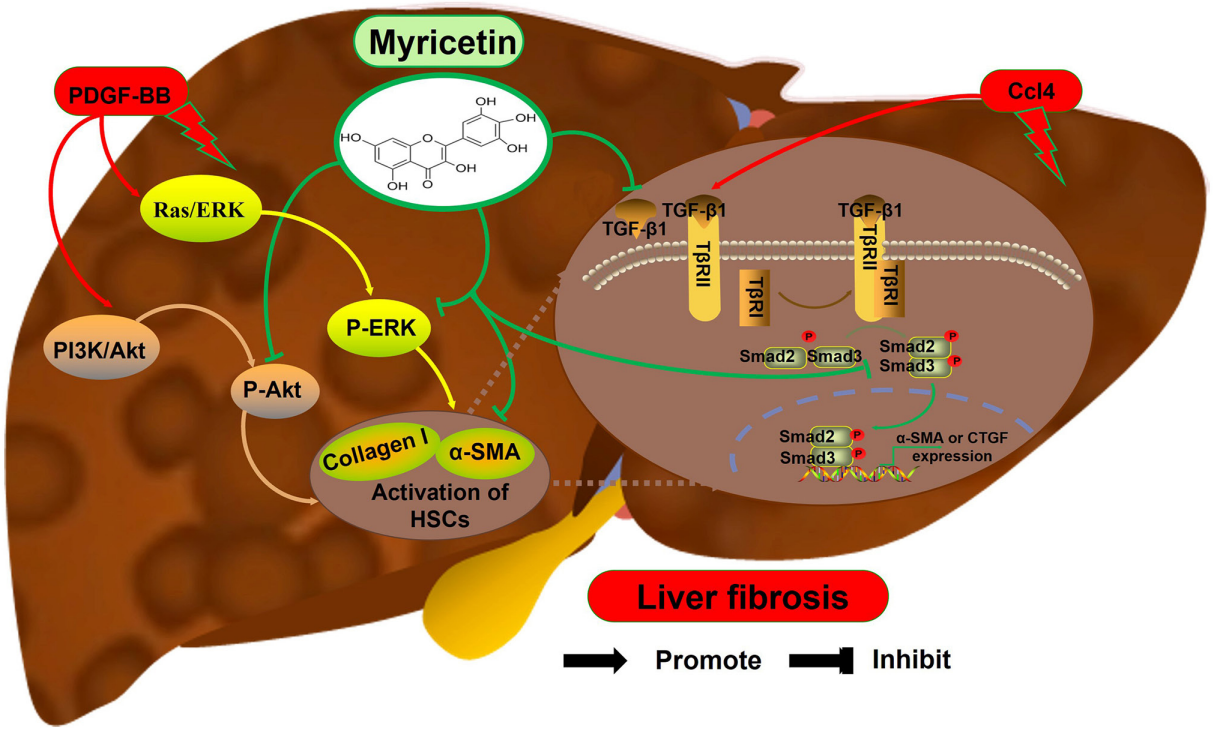

Figure 4. The molecular mechanism of myricetin alleviates liver fibrosis. PDGF BB; α-SMA, α-smooth muscle actin; p-, phosphorylated; TβRII, type II TGF-β receptors; TβRI, type I TGF-β; HSCs, hepatic stellate cells; CTGF, connective tissue growth factor.

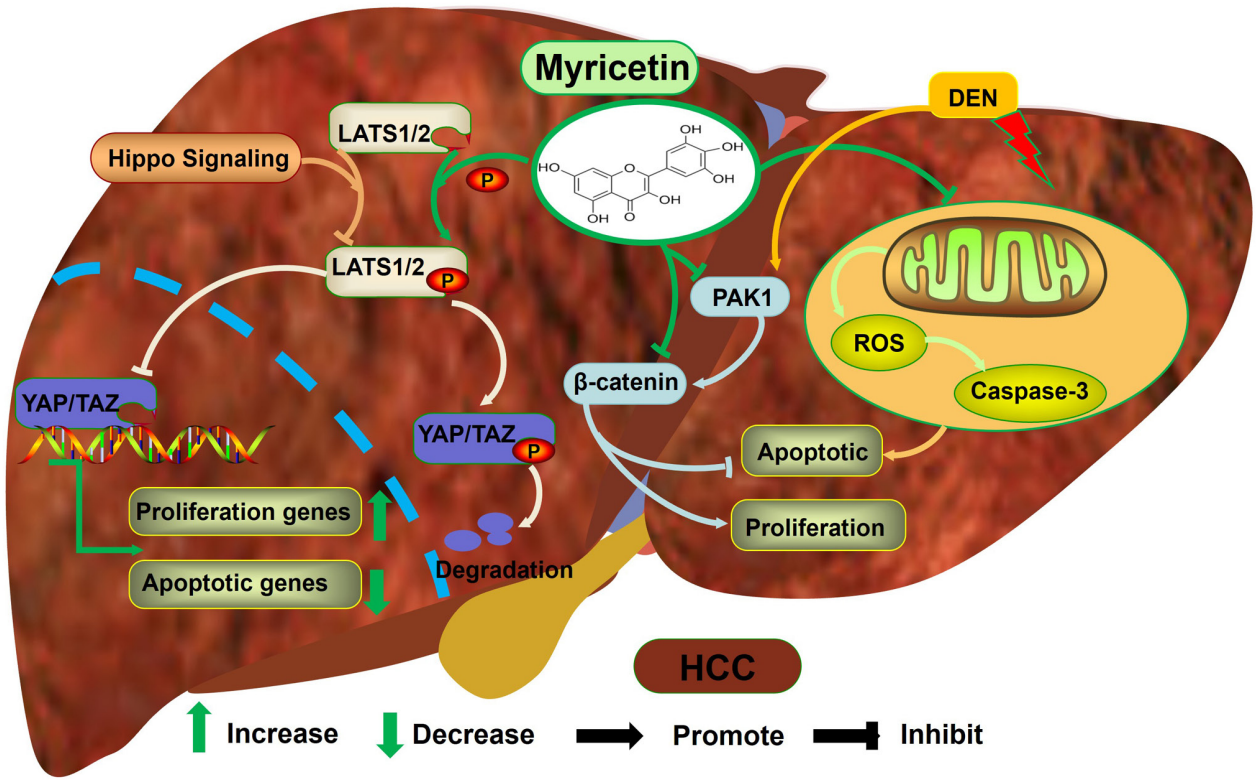

Figure 5. The molecular mechanism of myricetin inhibits the development of HCC by regulating cell proliferation and apoptosis. HCC, hepatocellular carcinoma; YAP, yes-associated protein; TAZ, transcriptional co-activator with PDZ-binding motif; LATS1/2, large tumor suppressor 1/2; DEN, diethylinitrosamine; PAK1, p21-activated kinase 1; ROS, reactive oxygen species.

and their content ratio is ~3:1:1 (55). Butyric acid can limit ATP synthesis by regulating uncoupling and participate in liver fatty acid oxidation to reduce lipid accumulation (56,57). Sun *et al* (58) found that myricetin can increase the abundance of *Bacteroides* to increase the butyric acid content and inhibit liver fat accumulation induced by a high-fat diet (Fig. 3).

Tight junctions [claudins, occludin and (ZO)], adherens junctions and intercellular junctions consisting of desmosomes are important components of the intestinal barrier, effectively preventing the invasion of harmful substances and bacteria. Decreased expression of tight junction proteins induces significant enlargement of cell pores and increased intestinal mucosal permeability leads to impairment of the intestinal barrier (59). Intestinal bacterial metabolites (such as LPS) can be released into the blood and liver via the portal venous system, stimulating the release of inflammatory factors from the liver, thereby inducing NAFLD (60). Peña-Rodríguez *et al* (61) found that butyric acid upregulates the expression of occludin and ZO-1 and maintains the integrity of the intestinal mucosal barrier, thereby inhibiting liver inflammation. Similarly, Sun *et al* (58) found that myricetin can increase butyric acid content and promote the expression of ZO-1, thereby inhibiting high-fat diet-induced liver inflammation (Fig. 3). LPS can bind to TLR2/TLR4 on the surface of macrophages, inducing macrophages to polarize to the M1 type and releasing large amounts of pro-inflammatory factors, such as TNF-α, IL-1β and IL-6 (62). Myricetin can alleviate macrophage polarization to the M1 type and promote its polarization to the M2 type with an anti-inflammatory effect by reducing the expression of TLR2/TLR4 in macrophages and thus attenuating the inflammatory response in NAFLD (Fig. 3) (63).

5. Role of myricetin in liver fibrosis

Liver fibrosis is usually recognized as the pathological process of massive synthesis and sustained accumulation of extracellular matrix (ECM) following chronic liver injury. The activation process of hepatic stellate cells (HSCs) expressing α-smooth muscle actin (α-SMA) and producing large amounts of ECM is considered as the key link in the development of liver fibrosis (64). TGF-β1 is the most potent HSC activator. During HSC activation, first, TGF-β1 binds to the type II TGF-β receptors (TβRII), recruiting type I TGF-β receptors (TβRI) to form the TGF-β1/TβRII/TβRI complex (65). Then, the complex generated in the previous step induces a conformational change in TGF-β1R, which promotes the binding of Smad2 to Smad3 and phosphorylation to form the p-Smad2/p-Smad3 complex (66). Finally, the complex generated in the previous step binds to either α-SMA of the nucleus or DNA of connective tissue growth factor, regulating their expression to promote the activation of HSCs (67). Notably, myricetin inhibits the expression of TGF-β1, p-Smad2, p-Smad3 and α-SMA in the livers of mice infected with *S. japonicum*, thereby alleviating the development of liver fibrosis (Fig. 4) (68).

In addition, platelet-derived growth factor (PDGF) secreted by platelets promotes the activation of HSCs and the deposition of ECM, contributing to the development of liver fibrosis. PDGF-BB promotes the activation and proliferation of HSCs by activating PI3K/Akt and Ras-ERK signaling pathways via promoting the expression of p-AKT and p-ERK in CFSC-8 cells (rat hepatic stellate cells)

Table I. Role of myricetin in different liver diseases.

First author, year	Type of liver disease	Animal/cell model	Functions	Role	(Refs.)
Xiao, 2021	Acute liver injury	Lipopolysaccharide-induced Balb/c mice model	Inhibits oxidative stress, inflammation	Alleviates liver injury	(24)
Kim, 2023	Acute liver injury	D-galactosamine-induced C57BL/6J mice model, HepG2 cell	Inhibits oxidative stress, inflammation, apoptosis	Alleviates liver injury	(26)
Shih, 2022	Acute liver injury	Pyrogallol-induced Wistar rat model	Inhibit DNA damage	Alleviates liver injury	(35)
Chang, 2012	AFLD	Ethanol-induced AML12 cells	Inhibits inflammation, fatty acid synthesis	Alleviates liver injury	(37)
Leung and Nieto, 2013	AFLD	Ethanol-induced Wistar rat model	Promote ethanol metabolism; Inhibits oxidative stress, inflammation	Alleviates liver injury	(42)
Chen, 2023	NAFLD	High-fat-fed C57BL/6J mice model	Promote lipid metabolism	Alleviates liver injury	(49)
Xia, 2019	NAFLD	*ob*/*ob* mice model	Inhibits oxidative stress, lipid accumulation	Alleviates liver injury	(50)
Lei, 2024	NAFLD	High-fat-fed C57BL/6J mice model	Inhibits oxidative stress, lipid accumulation	Alleviates liver injury	(52)
Zhang, 2023	NAFLD	High-fat-fed rat model	Inhibits inflammation, lipid synthesis	Alleviates liver injury	(57)
Peña-Rodríguez, 2022	NAFLD	High-fat-fed C57BL/6J mice model, RAW264.7 cells	Inhibit lipid accumulation, liver fibrosis, cell death, inflammation	Alleviates liver injury	(61)
Dewidar, 2019	Liver fibrosis	*Schistosoma japonicum*-Infected BALB/c mice model	Inhibits inflammation and fibrosis	Alleviates liver injury	(67)
Li, 2020	Liver fibrosis	Ccl4-induced BALB/c mice model and CFSC-8B cells	Inhibits HSC proliferation, migration, ECM accumulation	Attenuates liver fibrosis	(69)
Geng, 2017	Liver fibrosis	Ccl4-induced BALB/cN mice model	Inhibits oxidative stress, inflammation, fibrosis; Promote proliferation	Alleviates liver injury	(70)
Lee, 2021	HCC	HepG2 and Huh-7	Inhibits HCC cell proliferation, Promote apoptosis	Alleviates liver fibrosis	(72)
Li, 2019	HCC	DEN-induced rat model, HepG2	Promotes apoptosis	Inhibits HCC	(73)
Chandel and Tuveson, 2014	HCC	DEN/2-AAF-induced rat model	Promotes oxidative stress and apoptosis	Inhibits HCC	(78)

AFLD, alcoholic fatty liver disease; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma.

cells (69). Geng *et al* (70) found that myricetin reverses the PDGF-BB-induced increase in the expression of p-AKT and p-ERK and decreases the expression of α-SMA and collagen type I (Collagen I) in CFSC-8 cells (Fig. 4). Similarly, myricetin inhibits the expression of liver TGF-β1 and α-SMA in the Ccl4-induced mouse liver fibrosis model, thereby alleviating liver fibrosis (Fig. 4) (71).

6. Role of myricetin in HCC

HCC is one of the most common cancers worldwide. The signalling pathways that regulate its occurrence and formation have become the focus of researchers' attention in recent years. The hippo signalling pathway controls liver tumorigenesis by regulating the balance between cell proliferation and

apoptosis. In HCC, inactivation of the hippo signalling pathway promotes the entry of yes-associated protein (YAP)/transcriptional co-activator with PDZ-binding motif into the nucleus, leading to the abnormal proliferation of HCC cells (72). Myricetin alleviates the development of HCC by inhibiting cell proliferation and promoting apoptosis (Fig. 5) (73). Mechanistically, myricetin promotes the phosphorylation of large tumor suppressor 1/2 to degrade YAP protein and reduce its nuclear translocation (73). This leads to a decrease in the expression of proliferation-promoting genes and an increase in the expression of anti-apoptotic genes in HCC cells (73). As a serine/threonine protein kinase, p21-activated kinase 1 (PAK1) activates the β-catenin signalling pathway to promote the proliferation of cancer cells and inhibit their apoptosis (74). Myricetin inhibits the expression of PKA1 and β-catenin in the diethylinitrosamine-induced rat HCC model, contributing to decreased proliferation and increased apoptosis of HCC cells (75).

Mitochondria are double-membrane organelles that play an important role in cellular energy production, metabolism and signal transduction. The liver, as a major metabolic organ, is rich in mitochondria. Mitochondrial dysfunction in hepatocytes leads to an abnormal increase in ROS, which promotes the activation of oncogenes, inducing the development of HCC (28,76). Moreover, ROS can promote oxidative stress in the liver, causing telomere shortening and chromosomal abnormalities and inducing the transformation of normal hepatocytes into HCC cells (77). However, Chandel and Tuveson (78) found that high levels of ROS can also promote apoptosis and necrosis in HCC cells, thus inhibiting the development of HCC. Analogously, Seydi *et al* (79) found that myricetin can target mitochondria and increase ROS levels and caspase-3 activity in HCC cells, thereby promoting apoptosis of HCC cells (Fig. 5). Briefly, myricetin inhibits the development of liver cancer by regulating the proliferation and apoptosis of HCC cells.

7. Limitations and future prospects

As the main constituent of medicinal and edible bayberry, myricetin possesses biological characteristics such as anti-tumour, anti-oxidation, anti-inflammatory and anti-bacterial properties (18-20). In liver diseases, the mechanisms of myricetin's action on different types of liver diseases show diversity. However, these mechanisms still cannot fully explain the role of myricetin in various liver diseases and the specific molecular mechanisms need to be further explored. Although a large number of studies have confirmed that myricetin notably improves various liver diseases, this is only at the stage of animal or cellular experiments. To date, clinical trials with myricetin for the treatment of liver diseases have not yet been conducted. Therefore, the future work on myricetin in liver diseases needs to be more invested in clinical research. In addition, the stability of myricetin is limited, which leads to its lower bioavailability. Therefore, future research on the pharmaceutical dosage form of myricetin should be intensified to improve its bioavailability

As a monomer of TCM, myricetin is generally considered to be a safe drug. Yang *et al* (80) found no side effects in mice treated with 1,000 mg/kg of myricetin. In addition, human umbilical vein endothelial cells did not show significant cytotoxicity following treatment with myricetin (81). However, Canada *et al* (82) found that the cellular activity of isolated guinea pig intestinal cells was reduced and significant cellular damage occurred following treatment with myricetin. There are also those who consider that myricetin is capable of autoxidation, potentially leading to the development of oxidative stress (83). Therefore, there is an urgent need to further investigate the potential toxicity mechanisms of myricetin.

8. Conclusions

As a common disease, liver disease has become a serious threat to the health and lives of individuals all over the world. Although there are a wide variety of medications available for the treatment of liver diseases, they all possess significant side-effects and their efficacy remains unsatisfactory. Given the obvious advantages of TCM in research and development cost and therapeutic efficacy, the treatment of liver diseases with TCM has gradually been increasingly accepted and emphasized by researchers in recent years. The present study discussed the effectiveness and mechanism of myricetin in acute liver injury, fatty liver, liver fibrosis and HCC, which can facilitate further research on therapeutic drugs for liver diseases (Table I). It is hoped that the present review will draw the attention of liver disease research scholars to TCM.

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Author's contributions

CO and YL conceptualized the manuscript and revised and edited the manuscript. MC and SZ drafted the manuscript and prepared the figures. XH, DZha and DZhu supervised and revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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