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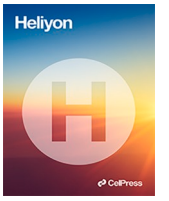

Review article

The impact of traditional Chinese medicine and dietary compounds on modulating gut microbiota in hepatic fibrosis: A review

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ABSTRACT

Traditional Chinese medicine (TCM) and dietary compounds have a profound influence on the regulation of gut microbiota (GM) in hepatic fibrosis (HF). Certain substances found in both food and herbs that are edible and medicinal, such as dietary fiber, polyphenols, and polysaccharides, can generate beneficial metabolites like short-chain fatty acids (SCFAs), bile acids (BAs), and tryptophan (Trp). These compounds contribute to regulate the GM, reduce levels of endotoxins in the liver, and alleviate fibrosis and inflammation in the liver. Furthermore, they enhance the composition and functionality of GM, promoting the growth of beneficial bacteria while inhibiting the proliferation of harmful bacteria. These mechanisms mitigate the inflammatory response in the intestines and maintain the integrity of the intestinal barrier. The purpose of this review is to analyze how the GM regulates the pathogenesis of HF, evaluate the regulatory effect of TCM and dietary compounds on the intestinal microflora, with a particular emphasis on modulating flora structure, enhancing gut barrier function, and addressing associated pathogenic factors, thereby provide new insights for the treatment of HF.

1. Introduction

As the largest organ in the body, the liver serves as the hub that connects significant amounts of nutrients, toxins, and hormones to the rest of the body [1]. The liver, the body's largest organ, functions as a central hub, processing and distributing nutrients, toxins, and hormones throughout the body. Chronic hepatic injury caused by metabolic, exogenous, immune, or microbiological triggers results in dysfunction and pathological changes, including inflammatory cell infiltration, hepatocyte degeneration, and proliferation [2]. HF is a serious liver disease with a high global prevalence. The World Health Organization (WHO) identifies liver disease imposes a major global health burden. HF, a critical stage in liver disease progression, poses significant risks to human health [3]. HF emerges from chronic liver conditions characterized by scar tissue formation, typically resulting from inflammatory reactions and tissue damage.

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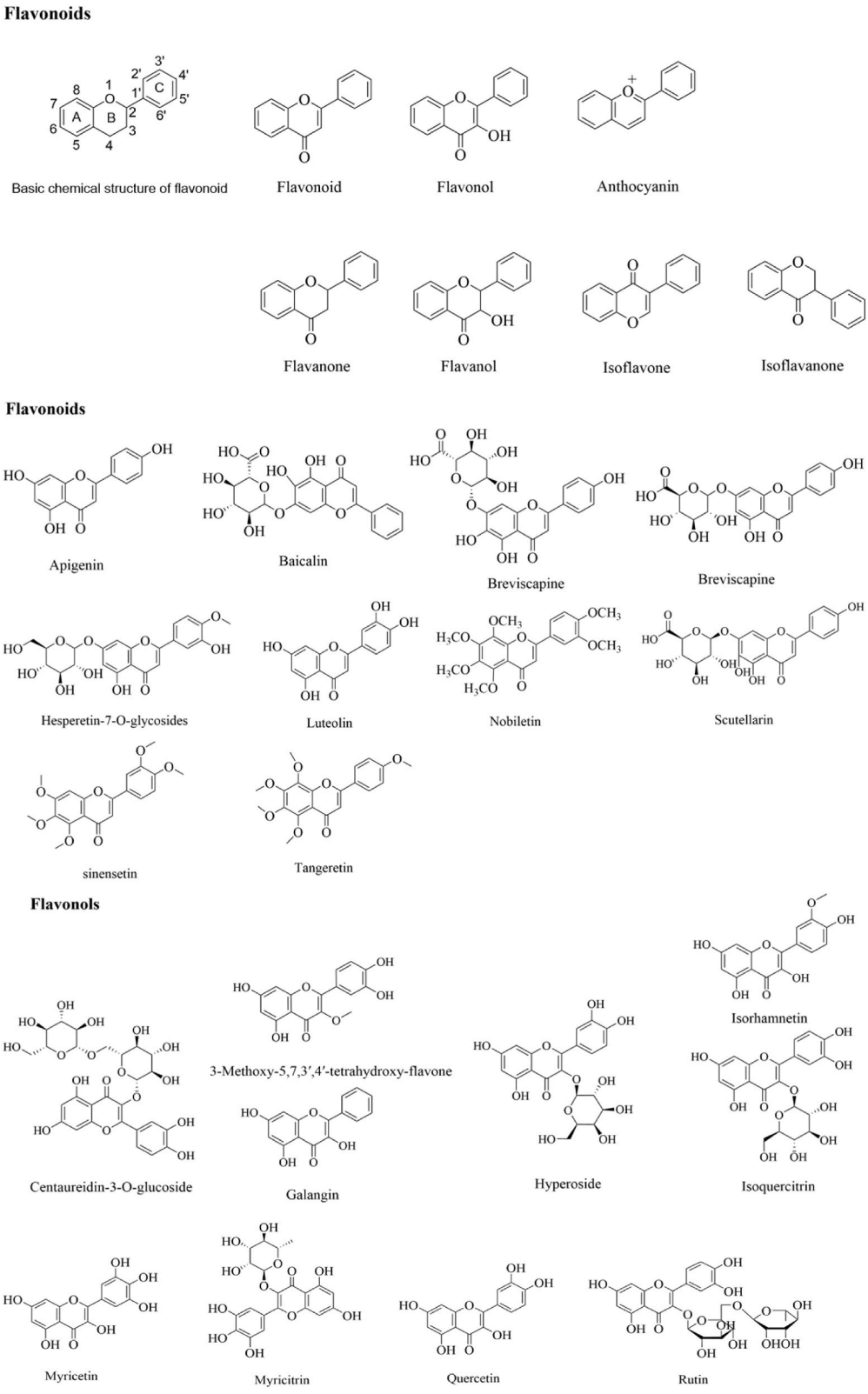
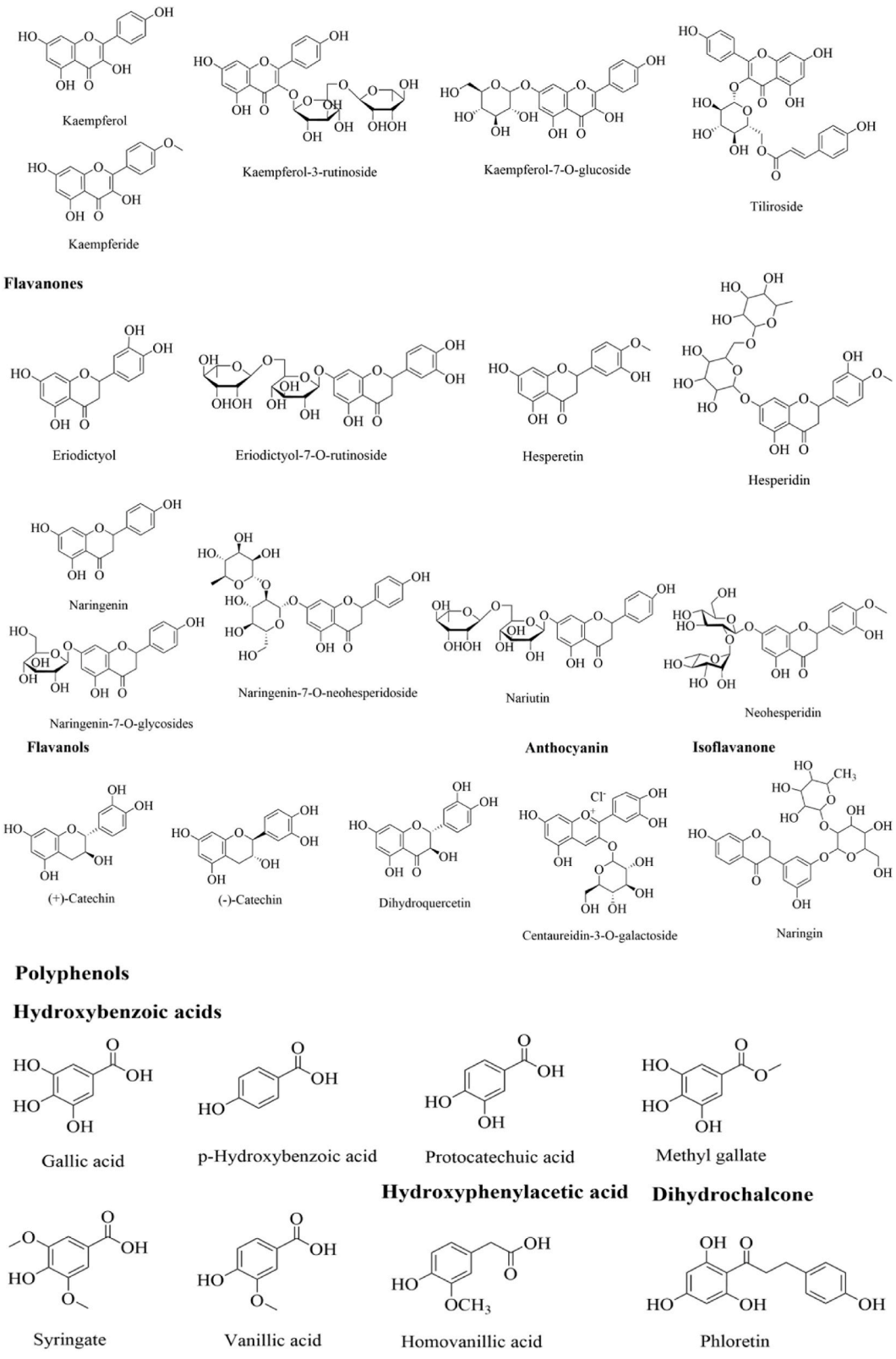


Fig. 1. Structures of several traditional Chinese medicine and dietary compounds.



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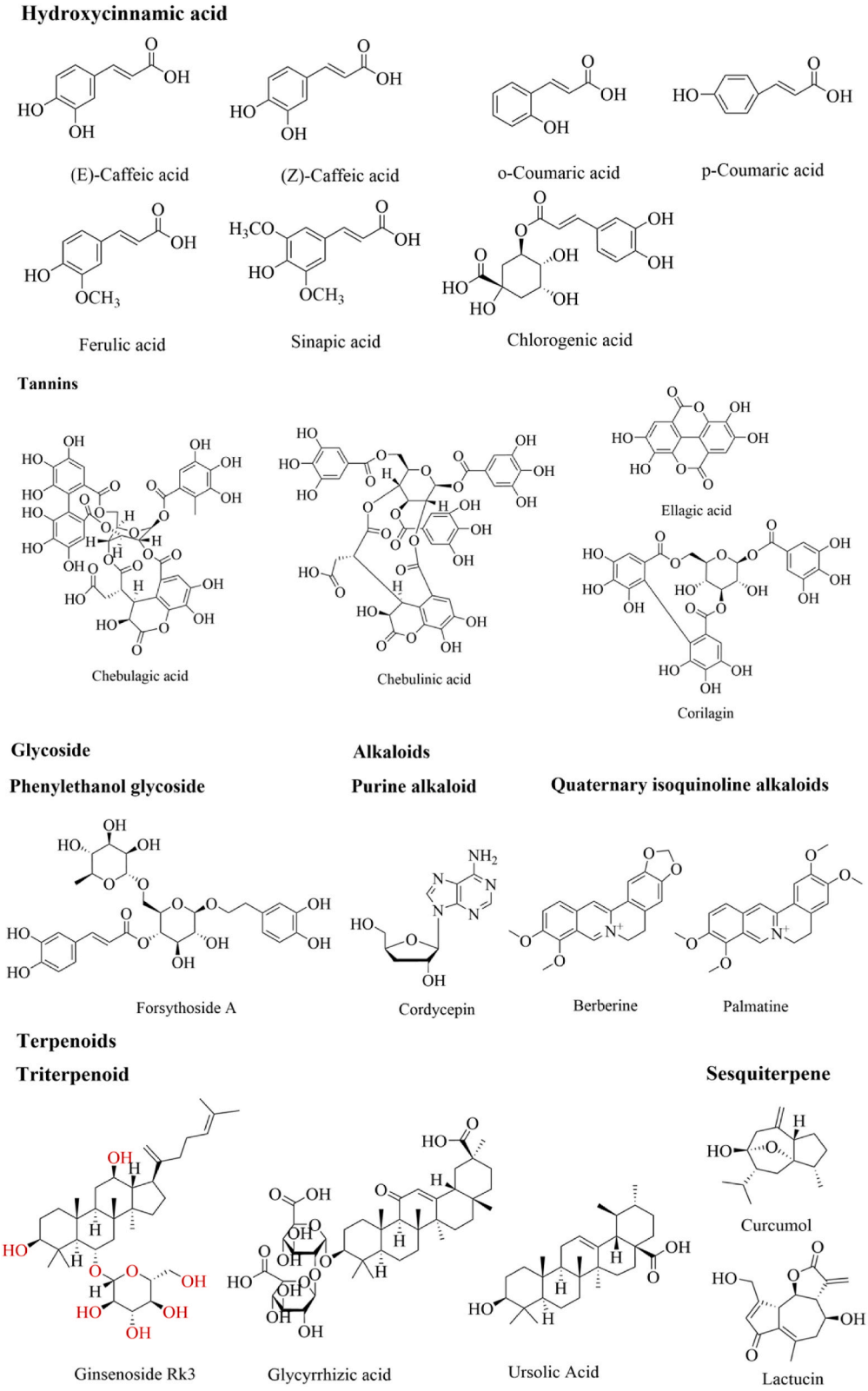

Fig. 1. (*continued*).

Typical causes include chronic hepatitis, viral infections, alcohol abuse, and fatty liver [4]. The progression of HF involves complex interactions among various cell types, including persistent viral antigen damage, extracellular matrix (ECM) alterations, hepatic stellate cells (HSCs) activation, oxidative stress, inflammation, and signaling pathways activation [5]. As HF advances, it induces liver structural changes, causing increased portal vein resistance and complications such as portal hypertension, ascites, and esophageal varices. Without treatment, HF can progress to irreversible cirrhosis or liver cancer, posing serious threats to patients' lives [6]. The study highlights the potential reversibility of HF and underscores the importance of timely detection and intervention to halt disease progression and improve outcomes [7].

Maintaining intestinal flora balance, enhancing intestinal barrier function, and regulating metabolites and immune responses are critical for preventing and treating HF. Recent research has demonstrated that GM, the microorganisms in the intestines, significantly affect human metabolic health [8]. Furthermore, there is a complex and reciprocal relationship among intestinal flora, the liver, and the immune system. Intestinal flora produces various active metabolites. These metabolites are absorbed into the bloodstream by the host and then enter the enterohepatic circulation. Metabolomics techniques can identify specific metabolites linked to disease phenotypes by analyzing blood, urine, and tissue samples. These analyses can reveal potential connections between the microbiome, metabolome, and host phenotype [9]. Disruptions in host-flora equilibrium may result from various internal and external factors. These disruptions can destabilize the gut micro-ecosystem, leading to compromised bodily functions and the diseases development [10]. The immune system must distinguish between beneficial and harmful microorganisms to maintain body health [11].

Over the past decade, scientists have thoroughly investigated the correlation between the gut-liver axis, GM, and chronic liver disease progression [12]. The gut-liver axis describes the complex interplay between the digestive tract and the liver [13]. These interactions impact the body both metabolically and immunologically through bidirectional connection between the biliary tree and portal circulation [14–16]. The GM comprises numerous bacteria in the human gut that play a crucial role in regulating the gut-liver axis [17]. The GM influences chronic liver disease progression through various mechanisms [18,19]. The microbial population produces SCFAs, which serve as energy sources for sustaining intestinal cells, maintaining barrier function, and reducing toxin release from the gut [20]. Microbial metabolites, such as BAs and Trp, may affect liver metabolism and immune responses [21,22]. This process helps reduce liver inflammation.TCM and dietary compounds may play a beneficial role in treating HF. TCM and dietary compounds primarily treat HF by modulating the GM and restoring equilibrium to the gut-liver axis [23]. These compounds can influence GM composition and function, regulate concentrations of bacterial metabolites, metabolic byproducts, and BAs, thereby impacting liver metabolism and immune responses [24]. By modulating GM and restoring balance to the gut-liver axis, certain TCM and dietary compounds have shown potential in treating HF (Fig. 1). This study explores how the GM regulates the development of HF. It is concluded that TCM and dietary compounds can prevent HF by modulating the intestinal flora, maintaining the intestinal barrier function, and regulating flora metabolites levels. These therapies focus on gut-liver axis and GM, providing novel strategies to improve liver function and treat chronic liver disease.

2. GM involved in HF

Many investigations have shown that patients with HF have altered GM. Extensive research has focused on understanding the precise mechanisms through which the GM influences the onset of liver disease. The intestinal flora is essential to human health because it mediates various physiological processes related to the host, including immunomodulation, nutritional metabolism, maintenance of the intestinal mucosal barrier's structural integrity, and defense against microbial invaders [25].

The gastrointestinal tract of a healthy individual hosts a diverse array of microorganisms. Over 400 different bacterial species inhabit the human colon, collectively forming the GM, a vast and intricate ecosystem. The GM comprises five primary phyla: *Firmicutes* (79.4 %) (*Ruminococcus*, *Clostridium*, and *Eubacteria*), *Bacteroidetes* (16.9 %) (*Porphyromonas, Prevotella*), *Actinobacteria* (2.5 %) (*Bifidobacterium*), *Proteobacteria* (1 %), and *Verrumicrobia* (0.1 %). In the gut, *Lactobacilli*, *Streptococci*, and *Escherichia coli* are present in trace amounts [26]. Environmental and genetic factors influence the composition of GM. The composition of GM in individuals is influenced by factors such as age, diet, medication, and the environment as they age [27]. *Bacteroidetes* and *Firmicutes* are the most abundant phyla in the intestinal mucosal bacterial community. When *Firmicutes/Bacteroidetes* ratio in the intestine is 2:1, indicates a healthy and stable GM. HF is characterised by an aberrant *Firmicutes/Bacteroidetes* ratio, indicating a disruption in the balance of the GM [28]. Inflammatory factors are released, and the intestinal barrier becomes dysregulated when *Firmicutes* increase and *Bacteroidetes* decrease in relative abundance [29]. In HF, abnormal regulation of gut flora is observed, with a significant increase in the *Firmicutes/Bacteroidetes* ratio [30]. These two phyla play a crucial role in providing energy and nutrition to the host [31]. *Firmicutes*, *Bacteroides*, and *Bifidobacterium* synergistically utilize indigestible carbohydrates to produce SCFAs [32]. *Desulfovibrio* and *Prevotellaceae_UCG_003* are beneficial microorganisms that mitigate intestinal illnesses by producing SCFAs [33]. The presence of Lachnospiraceae and Lactobacillaceae in the gut are strongly associated with acetic acid formation [34]. Additionally, research has demonstrated that higher levels of Lactobacillaceae in the gut are associated with lower levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the liver.

3. Microbiota metabolites involved in HF

3.1. SCFAs

SCFAs are produced by intestinal flora during the metabolism of dietary fiber and are primarily composed of acetic acid, propionic acid and butyric acid [35]. In recent years, SCFAs have been found to have anti-inflammatory possess anti-inflammatory properties HF,

inhibiting the development of hepatic inflammation and fibrosis [36]. Moreover, SCFAs can influence immune cell differentiation and function, regulating the immune response [37]. For example, acetic acid can inhibit HSC activation by activating the adenosine monophosphate-activated protein kinase (AMPK) signalling pathway, thereby slowing HF progression [38]. Inulin reduces inflammation by suppressing M1 macrophages (Mψ) and promoting M2 Mψ through SCFAs action, which may help regulate the disease [39]. Berberine (BBR) has been shown to regulate various mechanisms, including HSC activation, oxidative stress, inflammation, and lipid metabolism [40]. It has been discovered that BBR modulates signalling pathways linked to peroxisome proliferator-activated receptor γ (PPARγ), nuclear factor kappa B (NF-κB), and AMPK, as well as endoplasmic reticulum (ER) stress [41–45]. BBR increases SCFAs-secreting GM, particularly *Clostridia*, thereby maintaining host health [46,47].

SCFAs, significant microbiota metabolites, influence immunity and metabolism, thereby improving HF. SCFAs inhibit the activity of histone deacetylase (HDAC) and the activation pathways of G protein-coupled receptors (GPCRs). This inhibition prompts macrophages to release chemokines and anti-inflammatory substances. SCFAs inhibit the release of tumor necrosis factor (TNF) by macrophages and promote the growth and specialization of T lymphocytes. These properties may be harnessed in treating cancers [48,49]. SCFAs provide energy to intestinal epithelial cells, enhancing the barrier through cell differentiation, mucin production, antimicrobial peptide synthesis, and the upregulation of tight junction (TJ) protein [50]. Moreover, the two main genera that produce SCFAs, *Lactobacillus* and *Eubacterium*, are significantly reduced in HF patients [51]. Fig. 2 demonstrates the possible mechanisms by which microbiota metabolites——SCFAs are involved in HF.

3.2. Trp

Trp is an essential amino acid that is obtained through dietary protein. Trp can inhibit the activation of HSCs, thereby slowing the progression of HF. Additionally, Trp can promote the proliferation and regeneration of liver cells, aiding in the repair of damaged liver tissue and improving HF. Trp exerts antioxidant effects by scavenging free radicals and reducing oxidative stress in the liver, inhibiting HF onset and progression. Indole and other Trp-derived bacterial metabolites reduce the expression of pro-inflammatory cytokines in macrophages and regulate inflammatory responses in hepatocytes [52]. What I want to stress is that Trp anti-inflammatory effects, inhibiting the release of inflammatory factors and reduceing the degree of liver inflammation, thereby slowing down the progression of HF. Notably, Trp inhibits the production of collagen in the liver, a significant component of HF, thereby helping to reduce HF [4]. Lycium barbarum polysaccharide (LBP) may improve liver health by modulating metabolite levels, including the regulation of Trp and SCFAs [53].

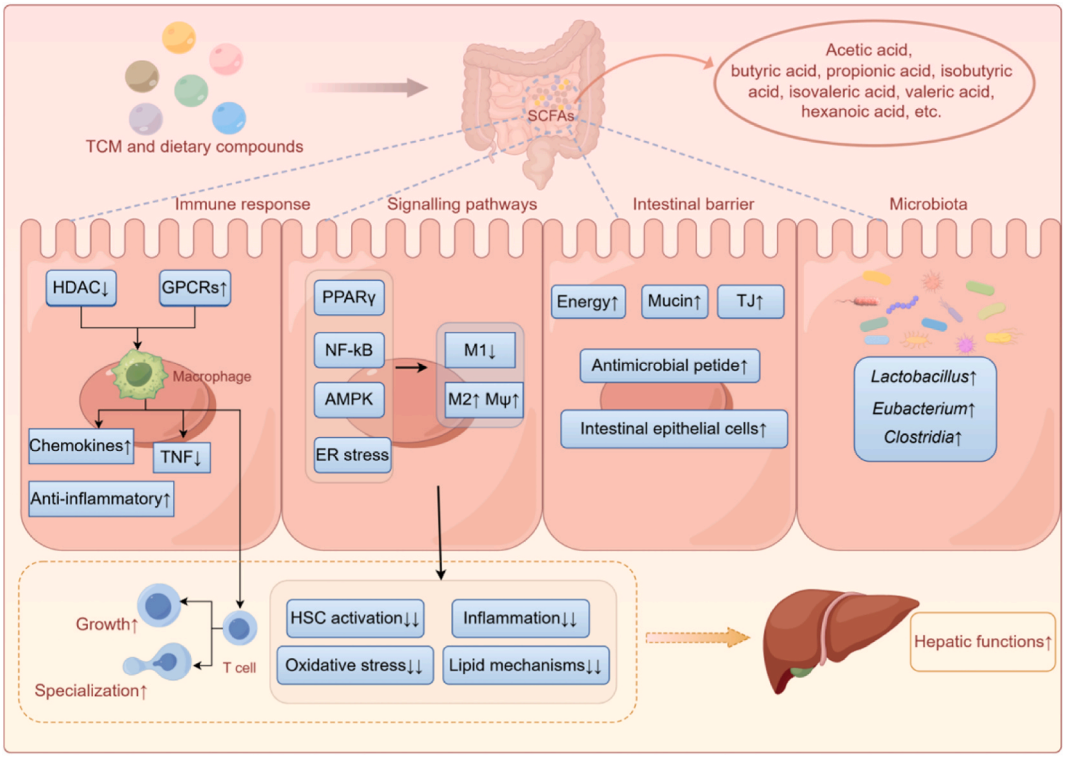

Fig. 2. The possible mechanism of microbiota metabolites——short-chain fatty acids (SCFAs) involved in hepatic fibrosis. Drawn by Figdraw.

3.3. BAs

BAs circulate between the liver and intestine, performing essential physiological functions, particularly in regulating lipid metabolism, the inflammatory response, and HF [54–56]. BAs are crucial for maintaining the balance of the intestinal flora, which, in turn, regulates the size and composition of the BAs pool. This balance ensures the proper excretion and circulation of BAs in the liver and intestines [57–59]. Research has shown that BBR significantly increases *Firmicutes*, especially *Clostridium*, which are essential for proper metabolic pathways and BA transport in the digestive tract and liver [60]. Additionally, changes in the GM may reduce BA synthesis, promoting the growth of harmful and inflammatory bacteria, including Enterobacteriaceae and Porphyromonadaceae [61]. BAs interact with the farnesoid X receptors (FXRs) and the cell surface receptor Takeda G protein-coupled receptor 5 (TGR5), which can modify BAs-mediated metabolism [62]. These interactions affect lipid metabolism, inflammation, and fibrosis [63,64]. Research suggests that BBR may alter lipid metabolism by affecting BAs metabolism [65,66].

It has been found that both primary and secondary BAs play a role in regulating the metabolic and immunological responses of the host, which in turn affects the development of HF. Secondary BAs levels, including deoxycholic acid (DCA), glycocholic acid (GCA), and taurocholic acid (TCA), were elevated, whereas primary BA levels, such as cholic acid (CA) and chenodeoxycholic acid (CDCA), were reduced. These changes resulted in improved BAs metabolism. In addition, the citrus flavonoids intervention significantly increased the relative abundances of Christensenellaceae and Porphyromonadaceae. Significant improvements were observed in the deficiencies of FXR and TGR5 [67].

4. Other metabolic pathways of microbiota metabolites involved in HF

4.1. Triglyceride

Metabolic syndrome and lipid profile abnormalities are associated with elevated triglyceride levels [68]. BBR effectively reduces triglyceride accumulation in the liver and alleviates liver injury, as demonstrated by animal studies. In the BBR group, the expression of the lipid metabolism-related gene stearoyl-coenzyme A desaturase 1 (SCD1) was lower compared to the control group [69]. Sacran can reduce serum triglyceride levels, attenuate hepatic steatosis, inhibit oxidative stress and inflammatory, and maintain liver function [70].

4.2. Trimethylamine N-oxide

Oxidative stress can disrupt the intestinal barrier by directly oxidizing biological components and causing cell death. Specifically, reactive oxygen species (ROS) change mucosal glycosylation, enhancing bacterial adhesion, internalization, and translocation across epithelial cells [71,72]. The antioxidant system comprises enzymatic and nonenzymatic components. Enzymatic antioxidants include catalase, glutathione peroxidase, and superoxide dismutase. On the other hand, non-enzymatic antioxidants include antioxidants vitamins, amino acids, and metalloproteins. The production of ROS in the gastrointestinal tract is facilitated by several enzyme systems, each of which is localized and expressed uniquely. The mitochondrial respiratory chain, xanthine oxidase, NOX, and nitric oxide synthase are components of this system [73]. NOX-induced intestinal oxidative stress is strongly associated with the deterioration of the intestinal mucosal barrier in several clinical situations [74].

4.3. Cholesterol metabolism

Cholesterol itself does not directly trigger an immune response. However, in the liver, abnormal cholesterol metabolism can promote immune cell activation and inflammatory responses, which indirectly drive the progression of HF. In cases of liver damage, cholesterol may combine with fatty acids to form cholesteryl esters, which activate HSC and promote fibrosis [75]. Liver X receptors (LXRs), negatively regulate cholesterol metabolism by promoting the catabolism, excretion, and reverse transport in hepatocytes. LXRs also have anti-inflammatory effects in immune cells, including macrophages. Activation of LXR has been shown to inhibit acute hepatitis mediated by Kupffer cells and macrophages [76]. BBR inhibits proprotein convertase subtilisin/kexin type IX, which regulates the degradation of low-density lipoprotein receptor (LDLR). This inhibition is responsible for BBR's capacity to reduce cholesterol levels [77]. Studies have shown that *Laminaria japonica* polysaccharides (LJP) regulated cholesterol metabolism-related gene expression, and significantly reduced serum triglycerides (TG), glucose, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) levels, highlighting LJP's therapeutic potential in metabolic and liver health [78]. GM plays an important role in cholesterol metabolism and gut health. *Bifidobacterium* and *Bacteroidetes* are positively correlated with cholesterol levels, whereas *Lactobacillus* and *Coccidioides* are negatively correlated with cholesterol levels [75].

4.4. Arachidonic acid pathway

Arachidonic acid is an essential unsaturated fatty acid that is commonly found in cell membranes as phospholipids under normal physiological circumstances. In response to stimuli, phospholipase A2 (PLA2) facilitates the release of arachidonic acid from phospholipids. Once released, arachidonic acid is converted into several active metabolites that trigger an inflammatory chain reaction. These metabolites include prostaglandin E2 (PGE2), thromboxane B2, and 15-deoxy-12,14-prostaglandin J2 (15d-PGJ2) [79]. Key enzymes in arachidonic acid metabolism include cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450) [80].

BBR inhibits COX and LOX expression and reduces the formation of PGE2 and leukotriene B4, both inflammatory metabolites. Consequently, BBR helps mitigate the effects of the inflammatory cascade [81].

4.5. *Pyruvate and lactic acid*

Pyruvate and lactate are common organic acids involved in the development and progression of HF. Pyruvate, an intermediate in the tricarboxylic acid (TCA) cycle, plays a role in energy metabolism and substance synthesis in the liver. Accumulation of pyruvate can lead to oxidative stress in liver cells, increasing the risk of HF. Lactate, a product of glycolysis, is normally converted to pyruvate by the liver, which then enters the TCA cycle for metabolism [82]. Accumulation of lactic acid can trigger an inflammatory response in the liver, worsening HF. Therefore, it is important to adjust the metabolic pathways of pyruvate and lactate to improve the physiological function of the liver in the treatment of HF.

5. The intestinal barrier involved in HF

The gastrointestinal tract and liver interact bidirectionally through portal circulation, forming the gut-liver axis [23,83,84]. GM and metabolites are the primary signals in this axis. The intestinal mucosal and vascular barriers create an environment that supports the gut-liver connection [85,86]. The intestinal epithelium is a vital part of the intestinal barrier, consisting of a layer of closely connected epithelial cells that form a physical barrier to prevent harmful substances and microorganisms from entering the body [87]. Key components of the intestinal barrier include the gut epithelium, villus height, villus width, and crypt depth. These structures play an important role in maintaining intestinal barrier function and preventing HF [88]. Higher villus height is typically associated with healthy intestinal absorption and barrier function. Reduced villus height may signal impaired absorption, which, in turn, affects intestinal barrier function and increases the risk of HF. Abnormal villus width may indicate abnormal differentiation or damage to the intestinal epithelium, compromising barrier function and allowing harmful substances to enter the liver. Crypt depth reflects the regenerative capacity of intestinal epithelial cells. Moderate crypt depth supports healthy regeneration, while excessive depth may indicate overproduction of epithelial cells, often linked to inflammation or pathology. This condition can impair intestinal barrier function and increase risk of HF [89–91]. Radix Puerariae thomsonii polysaccharides increase the thickness of the mucus layer within the intestinal barrier, thereby enhancing its function. These actions prevent harmful chemicals from entering the bloodstream from the gastrointestinal tract, protecting the body from intestinal bacteria [92].

The gut epithelium's TJs operate as a natural defence against bacteria and the byproducts of their metabolism [93]. TJ proteins, including occludin, claudins, and zonula occludens-1 (ZO-1), are crucial for maintaining the intestinal barrier. They help keep TJs

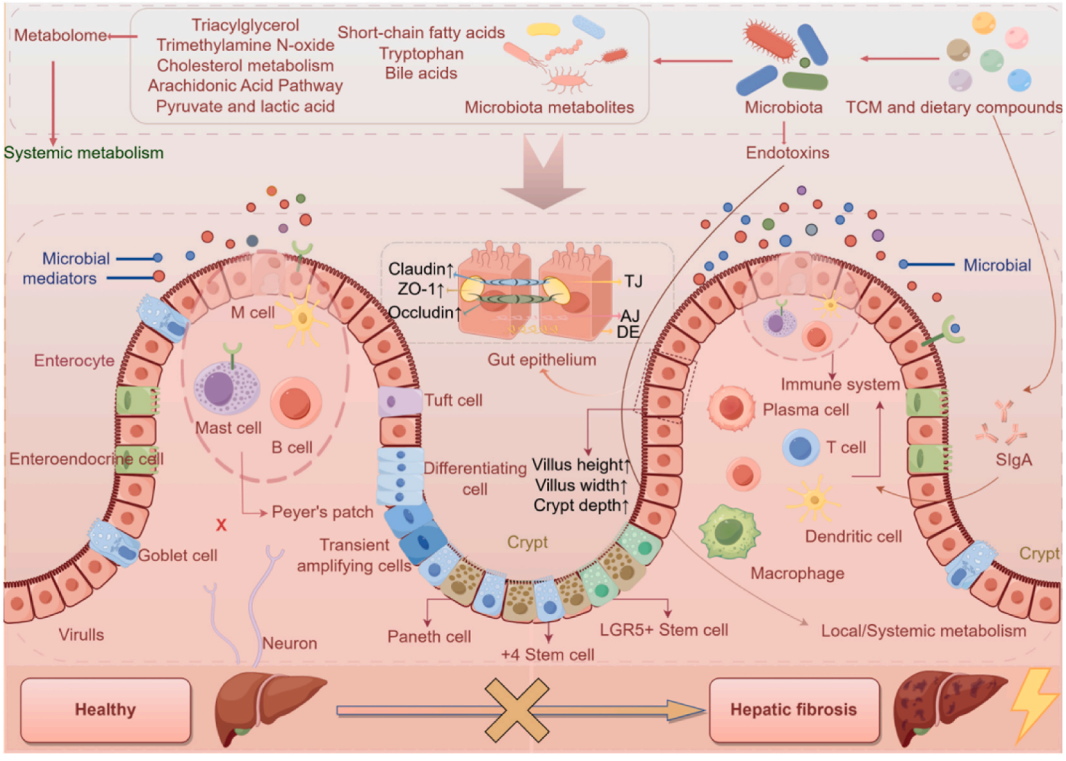

Fig. 3. The intestinal barrier involved in hepatic fibrosis. Drawn by Figdraw.

between epithelial cells and prevent harmful substances from crossing into the bloodstream [94,95]. Ursolic acid (UA) improved intestinal dysbiosis and increased the expression of the TJ proteins Claudin-1 and Occludin in the ileum of rats [96]. Peritoneal adipose tissue primarily maintains the integrity of the intestinal barrier, ensuring its optimal function. Supplementation with Phytic Acid (PA) in high-fat diet-fed mice preserved normal MUC2 protein levels in colon tissues and increased the expression of TJ proteins, such as Claudin 3, Occludin, and ZO-1 [97]. Upon passing through these linkages, pathogenic microbes or food-borne antigens (Ag) are either recognized by dendritic cells or activate the adaptive immune system by modulating the T-cell response. Infectious cytokines and chemokines are produced when toll-like receptors (TLRs) and Nod-like receptors (NLRs) activate the NF-κB [98]. This process occurs when low concentrations of pathogen-associated molecular patterns (PAMPs), such as flagellin, peptidoglycans, and lipopolysaccharides (LPS), enter the portal circulation. Activation of stellate cells by PAMPs not only leads to hepatocyte injury but can also promote the development of fibrosis. Kupffer cells are more sensitive to LPS than hepatocytes [99–104]. Subsequently, endotoxin can impede protein synthesis in intestinal lining cells, thereby harming the intestinal barrier. This damage may lead to bacterial migration from the intestines to other body parts, disrupting the microbial balance [87,105].

Multiple studies have demonstrated that maintaining the balance of the GM is crucial for safeguarding the integrity of the intestinal epithelial barrier and enhancing the immune defense of intestinal epithelial cells [106,107]. Bacteria such as *Neisseria*, *Vermicella*, and Enterobacteriaceae produce LPS, and are more prevalent in patients with HF [108]. The gut also contains trace levels of *Lactobacillus*, *Streptococcus*, and *Escherichia* [109]. Bacterial colonization can stimulate the development of HSC and the generation of mucus. Additionally, it can suppress the growth of *Salmonella* Typhimurium [110], Pathogenic *Escherichia coli* [111], and *Clostridium* difficile [112]. Certain bacteria are involved in the transformation of bioactive lipids and BAs, as discussed in the section on bioactive lipids and BAs [113]. Research has documented that *Akkermansia* positively impacts host metabolism by preventing endotoxin generation through thickening the intestinal mucus layer, thereby strengthening the intestinal barrier. These effects contribute to the proper functioning of epithelial cells and the maintenance of energy balance. Fig. 3 illustrates the role of the intestinal barrier involved in HF. Dysfunction of the gut barrier directly or indirectly contributes to the development of HF by increasing intestinal permeability, disrupting TJ proteins, triggering mucosal inflammation, and altering intestinal immune cell activity. Therefore, preserving gut barrier integrity and maintaining a healthy microbiota are crucial for preventing and treating HF.

6. TCM and dietary compounds regulate immunotherapy through GM intervention

LPS is a common endotoxin present in the outer membrane of the cell wall of Gram-negative bacteria. Disturbances in the GM often lead to elevated LPS levels. Disturbances in the intestinal flora disrupt TJ proteins. This disruption allows LPS to pass through the portal vein into the bloodstream and hepatic sinusoids, resulting in chronic liver inflammation and fibrosis. On the other hand, LPS can also

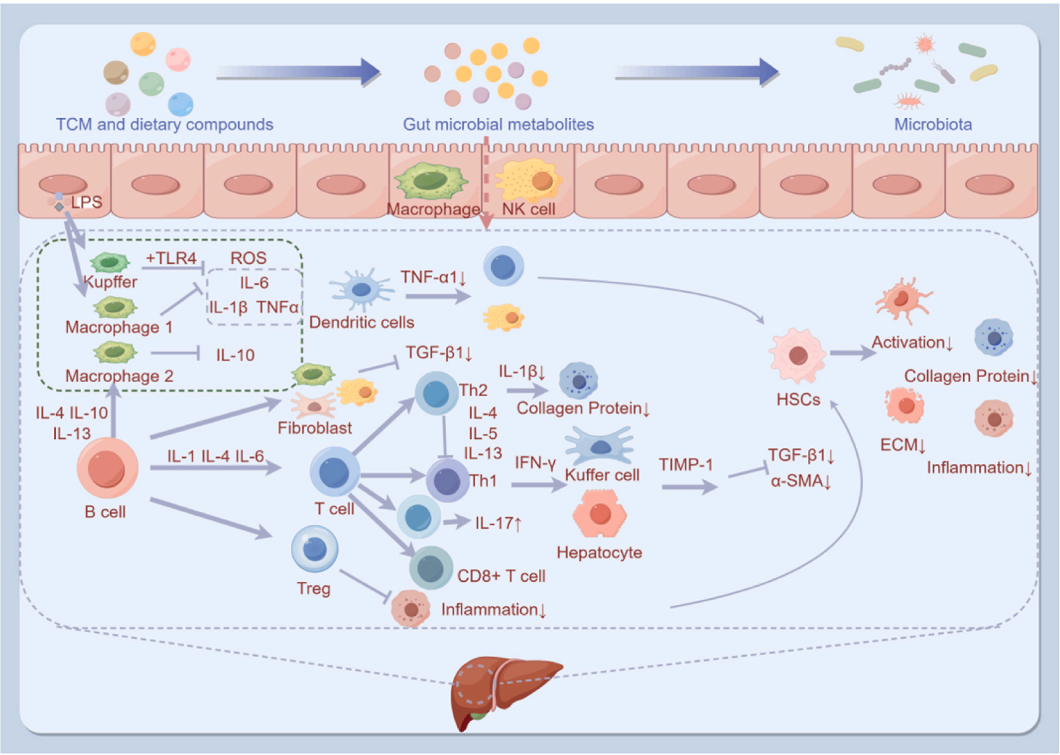

Fig. 4. The possible mechanism of immunotherapy through gut microbiota modulation in hepatic fibrosis. Drawn by Figdraw.

stimulate macrophages, leading to the release of inflammatory mediators such as macrophage inflammatory protein-1 alpha (MIP-1α) and TNF-α, which can induce HF [114–116]. LPS acts as a ligand for TLR4, activates TLR4 signal transduction, activates NF-κB, enhances the expression of interleukin 8 (IL-8), and consequently amplifies the inflammatory response [98,117]. Total flavonoids extracted from Rosa laevigata Michx fruits (TFs) protect against LPS-induced hepatic injury and regulate oxidative stress, inflammation, and lipid metabolism by modulating the FXR signaling pathway [118].

TCM and dietary compounds can reduce pro-inflammatory factors in the blood through various mechanisms (Fig. 4). These compounds suppress activities that produce pro-inflammatory cytokines, thereby reducing levels of TNF, interleukin IL-1, IL-6, and other related cytokines. Meanwhile, SCFAs can regulate the balance of GM, leading to a decrease in the production of inflammatory mediators. Research has shown that specific TCM and dietary compounds can increase the levels of anti-inflammatory cytokines, such as IL-10 and interferon-γ (IFN-γ). Cordyceps sinensis polysaccharide enhances the proliferation and cytokine secretion of human T-lymphocytes and murine RAW264.7 cells, thereby improving cellular immunity [119]. Furthermore, TCM and dietary compounds have been shown to reduce the levels of Cluster of Differentiation $CD3^+$, $CD4^+$, and $CD8^+$ T-lymphocytes in the liver [120]. BBR activates the AMPK signaling pathway [121], inhibits macrophage polarization and TGF-β1 signaling, alleviates HF [122]. It inhibits the activity of cytosolic PLA2 and COX-2 [123], by regulating the synthesis and metabolism of SCFAs [56].

Cytokines are multifunctional proteins that participate in immunomodulation, inflammation, hematopoiesis, and other biological processes [124]. The major cytokine families include interleukins, chemokines, colony-stimulating factors (CSFs), granulocyte-macrophage colony-stimulating factors (GM-CSFs), interferons (IFNs), and tumor necrosis factors (TNFs). IL-2, GM-CSF, TNF, and IFN-γ are secreted by Th1 cells and are involved in immune responses against tumor cells. IL-4, IL-5, IL-6, and IL-10 are secreted by Th2 cells and are associated with the immune evasion of tumor cells. Cytokine production is regulated by the transcription factor FoxP3, which enhances its own expression by promoting the signal transduction and phosphorylation of signal transducer and activator of transcription 5 (STAT5) [125]. Evidence suggests that baicalein is involved in the TGF-β1, STAT3, and NF-κB signaling pathways, and modulates levels of IL-6, IL-1β, TNF-α, MIP-2, and MIP-1α [126–128]. Cytokines can exert both direct and indirect effects on immune cells. An antibody is an immunoglobulin that specifically binds to a particular antigen. Antibodies are classified as IgG, IgA, IgM, IgE, and IgD, each having distinct immunomodulatory effects [129]. TCM and dietary compounds regulate the immune system, inhibit HSC and reduce collagen deposition, thereby improving HF [130]. Ophiopogon japonicus polysaccharide (OJP) enhances collagenase activity, which facilitates the degradation of fibrous structures [131]. Cordyceps sinensis polysaccharide exhibits a moderate ability to scavenge hydroxyl radicals and ABTS [132]. It may potentially alleviate HF by reducing collagen production and suppressing the activation of HSC [133]. Cordyceps sinensis polysaccharide protects the liver from damage by reducing oxidative stress and inflammatory response [134].It lowers levels of inflammatory cytokines IL-18 and IL-10, accelerates hepatocyte regeneration, and enhances the expression of proliferating cell nuclear antigen (PCNA) and signal-regulatory protein-α1 (SIRP-α1) [135]. Gynostemma pentaphyllum polysaccharides (GPP) enhance the activity of *Akkermansia*, *Lactobacillus*, and *A2*, while reduced the abundance of *uncultured_Clostridia*. GPP exhibit significant enrichment in several signaling pathways, including those related to chemokines, osteoclast differentiation, platelet activation, leukocyte migration across the endothelium, as well as toll-like receptor (TLR) and the NOD-like receptor (NLR) signaling pathways [136].

7. TCM and dietary compounds: interactions with GM in preventing HF

TCM and dietary compounds, including flavonoids, polyphenols, polysaccharides, glycosides, terpenoids, and alkaloids, are suitable for both medicinal use and consumption. These compounds can effectively prevent HF by regulating the structure of GM and enhancing the barrier function. Table 1 systematically summarizes the modulatory effects of TCM and dietary compounds on GM and intestinal metabolites reported over the past five years.

7.1. Flavonoids

Ampelopsis grossedentata extract (VTE) attenuated hepatic tissue inflammation, prevented damage to the intestinal epithelial barrier, and restored intestinal dysbiosis. VTE effectively restored the thinning of the damaged intestinal muscularis propria caused by CCl_4 and reduced TLR4 protein levels in intestinal tissues. VTE inhibited the inflammatory cascade response through the TLR4/JNK signaling pathway and suppressed hepatic inflammatory macrophage infiltration [155].

The health benefits of citrus products are enhanced by the flavonoids present in the citrus peel. Pure total flavonoids from citrus (PTFC) effectively prevent HF. An investigation examined on citrus flavonoids such as hesperidin (HD), hesperetin (HT), nobiletin (NOB), naringenin (NIN), neohesperidin (NSC), naringin (NRG), eriodictyol (ED), and tangeretin (TN) [146]. PTFC also significantly altered the structure and composition of GM. At the genus level, PTFC significantly increased the abundance of *Eubacterium* and decreased the abundance of *Allobaculum*. At the family level, PTFC significantly increased the relative abundances of Christensenellaceae and Bacteroidaceae, while decreasing the abundances of Porphyromonadaceae and Streptococcaceae [67]. Citrus flavonoids significantly contributed to intestinal barrier function. Citrus flavonoids enhanced intestinal barrier function and decreased intestinal permeability [148]. Citrus flavonoids enhanced the TJs of intestinal epithelial cells, modulated the intestinal flora, and influenced immune cytokine activity. These molecules maintain intestinal barrier function and limit the release of inflammatory factors [149].

Red-fleshed apple flavonoid extract (RAFE) has several significant applications in both food and medicine. Research indicates that RAFE contains various flavonoids, including quercetin, centaureidin-3-O-galactoside, and centaureidin-3-O-glucoside. It also contains polyphenols such as catechin and phloretin. RAFE decreases the abundance of harmful bacteria such as *Pseudomonas*, *Staphylococcus*, and *Fusobacterium*, while increasing the abundance of beneficial bacteria like *Lactobacillus* acidophilus, *Clostridium,* and

Table 1
Traditional Chinese medicine and dietary compounds as active substances in anti-fibrosis treatments. ↑ increase, ↓ decrease.

Type	Compound	Source	Bacterial Population	Microbiota Metabolites	Intestinal Barrier	Reference
Flavonoids	3-methoxy-5,7,3′,4′-tetrahydroxyflavone	*Hippophae rhamnoides* L.	*Fimicutes/Bacterodietes*(↓), *Fimicutes* (↓), *Bacterodietes*(↑), *Proteobacteria* (↑), *Clostridiales*(↓), Lachnospiraceae (↓), *S24-7*(↑), *Prevotella*(↑)			[137,138]
	Apigenin	*Rosa laevigata* Michx Fruit *Hippophae rhamnoides* L.	*Fimicutes/Bacterodietes*(↓), *Fimicutes* (↓), *Bacterodietes*(↑), *Lactobacillus*(↓), *Proteobacteria*(↑), *Clostridiales*(↓), Lachnospiraceae(↓), *S24-7*(↑), *Prevotella*(↑)		LPS(↓)	[118,138]
	Baicalin, Scutellarin	*Gardenia jasminoides* Ellis	*Lactobacillus*(↑)	SCFAs(↑) BAs (↓) TGR5, FXR	Intestinal wall lesions(↑) Intestinal villi exhibiting more uniformity and alignment ZO-1 (↑) Claudin-1(↑) TJ(↑)	[139–142]
	Breviscapine	*Chrysanthemum morifolium* Ramat.	*Firmicutes/Bacteroidetes*(↓), *Firmicutes* (↓) *Bacteroidetes*(↑)	SCFAs(↑)		[143]
	Centaureidin-3-O-galactoside, Centaureidin-3-O-glucoside	Red-fleshed apple	*Pseudomonas*(↓), *Staphylococcus*(↓), *Fusobacterium*(↓), Lachnospiraceae (↑), *Lactobacillus*(↓), *Acidophilus*(↑), *Clostridium*(↑)		Oxidative stress (↓), Inflammatory response(↓)	[144]
	Eriodictyol, Eriodictyol-7-O-rutinoside, Hesperetin, Hesperetin-7-O-glycosides, Hesperidin, Naringenin, Naringenin-7-O-glycosides, Naringin, Nariutin, Neohesperidin, Nobiletin, Sinensetin, Tangeretin	Citrus peel	*Eubacterium*(↑), *Allobacullum*(↓) Christensenellaceae(↑), Erysipelotrichaceae(↑), Porphyromonadaceae(↓), Streptococcaceae(↓)		Intestinal barrier function(↑), Intestinal permeability(↓), TJs(↑), Immune cytokine activity (↑), Inflammatory factors(↓)	[67, 145–150]
	Galangin	*Alpinia officinarum* Hance Propolis			MMP-2(↓), Fibronectin(↓), α-SMA(↓)	[151–153]
	Hyperoside	*Rubus chingii* Hu.	*Bifdobacterium*(↑), *Turicibacter*(↑)			[137,154]
	Isorhamnetin	*Rosa laevigata* Michx Fruit	*Lactobacillus*(↓), *Bacteroidetes*(↑)		LPS(↓)	[118]
	Isquercetin, Kaempferol-3-rutinoside, Tiliroside	*Rubus chingii* Hu.	*Bifdobacterium*(↑), *Turicibacter*(↑)	SCFAs(↑)		[137]
	Kaempferide	*Rosa laevigata* Michx Fruit	*Lactobacillus*(↓), *Bacteroidetes*(↑)		LPS(↓)	[118]
	Kaempferol, Myricetin	*Ampelopsis grossedentata* (Hand.-Mazz.) W. T. Wang	*Verrucomicrobia*(↓), *Helicobacter*(↓), *Oscillibacter*(↓), Ruminococcaceae(↓), Streptococcaceae(↓), Verrucomicrobiaceae(↓), Helicobacteraceae(↓), Anaeroplasmataceae(↓), *Cyanobacteria*(↑), *Ruminococcaceae_UCG-014*(↑), *Eubacterium_fissicatena_group*(↑), Lachnospiraceae(↑), Bacteroidales_S24-7_group(↑), Staphylococcaceae(↑)	SCFAs(↑), BAs(↓)	The thickness of the intestinal muscle layer(↑), ZO-1(↑), Occludi (↑), Mucin1(↑), TJ(↑), TLR4(↓)	[155]
	Kaempferol-7-O-glucoside	*Hippophae rhamnoides* L. *Rubus chingii* Hu.	*Fimicutes/Bacterodietes*(↓), *Fimicutes* (↓), *Bacterodietes*(↑), *Proteobacteria* (↑), *Clostridiales*(↓), Lachnospiraceae (↓), *S24-7*(↑), *Prevotella*(↑)			[137,138]
	Luteolin	*Hippophae rhamnoides* L. *Rubus chingii* Hu.	*Fimicutes/Bacterodietes*(↓), *Fimicutes* (↓), *Bacterodietes*(↑), *Bifdobacterium* (↑), *Proteobacteria*(↑), *Prevotella*(↑), *S24-7*(↑), *Turicibacter*(↑) *Clostridiales* (↓), Lachnospiraceae(↓)	SCFAs(↑)	TJ(↑)	[137,138, 156]

(*continued on next page*)

Table 1 (*continued*)

Type	Compound	Source	Bacterial Population	Microbiota Metabolites	Intestinal Barrier	Reference
	Myricitrin	*Ampelopsis grossedentata* (Hand.-Mazz.) W. T. Wang *Hippophae rhamnoides* L.	*Fimicutes/Bacterodietes*(↓), *Fimicutes* (↓), *Bacterodietes*(↑), *Proteobacteria* (↑), *Clostridiales*(↓), *S24-7*(↑), *Prevotella*(↑) *Cyanobacteria*(↑), *Ruminococcaceae_UCG-014*(↑), *Eubacterium_fissicatena_group*(↑), Bacteroidales_S24-7_group(↑), Staphylococcaceae(↑) *Verrucomicrobia*(↓), *Helicobacter*(↓), *Oscillibacter*(↓), Ruminococcaceae(↓), Streptococcaceae(↓), Verrucomicrobiaceae(↓), Helicobacteraceae(↓), Anaeroplasmataceae(↓), Lachnospiraceae(↓)	SCFAs(↑), BAs(↓)	The thickness of the intestinal muscle layer(↑), ZO-1(↑), Occludi (↑), Mucin1(↑), TJ(↑), TLR4(↓)	[138,155]
	Quercetin	*Ampelopsis grossedentata* (Hand.-Mazz.) W. T. Wang *Fagopyrum tataricum* (L.) Gaertn. *Hippophae rhamnoides* L. *Rosa laevigata* Michx Fruit *Rubus chingii* Hu. Red-fleshed apple	*Firmicutes/Bacteroidetes*(↓), *Firmicutes* (↓), *Verrucomicrobia*(↓), *Helicobacter* (↓), *Oscillibacter*(↓), *Lactobacillus*(↓), Ruminococcaceae(↓), Streptococcaceae(↓), Verrucomicrobiaceae(↓), Helicobacteraceae(↓), Anaeroplasmataceae(↓), *Proteobacteria*(↑), *Bacteroidetes*(↑), *Deferribacter*(↑), *Akkermansia*(↑), *Cyanobacteria*(↑), Ruminococcaceae_UCG-014(↑), *Eubacterium_fissicatena_group*(↑), Lachnospiraceae(↑), *Bacteroidales_S24-7_group*(↑), Staphylococcaceae(↑)	SCFA(↑), BA (↓)	The thickness of the intestinal muscle layer(↑), ZO-1(↑), Occludi (↑), Mucin1(↑), TJ(↑), TLR4(↓), LPS(↓)	[118,137, 138,144, 155,157]
	Rutin	*Fagopyrum tataricum* (L.) Gaertn. *Hippophae rhamnoides* L. *Rubus chingii* Hu.	*Fimicutes/Bacterodietes*(↓), *Fimicutes* (↓), *Bacterodietes*(↑), *Proteobacteria* (↑), *Clostridiales*(↓), *Lachnospiraceae* (↓), *S24-7*(↑), *Prevotella*(↑), *Bifdobacterium*(↑), *Turicibacter*(↑)		LPS(↓)	[137,138]
	Tartary Buckwheat Flavonoids	*Fagopyrum tataricum* (L.) Gaertn.	*Dubosiella*(↑), *Bacteroidetes*(↑)			[158]
Polyphenols	Adlay Polyphenol	*Coix lacryma-jobi* L.	*Lactobacillus*(↑)	BAs(↓)		[159]
	Citrus peel powder	Citrus fruits	*Firmicutes*(↑), *Bacteroidota*(↓), *Faecalibaculum*(↑), *Lactobacillus*(↑), *Dubosiella*(↑), *Helicobacte*(↓), *Bacteroides*(↓), Lachnospiraceae_NK4A136_group(↑)			[155,160]
	(E)-Caffeic acid, (Z)-Caffeic acid, o-Coumaric acid, p-Coumaric acid, Protocatechuic acid, Vanillic acid	*Fructus Mori* L.	*Firmicutes/Bacteroidetes*(↓), *Firmicutes* (↓), *Proteobacteria*(↓), *Actinobacteria* (↓), *Bacteroidetes*(↑), *Prevotella_2*(↓), *Fusobacterium*(↓), *Faecalibacterium* (↓), *Bacteroides*(↓), *Muribaculum*(↑), Lachnospiraceae_NK4A136_group(↑)			[161,162]
	Catechin, Phloretin	Red-fleshed apple	*Pseudomonas*(↓), *Staphylococcus*(↓), *Fusobacterium*(↓), Lachnospiraceae (↑), *Lactobacillus acidophilus*(↑), *Clostridium*(↑)		Oxidative stress (↓), Inflammatory response(↓)	[144]
	Chebulagic acid, Chebulinic acid, Corilagin, Methyl gallate	*Phyllanthus emblica* L.	*Actinobacteria*(↑), *Desulfobacterota*(↓), *Faecalibaculum*(↓), *Romboutsia*(↓), Peptostreptococcaceae(↑), Muribaculaceae(↓), Streptococcaceae (↓)	SCFAs(↑)		[163,164]
	Chlorogenic acid	*Fructus Mori* L. *Phyllanthus emblica* L.	*Firmicutes/Bacteroidetes*(↓), *Firmicutes* (↓), *Proteobacteria*(↓), *Bacteroidetes* (↑), *Prevotella_2*(↓), *Fusobacterium*(↓), *Bacteroides*(↓), Lachnospiraceae_NK4A136_group(↑), *Actinobacteria*(↑), *Desulfobacterota*(↓),	SCFAs(↑)		[161–164]

(*continued on next page*)

Table 1 (*continued*)

Type	Compound	Source	Bacterial Population	Microbiota Metabolites	Intestinal Barrier	Reference
			Faecalibaculum(↓), *Romboutsia*(↓), Peptostreptococcaceae(↑), Muribaculaceae(↓), Streptococcaceae (↓)			
	Ellagic acid Gallic acid	*Fructus Mori* L. *Phyllanthus emblica* L. *Rubus chingii* Hu.	*Firmicutes/Bacteroidetes*(↓), *Firmicutes* (↓), *Proteobacteria*(↓), *Bacteroidetes* (↑), *Prevotella_2*(↓), *Fusobacterium*(↓), *Bacteroides*(↓), Lachnospiraceae_NK4A136_group(↑), *Actinobacteria*(↑), *Desulfobacterota*(↓), *Faecalibaculum*(↓), *Romboutsia*(↓), Peptostreptococcaceae(↑), Muribaculaceae(↓), Streptococcaceae (↓), *Bifdobacterium*(↑), *Turicibacter*(↑)	SCFAs(↑)		[137, 161–164]
	Ferulic acid	*Angelica sinensis Fructus Mori* L.	*Firmicutes/Bacteroidetes*(↓) *Lactobacillus*(↓), *Firmicutes*(↓) *Proteobacteria*(↓) *Actinobacteria*(↓) *Bacteroidetes*(↑) *Prevotella_2*(↓) *Fusobacterium*(↓) *Faecalibacterium*(↓) *Bacteroides*(↓) *Muribaculum*(↑) Lachnospiraceae_NK4A136_group(↑)	SCFAs(↑), BAs(↓)	TJ(↑)	[161,162]
Polysaccharides	Aronia melanocarpa polysaccharide	*Aronia melanocarpa*	*Firmicutes/Bacteroidetes*(↓)		Integrity of the intestinal barrier (↑)	[130]
	Astragalus polysaccharide	*Astragalus membranaceus*	*Lactobacillus*(↑), *Bifidobacterium*(↑), *Salmonella* Typhimurium(↓)	SCFAs(↑)	ZO-1(↑), TJ(↑)	[165–167]
	Atractylodes macrocephala polysaccharides	*Atractylodis Macrocephalae* Rhizoma	*Bacteroides*(↑), *Peptococcus*(↓), *Intestinibacter*(↓), *Romboutsia*(↓), Lachnospiraceae(↑), Lachnospiraceae_UCG_006(↑), Lachnospiraceae_UCG_008(↑)		LPS(↓), TJs(↑), Intestinal epithelial barrier (↑), Energy(↑)	[116,168]
	Auricularia auricula polysaccharides	*Auricularia auricula*	*Lactobacillus*(↑), *Bifidobacterium*(↑) *Allobaculum*(↓), *Olsenella*(↓), *Ruminococcus_2*(↓), *Clostridium_XVIII* (↓)			[169]
	Cordyceps sinensis polysaccharide	*Cordyceps sinensis* (BerK.) Sacc.	*Firmicutes/Bacteroidetes*(↓), *Firmicutes* (↓), *Bacteroidetes*(↑)		Oxidative stress (↓), Inflammatory response(↓)	[119, 132–135, 170]
	Crataegus pinnatifida polysaccharide	*Crataegus pinnatifida* Bunge	*Firmicutes/Bacteroidetes*(↓), *Akkermansia*(↑)	SCFAs(↑)	TJ(↑), MUC5(↑)	[171]
	Dendrobium officinale polysaccharide	*Dendrobium officinale* Kimura & Migo	*Firmicutes/Bacteroidetes*(↓), *Firmicutes* (↓), *Bacteroidetes*(↑)		TJ(↑), LPS(↓)	[172]
	Flammulina velutipes polysaccharides	*Flammulina velutipes*	*Lactobacillus*(↑), *Ruminococcus*(↓), *Bacteroides*(↓), *Atopostipes*(↓), *Sporosarcina*(↓)	SCFAs(↑), Trp(↑)		[173]
	Fructus Mori polysaccharides	*Fructus Mori* L.	*Firmicutes/Bacteroidetes*(↓), *Firmicutes* (↓), *Proteobacteria*(↓), *Actinobacteria* (↓), *Bacteroidetes*(↑), *Prevotella_2*(↓), *Fusobacterium*(↓), *Faecalibacterium* (↓), *Bacteroides*(↓), *Muribaculum*(↑), Lachnospiraceae_NK4A136_group(↑)			[161,162]
	Gardenia jasminoides polysaccharide	*Gardenia jasminoides* Ellis	*Bacteroidetes*(↑), *Firmicutes*(↑), *Proteobacteria*(↓), *Verrucomicrobia*(↓), Enterobacteriaceae(↓), Bacteroidales_S24-7_group(↑), Lachnospiraceae(↑) Enterobacteriaceae(↓), Enterococcaceae(↓), *Enterobacteriales* (↓), *Proteobacteria*(↓), *γ_ proteobacteria*(↓) *Bacteroides*(↑), *Gastranaerophilales*(↑)		Occludin(↑), ZO-1(↑), Intestinal permeability(↓)	[174]
	Garlic polysaccharide	Garlic	*Lactobacillus*(↑), *Bifidobacterium*(↑), *Firmicutes*(↓) *Faecalibacterium*(↓)	SCFAs(↑)	Lymphocytes(↑), Intestinal flora balance(↑)	[175]

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Table 1 (*continued*)

Type	Compound	Source	Bacterial Population	Microbiota Metabolites	Intestinal Barrier	Reference
	Grifola frondosa heteropolysaccharide	*Grifola frondosa*	*Allobaculum*(↑), *Bacteroides*(↑), *Bifidobacterium*(↑), *Acetatifactor*(↓), *Alistipes*(↓), *Flavonifractor*(↓), *Paraprevotella*(↓), *Oscillibacter*(↓)	BAs(↓)		[176]
	Gynostemma pentaphyllum polysaccharides	*Gynostemma pentaphyllum*	*Akkermansia*(↑), *Lactobacillus*(↑), *A2* (↑), *uncultured_Clostridia*(↓)	SCFAs(↑)	Chemokines(↑), TLR(↑)	[136]
	Laminaria japonica polysaccharide	*Laminaria japonica*	*Firmicutes/Bacteroidetes*(↓), *Verrucomicrobia*(↑), *Bacteroides*(↑), *Akkermansia*(↑)	Cholesterol metabolism (↑)	Intestinal permeability(↓)	[78]
	Lycium barbarum polysaccharide	*Lycium barbarum* L.	*Firmicutes/Bacteroidetes*(↓), *Firmicutes* (↓), *Bacteroidetes*(↑)	SCFAs(↑), Trp(↑)		[53]
	Mesona chinensis Benth polysaccharide	*Mesona chinensis* Benth.	*Bacteroides*(↓), Ruminococcaceae(↑)	SCFAs(↑)	LPS(↓), Oxidative stress (↓), Inflammatory response(↓)	[177]
	Ophiopogon japonicus polysaccharide	*Ophiopogon japonicus* (L. f.) Ker Gawl.	*A. municiphila*(↑), *Roseburia*(↑), *Butyrivibrio*(↑), *Bifidobacterium*(↑)	SCFAs(↑)	Inflammatory response(↓)	[131]
	Pleurotus citrinopileatus polysaccharide-peptides	*Pleurotus citrinopileatus* Singer.	*Bifidobacteria*(↑), *Lactobacillus*(↑), *Faecalibacterium*(↑), *Prevotella*(↑), *Escherichia-Shigella*(↓), *Bacteroides*(↓)	SCFAs(↑)		[178]
	Poria cocos polysaccharides	*Poria cocos (Schw.)* Wolf.	*Faecalibaculum*(↑), *Escherichia_Shigella*(↑), *unclassified Oscillospirales*(↑), *Tuzzerella*(↓), *Enterococcus*(↓), *Staphylococcus*(↓)			[179]
	Radix Puerariae thomsonii polysaccharides	*Pueraria thomsonii* Benth.	*Firmicutes/Bacteroidetes*(↓), *Lactobacillus*(↑)	BAs(↓), SCFAs(↑)	Intestinal barrier integrity(↑), Intestinal function(↑), The thickness of the mucus layer(↑), TJ(↑), LPS(↓)	[92]
	Sacran	*Aphanothece sacrum*	*Firmicutes*(↑), *Fusobacteria*(↑) *Blautia* (↑), *Fusobacterium*(↑), *Bacteroidetes* (↓), *Proteobacteria*(↓), *Prevotella*(↓), *Morganella*(↓), *Sutterella*(↓), *Eubacterium*(↓)	BAs(↓), Lipid metabolism (↓), Triglyceride (↓)	Intestinal barrier (↑)	[70]
	Sea buckthorn polysaccharides	*Hippophae rhamnoides* L.	*Fimicutes/Bacterodietes*(↓), *Fimicutes* (↓), *Bacterodietes*(↑), *Proteobacteria* (↑), *Clostridiales*(↓), Lachnospiraceae (↓), *S24-7*(↑), *Prevotella*(↑)			[165]
Glucosides	Forsythiaside A	*Forsythia suspensa* (Thunb.) Vahl	*Prevotellaceae UCG-001*(↑), *Ruminococcus-1*(↑), *Bacteroides*(↑), *Mucispirillum*(↓) *Lactobacillus*(↓)	SCFAs(↑), BAs(↓),	TJ(↑), ZO-1(↑), Claudin-1(↑), Occludin(↑), Villus width(↑), Villus height(↑), Crypt depth(↑), LPS(↓),	[180]
Terpenoids	Curcumin	*Curcuma longa* L.	*Lactobacillus*(↓), *Akkermansia*(↑),	SCFAs(↑)	ZO-1(↑)	[181]
	Ginsenoside Rk3	*Panax ginseng* C. A. Mey.	*Firmicutes*(↓), *Firmicutes/Bacteroidetes* (↑)	SCFAs(↑)		[182]
	Glycyrrhizic acid	*Glycyrrhiza uralensis* Fisch.	*Lactobacillus*(↓), *Bifidobacterium*(↑),	SCFAs(↑), BAs(↓)	ZO-1(↑), TJ(↑)	[183]
	Lactucin	*Cichorium pumilum* Jacq	*Firmicutes/Bacteroidetes*(↓), *Acidobacteria*(↓), *Firmicutes*(↓), *Proteobacteria*(↓), *Bacteroidetes*(↑), *Ochrobactrum*(↓), *Ruminococcus*(↑), *Acinetobacter*(↑)	SCFAs(↑)	Intestinal mucosal tissue (↑)	[184]
	Ursolic acid	*Prunella vulgaris* L.	*Firmicutes*(↑), *Lactobacillus*(↑), *Proteobacteria*(↓), *Akkermansia*(↓)	SCFAs(↑), BAs(↓)	Claudin-1(↑), Occludin(↑), LPS (↓)	[96, 185–187]
	Ganoderma lucidum total triterpenes	*Ganoderma lucidum*	*Firmicutes/Bacteroidetes*(↑), *Firmicutes* (↑), *Bacteroidetes*(↓) *Proteobacteria*(↓) *Oscillospira*(↑), *Clostridium*(↑), *Psychrobacter*(↑), *Corynebacterium*(↓) *Ruminococcaceae*(↑),	SCFAs(↑), BAs(↓)	LPS(↓)	[188]

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Table 1 (*continued*)

Type	Compound	Source	Bacterial Population	Microbiota Metabolites	Intestinal Barrier	Reference
			Lachnospiraceae(↑), *Closteridiaceae*(↑), *Peptostreptococcaceae*(↓) *g_Ruminococcus*(↑)			
Alkaloids	Berberine	*Coptis chinensis* Franch.	*Lactobacillus*(↓), *Bifidobacterium*(↑), *Clostridium*(↑), *Prevotellaceae/ Erysipelotrichaceae*(↓)	SCFAs(↑), BAs(↓), Arachidonic acid(↓)	LPS(↓), Inflammatory response(↓)	[47,56,69, 121,122, 189]
	Cordycepin	*Cordyceps sinensis* (BerK.) Sacc.			LPS(↓), Oxidative stress (↓), Inflammatory response(↓)	[190]
	Palmatine	*Corydalis saxicola* Bunting.	*s_Lactobacillus_murinus*(↑), *s_Lactobacillus_reuteri*(↑), *s_Lactobacillus_johnsonii*(↑), *s_Lactobacillus_acidophilus*(↑), *s_Faecalibaculum_rodentium*(↑)	SCFAs(↑)	LPS(↓), Energy (↑)	[191]

Lachnospiraceae. Additionally, RAFE ameliorated CCl_4-induced liver injury, alleviated oxidative stress, reduced the inflammatory response, and provided liver protection [144].

In TCM, the unripe fruit of *Rubus chingii* Hu., known as Fu Pen Zi, is a well-known remedy for the kidneys and liver. Using Fu Pen Zi, 89 different chemical compounds were identified, including gallic acid, isoquercitrin, ellagic acid, hyperoside, rutin, quercetin, kaempferol-3-rutinoside, luteolin, and tiliroside. Mice with CCl_4-induced HF exhibited a significant reduction in inflammation, histological abnormalities, and collagen fibrosis deposition when treated with RF. Fu Pen Zi therapy effectively adjusted the balance of GM by promoting *Bifidobacterium* and *Turicibacter*. This recovery contributed to reestablishing the normal level of GM, which had been disrupted by the CCl_4-induced imbalance [137].

7.2. Polyphenols

Citrus fruits, belonging to the Rutaceae family, are among the most nutrient-rich fruits worldwide and serve as a major source of phenolic compounds primarily found in the peels. Citrus peel powder (CPP) was produced through a freeze-drying process and combined in a 50:50 ratio of grapefruit and orange peel powders. CPP attenuated hepatic and lipid metabolism disorders, reduced hepatic injury, and inhibited the release of hepatic inflammatory cytokines. CPP particularly regulates the composition of GM. At the phylum level, CPP significantly increased the abundance of *Firmicutes* while decreasing the abundance of *Bacteroidota*. At the genus level, CPP significantly increased the abundance of *Faecalibaculum*, *Lactobacillus*, and *Dubosiella* while decreasing that of *Helicobacter* and *Bacteroides*. CPP also increased the abundance of Lachnospiraceae_NK4A136_group [160].

Adlay polyphenol (AP), an active component derived from the plant *Coix lacryma-jobi* L., effectively inhibits the development of HF. The abundance of *Lactobacillus* at the genus level significantly increased in mice following AP therapy. AP increases the abundance of *Lactobacillus* and influences GM metabolism through the mTOR signaling pathway, urea metabolism, and bile secretion [159].

Studies have shown that *Fructus Mori* L. is a nutritious and functional food for preventing metabolic syndrome, with GM potentially serving as drug targets. The fruit polyphenols and polysaccharides from *Fructus Mori* L., classified as secondary metabolites, are not readily absorbed in the small intestine and instead reach the colon in an almost unchanged form. The primary phenolic acids in mulberry are hydroxycinnamic acid derivatives, including chlorogenic, gallic, protocatechuic, p-coumaric, o-coumaric, ferulic, caffeic and vanillic acids [161]. These compounds also improved hepatic fat deposition, reduced oxidative stress, mitigated intestinal micro-ecological imbalance, enhanced intestinal barrier function, and bolstered the immune system. The Lachnospiraceae_NK4A136_group is a member of the Lachnospiraceae family. This bacterium produces butyrate, which helps maintain the integrity of the intestinal barrier in mice [162].

Phyllanthus emblica L. (PE) is a plant recognized for its diverse bioactivities. The aqueous extracts of this plant (AEPE) have been shown to slow the development of HF and protect the liver from damage. The components of AEPE include gallic acid, corilagin, methyl gallate, chlorogenic acid, chebulinic acid, chebulagic acid, and ellagic acid. Additionally, AEPE may reduce HF, improve liver function, inhibit HSC activation, significantly decrease collagen deposition, and exhibit antioxidant and anti-inflammatory effects [164]. AEPE has been found to effectively improve alterations in GM. At the phylum level, the abundance of *Actinobacteria* significantly increased, while that of *Desulfobacterota* decreased. Both the genus *Faecalibaculum* and the species *Romboutsia* experienced significant declines. Peptostreptococcaceae experienced a sharp increase in relative abundance within its family, whereas Streptococcaceae and Muribaculaceae showed declines [163].

7.3. Polysaccharides

Polysaccharides are heteropolysaccharides composed of glycosamine hydrochloride (GlcN), rhamnose (Rha), arabinose (Ara),

galactose (Gal), glucose (Glc), xylose (Xyl), and mannose (Man). The structure includes 1 → 4 and 1 → 3 bonds connecting Glcp, with branching points at either O-2 or O-6 of Glcp [170]. The immunomodulatory effects of polysaccharides primarily arise from the activation of macrophages, T lymphocytes, and B lymphocytes. Polysaccharides from mushrooms enhance cellular immunity. The microbiome in the body metabolizes polysaccharides, which are complex macromolecular carbohydrates. Certain polysaccharides break down SCFAs such as propionic acid, butyric acid, and acetic acid in the digestive tract. These SCFAs not only provide energy for the proliferation of intestinal cells but also regulate the gut pH, influencing the composition of resident microbes. Specifically, The *Firmicutes/Bacteroidetes* ratio increased, along with the abundance and diversity of the GM, thereby strengthening the integrity of the gut barrier. These metabolites may positively impact the liver through the gut-liver axis. These polysaccharides enhance intestinal health, regulate blood sugar and cholesterol, and bolster the immune system, collectively working to protect the liver.

The families Ruminococcaceae and Lachnospiraceae contain gut commensal strains that produce SCFAs. These strains help maintain the integrity of the intestinal epithelial barrier and provide energy to local enterocytes [116]. Crataegus pinnatifida polysaccharide (CPP) decreased the ratio of *Firmicutes/Bacteroidetes*, increased the abundance of *Akkermansia*, and elevated total SCFA levels, particularly butyrate and acetate. Meanwhile, butyrate upregulated the expression of TJ proteins and mucosal integrity protein (MUC5) [171]. Flammulina velutipes polysaccharides (FVPs) regulate bacterial metabolites by modulating the metabolism of SCFAs, Trp, and xenobiotics through the cytochrome P450 pathway [173]. Gardenia jasminoides Ellis polysaccharide (GPS) elevated occludin and ZO-1 levels, preventing the degradation of the intestinal mucosal barrier and improving intestinal permeability [174]. S24-7, a member of the *Bacteroidetes* family potentially involved in human metabolism, showed increased relative abundance in the presence of sea buckthorn polysaccharide [165]. *Pleurotus citrinopileatus*, commonly known as golden oyster mushroom, contains polysaccharide-peptide constituents that possess hepatoprotective properties. It can modulate the structure of the GM. Specifically, pleurotus citrinopileatus polysaccharide-peptides increased the relative abundance of beneficial genera such as *Bifidobacteria*, *Lactobacillus*, *Faecalibacterium*, and *Prevotella*, while significantly reducing the relative abundance of harmful genera like *Escherichia-Shigella* and *Bacteroides*. It acts through the liver-intestinal axis system. It is metabolized by the intestinal microbiota to produce SCFAs, which subsequently influence liver function [178].

7.4. Glucosides

Flavescin A (FTA), a phenylethanoside, inhibits HSC activation, reducing hepatic inflammation and oxidative stress in mice. Additionally, FTA regulates CCl_4-induced intestinal ecological dysregulation by upregulating beneficial genera such as *Prevotellaceae-UCG-001*, *Ruminococcus-1*, *Bacteroides*, downregulating *Mucispirillum*, *Lactobacillus*, etc. Furthermore, FTA enhances the TJs of intestinal cells such as ZO-1, Claudin-1, and Occludin. FTA enhances the integrity of intestinal mucosal epithelium, villus width, villus height, and crypt depth, reduces bacterial and toxin penetration, and maintains intestinal barrier function. The levels of SCFAs such as acetic, propionic, isobutyric, butyric, and caproic acids, especially butyric acid, were significantly increased by FTA treatment compared to CCl_4 treatment groups [180].

7.5. Terpenoids

Curcumol modulated the levels of *Bacteroidota* and *Bacteroides*, affecting the function of nine metabolic pathways. Inhibition of the TLR4/NF-B signaling pathway reduced inflammatory cytokines and improved liver inflammation [181].

Ginsenoside Rk3 induces changes in beneficial GM, shedding light on host-microbe interactions. The abundance of SCFAs significantly increased after treatment with Ginsenoside Rk3. However, Ginsenoside Rk3 significantly reduced the levels of acetic, propionic, and isobutyric acids. TPositive changes in the diversity and composition of the GM were associated with these alterations [182].

Herbal extract CGEA, which stands for *Cichorium pumilum* Jacq, primarily consists of sesquiterpenoids. The ratio of *Firmicutes* to *Bacteroidetes* increased, and the total abundance of GM was higher due to CGEA. CGEA reduced the abundance of *Acidobacteria*, *Firmicutes*, and *Proteobacteria*, while enhancing the quantity of *Bacteroidetes*. The CGEA intervention has the potential to restore normal levels of GM by decreasing *Ochrobactrum* and increasing the prevalence of *Ruminococcus* and *Acinetobacter* at the genus level. Furthermore, CGEA significantly protected rat intestinal mucosal tissue and improved intestinal barrier function [184].

7.6. Alkaloids

Alkaloids are a group of chemical compounds that contain nitrogen and are essential constituents of TCM due to their notable physiological effects.

Research has shown that cordycepin can inhibit the activation of HSC, reduce collagen accumulation, and decrease HF. Cordycepin inhibits inflammatory responses and oxidative stress by activating the AMPK signaling pathway, thereby protecting the liver against fibrosis [190].

Corydalis saxicola Bunting (CS) is a traditional folk medicine that has been effectively used to treat liver disease in the Zhuang people of South China. Palmatine (PAL) is one of the active ingredients that improve HF. PAL regulates the GM, improving the balance of beneficial microorganisms in the intestines. Additionally, it enhances the function of the intestinal barrier and prevents the activation of inflammatory factors in the liver. PAL increases the production of SCFAs, particularly butyric acid and propionic acid, in the gut. These SCFAs serve as the primary energy source for intestinal epithelial cells and contribute to maintaining the integrity of the intestinal barrier [191].

8. Discussion

In addition, the review offers a prospective objective for the practical design and application of TCM and dietary compounds in the therapy of HF.

The review revealed that 98 chemical components from 25 TCM and dietary compounds are effective in treating HF. The primary mechanisms of action include inhibition of hepatic inflammation and oxidative stress, modulation of the GM, enhancement of metabolites produced by the intestinal flora, particularly an increase in SCFAs, and preservation of the integrity of the intestinal barrier. In the present study, TCM and dietary compounds primarily regulated *Firmicutes* and *Bacteroidetes* at the phylum level. Summarizing previous studiesrevealed that the abundance of *Bacteroidetes* decreased while that of *Firmicutes* increased in HF. TCM and dietary compounds effectively improved the structure of the GM at the genus level. This significantly decreased the abundance of *Lactobacillus* and *Mucoribacterium* while increased the abundance of *Prevotellaceae_UCG_001*, *Ruminococcus_1*, *Bacteroidetes*, and others. Additionally, it could increase the expression of TJ proteins (Claudin, ZO-1, and Occludin) and decrease the serum levels of LPS, MIP-1α, and TNF-α, effectively prevented liver inflammation and fibrosis. TCM and dietary compounds are closely linked to the modulation of GM, intestinal barrier function, and immunomodulation in HF (Fig. 5).

TCM and dietary compounds, which can function both as food and medicinal herbs, have been extensively studied due to their well-established sources, excellent safety records, and diverse biological effects. This paper provides a comprehensive analysis of recent literature on therapeutic approaches for HF, along with the use of TCM and dietary compounds for liver protection. It summarizes the effects of these compounds on various aspects, including liver function, antioxidant activity, anti-inflammatory properties, prevention of fibrosis, modulation of GM, immunomodulation, and the interaction between the intestines and the liver. TCM and dietary compounds have demonstrated specific therapeutic or restorative effects on the markers mentioned in research studies. This study investigates the therapeutic and hepatoprotective effects of TCM and dietary compounds on HF, laying a theoretical foundation for their future pharmacological and clinical development. This study offers new insights for the development of efficient, safe, and cost-effective treatments for HF. The current research on pharmacophore compounds to modulate GM for preventing HF faces by several limitations. Notably, there is an over-reliance on animal studies, coupled with a lack of clinical data. The absence of standardized treatment protocols, including variations in types, dosages, and treatment durations of TCM and dietary compounds, complicates establishing consistent therapeutic standards. Although some preclinical and clinical studies suggest potential benefits, the quality and quantity of clinical trials remain insufficient. Large-scale, randomized controlled trials are essential to validate these therapeutic effects. Additionally, while some studies indicate that medicinal food compounds can influence HF by modulating GM, the exact mechanisms remain unclear, necessitating further investigation. In conclusion, despite the promising aspects of current research, significant challenges and limitations persist. Future efforts should prioritize enhancing clinical studies to evaluate the safety, efficacy, and mechanisms of action of TCM and dietary compounds in treating HF, thereby supporting their clinical application.

Ethical statement-studies in human and animal

No animal and human studies were done in this article.

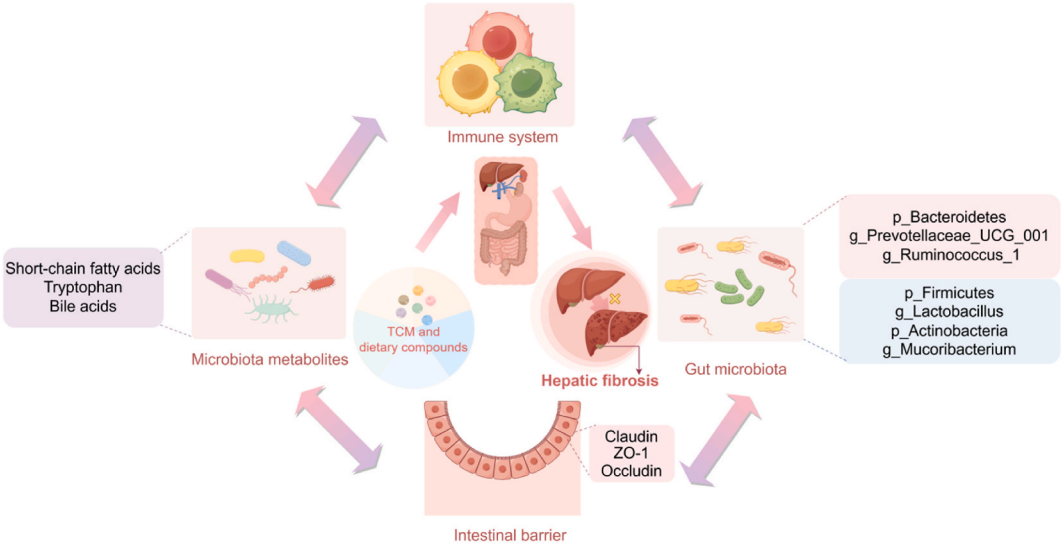

Fig. 5. The possible mechanism of traditional Chinese medicine and dietary compounds in the treatment of hepatic fibrosis. Drawn by Figdraw.

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Data availability statement

Not applicable.

CRediT authorship contribution statement

Xingting Xue: Writing – original draft, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Hongbing Zhou:** Writing – original draft, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Jiaxing Gao:** Writing – original draft, Methodology, Data curation, Conceptualization. **Xinghua Li:** Writing – original draft, Supervision, Data curation, Conceptualization. **Jia Wang:** Writing – review & editing, Resources, Data curation, Conceptualization. **Wanfu Bai:** Writing – review & editing, Visualization, Data curation. **Yingchun Bai:** Writing – review & editing, Data curation. **Liya Fan:** Writing – review & editing, Data curation. **Hong Chang:** Writing – review & editing, Project administration. **Songli Shi:** Writing – review & editing, Funding acquisition.

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.

Abbreviations

Abbreviation	Full Term	Abbreviation	Full Term
AhR	Aryl hydrocarbon receptor	IFN-γ	Interferon-γ
ALT	Alanine aminotransferase	IFNs	Interferons
AMPK	Adenosine monophosphate-activated protein kinase	IL-1β	Interleukin-1beta
AST	Aspartate aminotransferase	IL-6	Interleukin-6
BAs	Bile acids	IL-8	Interleukin 8
BBR	Berberine	LDLR	Low-density lipoprotein receptor
CA	Cholic acid	LPS	Lipopolysaccharides
CDCA	Chenodeoxycholic acid	LOX	Lipoxygenase
COX	Cyclooxygenase	MIP-1α	Macrophage inflammatory protein-1 alpha
CSFs	Colony-stimulating factors	NF-κB	Nuclear factor kappa B
DCA	Deoxycholic acid	NLRs	Nod-like receptors
ECM	Extracellular matrix	NO	Nitric oxide
ER	Endoplasmic reticulum	PAMPs	Pathogen-associated molecular patterns
FXRs	Farnesoid X receptors	PGE2	Prostaglandin E2
GCA	Glycocholic acid	PLA2	Phospholipase A2
GM	Gut microbiota	PPARγ	Peroxisome proliferator-activated receptor γ
GPCRs	G protein-coupled receptors	ROS	Reactive oxygen species
HFD	High-fat diet	SCD1	Stearoyl-Coenzyme A desaturase 1
HF	Hepatic fibrosis	SCFAs	Short-chain fatty acids
HFHC	High fat and high cholesterol	STAT5	Signal Transducer and Activator of Transcription 5
HSCs	Hepatic stellate cells	TC	Total cholesterol
HDAC	Histone deacetylase	TCA	Tricarboxylic acid cycle

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