Therapeutic potential of traditional Chinese medicine for the treatment of NAFLD: A promising drug Potentilla discolor Bunge

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Abstract
Nonalcoholic fatty liver disease (NAFLD) is characterized by excessive accumulation of hepatic lipids and metabolic stress-induced liver injury. There are currently no approved effective pharmacological treatments for NAFLD. Traditional Chinese medicine (TCM) has been used for centuries to treat patients with chronic liver diseases without clear disease types and mechanisms. More recently, TCM has been shown to have unique advantages in the treatment of NAFLD. We performed a systematic review of the medical literature published over the last two decades and found that many TCM formulas have been reported to be beneficial for the treatment of metabolic dysfunctions, including Potentilla discolor Bunge (PDB). PDB has a variety of active compounds, including flavonoids, terpenoids, organic acids, steroids and tannins. Many compounds have been shown to exhibit a series of beneficial effects for the treatment of NAFLD, including anti-oxidative and anti-inflammatory functions, improvement of lipid...
1. Introduction

Nonalcoholic fatty liver disease (NAFLD), recently also named as metabolic associated fatty liver disease\(^1\), is one of the leading causes of chronic liver diseases and one of the most prevalent metabolic disorders worldwide\(^2\). NAFLD comprises a series of liver abnormalities, ranging from simple hepatic steatosis to steatohepatitis, liver cirrhosis and hepatocellular carcinoma. Multiple conditions of the metabolic syndrome are regarded as the main risk factors of NAFLD, including obesity, dyslipidemia and type 2 diabetes (T2DM). The “multiple hits” hypothesis\(^3\) reveals that several hepatic insults act together in the pathogenesis of NAFLD. The mechanisms contributing to the development of NAFLD include hyperlipidemia, insulin resistance (IR), abnormal adipocyte stimulation, secretion of inflammatory mediators by immune cells and adipose tissue, oxidative stress, endoplasmic reticulum (ER) stress, dysregulation of intestinal microflora, disturbance in genetic and epigenetic functions, dysfunction of mitochondria and environmental and dietary factors\(^4\). Due to the complexity of the disease, no effective pharmacological treatments have been currently approved to treat NAFLD.

Nowadays, traditional Chinese medicine (TCM) has been recognized worldwide as a complementary and alternative therapy. Chinese herbs and their extracts have been identified as new sources of potential therapeutic agents for the prevention and treatment of NAFLD\(^5\). More specifically, many Chinese medicine formulas containing Potentilla discolor Bunge (PDB) have been found to play a beneficial role in the treatment of metabolic dysfunctions\(^6\). PDB was first described in the ‘*Meteria Medica for Relief of Famines*’, which is the earliest monograph of agronomy and botany of China published in the 14th–15th century\(^7\). PDB, growing in temperate zones and mountainous areas, is a dry grass of the *Rosaceae* species. There are 88 species of PDB in China, which are mainly produced in Shandong, Liaoning and Anhui provinces and are widely used in Hebei, Henan, Inner Mongolia and Hunan provinces\(^8\). Extracts of the aerial and underground parts of the plant have been used in formulations for the treatment of several diseases, including inflammations, wounds, cancers, infections induced by bacteria, fungi and viruses, diarrhea and diabetes mellitus\(^9\). In this review, we discuss the medicinal properties of PDB and the underlying mechanisms of its active compounds for the treatment of NAFLD.

2. Therapeutic effects and mechanisms of TCM in treating NAFLD

2.1. Pathogenesis of NAFLD and current therapeutic targets

NAFLD is a major cause of liver-related morbidity worldwide, impacting nearly 25% of the global population\(^10,11\). The comprehensive inter-tissue crosstalk between the liver, the intestine, adipose tissue, and the nervous system plays a role in the development of NAFLD\(^12,13\). Also, the liver immune microenvironment, and particularly macrophages and neutrophils are involved in lipid accumulation and inflammation during NAFLD\(^14\) (Fig. 1).

2.1.1. Gut microbiome

Gut microbiota play a significant role in the pathogenesis of NAFLD. The gut microbiota is affected by environmental, dietary and host factors, such as gastrointestinal anatomy and pH\(^15\). Gut barrier dysfunction and disruption of barrier integrity cause translocation of bacteria or bacterial products into the blood circulation, which is the essential condition for liver inflammation and the progression of NAFLD towards nonalcoholic steatohepatitis (NASH)\(^16\).

2.1.2. Crosstalk between adipose tissue and the liver

The intricate crosstalk between adipose tissue and the liver affects systemic metabolism and IR. Adipose tissue plays an important role in regulating NASH development by secreting adiponectin, leptin, tumor necrosis factor (TNF) and IL-6\(^19,20\). In addition, some lipid moieties (palmitic acid, ceramide) released by adipocytes also hinder the function of the ER and mitochondria, which causes cell stress and even hepatocyte death\(^21\). Hepatocyte death is one of the crucial triggers of liver inflammation in NAFLD progression\(^22\). It has been recently found that E-selectin-mediated neutrophil recruitment promotes inflammation and lipolysis in adipose tissue, thereby inducing the release of free fatty acids and proinflammatory adipokines that exacerbate the steatosis-to-NASH progression\(^23,24\).

2.1.3. Macrophages

Liver-resident macrophages, also termed Kupffer cells (KCs), and recruited macrophages play a central role in the progression of NAFLD. KCs are the major source of cytokines and chemokines. KCs produce TNF, TNF-related apoptosis inducing ligand (TRAIL), and fatty acid synthase (FAS) ligands through phagocytosis of apoptotic bodies, which subsequently promotes hepatocyte apoptosis and causes hepatitis and fibrosis\(^25\). In addition, extracellular vesicles (EVs) released from hepatocytes contribute to key processes involved in the pathogenesis and progression of NAFLD\(^26,27\). The EVs can promote the expression of proinflammatory cytokines and polarize hepatic macrophages to the proinflammatory (M1) phenotype\(^28-30\). Mixed-lineage kinase 3 induces lipid-treated hepatocytes to release EVs containing C=\(\sim\)X=\(\sim\)C motif chemokine ligand 10 to recruit macrophages\(^31\). Moreover, EVs can contribute to hepatic recruitment of monocyte-derived macrophages\(^32\), which results in inflammation\(^33\). The identification of the pivotal molecules associated with the dynamic
changes of macrophages could be crucial in the quest for novel therapeutic approaches against NAFLD.

2.1.4. Neutrophils

NASH, a more severe type of NAFLD, is accompanied by hepatocellular injury and ballooning with lobular inflammation in addition to lipid accumulation. The hepatic upregulation of chemokines, including C–X–C motif chemokine ligand 1 (CXCL1) and interleukin (IL)-8, resulting in infiltration of neutrophils in the liver are hallmarks of NASH. Hepatic overexpression of Cxcl1 is sufficient to drive steatosis-to-NASH progression in high fat diet (HFD)-fed mice through neutrophil-driven reactive oxygen species (ROS) and activation of stress kinases. This can be reversed by IL-22 treatment via the induction of metallothionein. In addition, neutrophil-specific microRNA-223 (miR-223) is elevated in hepatocytes and limits NASH progression in obese mice. This elevation of Cxcl1 is due to preferential uptake of miR-223-enriched EVs mainly derived from neutrophils. Once internalized by hepatocytes, the EV-derived miR-223 acts to inhibit hepatic inflammatory and fibrogenic gene expression.

2.2. Potential therapeutic effects of TCM for treating NAFLD

TCM has been widely used in China and other Asian countries for thousands of years. TCM formulas are developed under the guidance of TCM theory. The therapeutic effects of TCM on NAFLD have been gradually reported in clinical practices, leading to an increased recognition. TCM discriminates between different types of syndromes in different patients with NAFLD, and therefore, diverse prescriptions and treatments are administered to different patients, based on the four properties of Chinese medicinal herbs (cold, hot, warm, cool), five flavors (sour, bitter, sweet, spicy, salty) and efficiency.

2.2.1. The classical formulas of TCM for the treatment of NAFLD

Based on clinical experience, the pathogeneses of NAFLD can be summarized as the deficiency of spleen, dampness-heat, phlegm and stasis, cold coagulation and qi-stagnation. The syndromes in patients with NAFLD can be classified into the following types: (i) spleen-deficiency and phlegm-turbid stagnation; (ii) stagnation of liver-qi; (iii) accumulated damp-heat; (iv) stasis blocking channels and (v) deficiency of liver and kidney. According to these TCM syndromes, the treatment principle and the relevant classical formulas to treat NAFLD are as follows: (i) formulas for invigorating spleen, removing dampness and phlegm: shenlingbaizhu powder (Tai Ping Hui Min He Ji Ju Fang); (ii) formulas for relieving liver and regulating qi: xiaochaihu decoction (Shang Han Lu); (iii) formulas for clearing heat, promoting dampness and dispersing knot: dachaihu decoction.
| Treatment principle                          | Chinese medicinal formula                    | Model                             | Effects of TCM treating NAFLD                                                                                                                                                                                                                      | Ref. |
|--------------------------------------------|---------------------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Invigorate spleen, remove dampness and phlegm | Shenlingbaizhu powder (SLBZS)               | HFD-induced NAFLD rats            | ↓ Hepatic injury; ↓ Lipid accumulation; ↓ The serum level of endotoxin, TNF-α, IL-1β; ↓ TLR4, TRAF6 in the liver tissue; ↑ The abundance of intestinal microbiota; ↑ The abundance of short-chain fatty acid; ↑ Adiponectin; ↓ SREBP-1c, FAS; ↓ Acly, Fas, Acc, Scd1; ↓ IL-1β, NLRP-3; ↑ The biosynthesis of fatty acids; ↑ Gut microbiota composition; ↑ Insulin secretion pathway | 42, 43 |
|                                            | CDAA-fed rats                               |                                   |                                                                                                                                                                                                                                            |      |
|                                            |                                             | Y                                 |                                                                                                                                                                                                                                            |      |
|                                            |                                             | Y                                 |                                                                                                                                                                                                                                            |      |
|                                            |                                             | Y                                 |                                                                                                                                                                                                                                            |      |
| Simiao powder (SMS)                        | HFHS-induced NAFLD mice                     |                                   | ↓ Hepatic injury; ↓ Lipid accumulation; ↓ The serum level of endotoxin, TNF-α, IL-1β; ↓ TLR4, TRAF6 in the liver tissue; ↑ The abundance of intestinal microbiota; ↑ The abundance of short-chain fatty acid; ↑ Adiponectin; ↓ SREBP-1c, FAS; ↓ Acly, Fas, Acc, Scd1; ↓ IL-1β, NLRP-3; ↑ The biosynthesis of fatty acids; ↑ Gut microbiota composition; ↑ Insulin secretion pathway | 44   |
| Sanziyangqin decoction (SZYQT)             | HFD-induced NAFLD mice                      |                                   | ↓ Hepatosteatosis; ↓ Inflammatory cell infiltration in liver tissues; ↑ Insulin resistance; ↑ p-AKT; ↓ apoptosis; ↑ Lipid metabolism; ↑ Enterobacteriaceae, Staphylococcaceae families and Veillonella genus; ↑ Anaeroplasma genus; ↓ Fat accumulation; ↓ Inflammatory factors (TNF-α, IL-1β, IL-18, IL-6); ↓ NLRP3, ASC, CASPASE-1; ↓ TLR4, p-p38 MAPK; ↑ Adiponectin; ↓ leptin | 45   |
|                                            |                                             | Y                                 |                                                                                                                                                                                                                                            |      |
| Relief liver and regulate Qi               | Xiaochaihu decoction (XCHT)                 | Patients with NAFLD               | ↓ TNF-α; ↓ Hepatic lipid accumulation; ↓ C/EBPα, PPARγ, p-AMPK; ↑ IRS-1, pAKT; ↓ The ratio of BAX to BCL-2 expression; ↑ AMPKα, PPAR-γ; ↑ ACC-α, p-ACC-α, SREBP2, HMGR | 50, 51|
|                                            | Chaihushugan powder (CHSGS)                 | High fat and sugar emulsion-induced NAFLD rats |                                                                                                                                                                                                                                            |      |
|                                            |                                             |                                   |                                                                                                                                                                                                                                            |      |
| Clear heat, promote dampness and disperse knot | Dachaihu decoction (DCHT)                  | Patients with NAFLD               | ↓ TNF-α; ↓ Hepatic lipid accumulation; ↓ C/EBPα, PPARγ, p-AMPK; ↑ IRS-1, pAKT; ↓ The ratio of BAX to BCL-2 expression; ↑ AMPKα, PPAR-γ; ↑ ACC-α, p-ACC-α, SREBP2, HMGR | 52   |
|                                            | High-fat high-fructose diet-induced NAFLD rats |                                   |                                                                                                                                                                                                                                            |      |
|                                            |                                               | Y                                 |                                                                                                                                                                                                                                            |      |
|                                            |                                               | Y                                 |                                                                                                                                                                                                                                            |      |
|                                            |                                               | Y                                 |                                                                                                                                                                                                                                            |      |
| Promote blood circulation and dissipate blood stasis | Yinchenhao decoction (YCHT)              | HHHC-induced NAFLD mice          | ↓ TNF-α; ↓ Hepatic lipid accumulation; ↓ C/EBPα, PPARγ, p-AMPK; ↑ IRS-1, pAKT; ↓ The ratio of BAX to BCL-2 expression; ↑ AMPKα, PPAR-γ; ↑ ACC-α, p-ACC-α, SREBP2, HMGR | 53   |
|                                            | Taohongsiwu decoction (THSWT)                | High-fat and sugar emulsion-induced NAFLD rats |                                                                                                                                                                                                                                            |      |
|                                            |                                               |                                   |                                                                                                                                                                                                                                            |      |
| Warm Yang and invigorate spleen            | Chaihulizhong decoction (CHLZT)             | HFD-induced NAFLD rats           | ↑ GS, ACC, SREBP-1c, HMGR; ↑ PYGL activity; ↑ GS, ACC, SREBP-1c, HMGR; ↑ PYGL activity | 54   |
|                                            | A long chain fat emulsion-treated HepG2 cells |                                   |                                                                                                                                                                                                                                            |      |
|                                            |                                               |                                   |                                                                                                                                                                                                                                            |      |
|                                            | Lingguizhugan decoction (LGZGT)              | HFD-induced NAFLD rats           | ↑ GS, ACC, SREBP-1c, HMGR; ↑ PYGL activity; ↑ GS, ACC, SREBP-1c, HMGR; ↑ PYGL activity | 55, 56, 57 |
|                                            | HFD-induced NAFLD mice                      |                                   |                                                                                                                                                                                                                                            |      |
|                                            |                                               | Y                                 |                                                                                                                                                                                                                                            |      |
A promising drug *Potentilla discolor* Bunge for the treatment of NAFLD

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**Hepatosteatosis**
- Insulin resistance;
- Oxygen consumption rate;
- The expression and protein the liver;
- Apoptosis

**Gut microbiota**
- **Fuzilizhong decoction** (FZLZT) HFD-induced NAFLD rats
- **Sini powder** (SNS) Stress-induced NAFLD rats
- **Ganjianglingzhu decoction** (GJLZT) HFD-induced NAFLD mice

**Treatise on Febrile Disease**
- Yinchenhao decoction (Shang Han Lun)
- Muqingheng decoction
- Baihu decoction
- Taohongsiwu decoction (San Yin Ji decoction)

**Electroacupuncture**
- Acupuncture is an ancient Chinese medical technique that involves the insertion of needles into specific points on the body's acupoints. It is used to treat a variety of conditions, including NAFLD.

**Benefits of PDB**
- **Flavonoids**: These compounds are present in PDB and have been shown to have antioxidant and anti-inflammatory properties.
- **Terpenoids**: These are another type of compound found in PDB that have been associated with anti-inflammatory effects.

**Clinical Application**
- Electroacupuncture combined with lifestyle changes, such as diet and exercise, can be used to treat NAFLD.

**Conclusion**
- The use of TCM, including PDB, shows promise in the treatment of NAFLD. Further research is needed to fully understand the mechanisms of action and effectiveness of these treatments.

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2.2.2. Acupuncture for the treatment of NAFLD

Acupuncture, which is a classical TCM method, has been used to treat NAFLD during clinical practice. The safety profile of acupuncture therapy for the treatment of NAFLD is satisfactory. Taichong (LR3), Zusanli (ST36), Fenglong (ST40), and Sanyinjiao (SP6) are the most commonly used acupuncture points. Electroacupuncture combined with lifestyle control can effectively treat patients with NAFLD by reducing serum leptin levels, increasing the sensitivity of hepatocytes to insulin and improving IR ameliorating blood glycolipid metabolism and reducing hepatic fat, waist circumference and waist-to-hip ratio.

In addition, acupuncture has been shown to ameliorate NAFLD by regulating lipid metabolism, improving IR and ER stress, alleviating oxidative stress, inhibiting the expression of inflammatory cytokines, and alleviating steatosis, necrosis and inflammatory cell infiltration of liver tissue in NAFLD rat model. Furthermore, acupuncture can alleviate bullous steatosis of liver tissue and the expansion and disorder of rough endoplasmic reticulum in NAFLD rat model.

3. Beneficial effects of Chinese medicinal formulas containing PDB

According to the *Compendium of Materia Medica*, PDB has the effects of “clearing heat and cooling blood, detoxification, hemostasis and detumescence”. An increasing number of studies show that many formulas of TCM containing PDB exert beneficial effects for the treatment of metabolic, inflammatory and hematologic diseases. In Table 2, we summarize Chinese herbal products containing PDB and their medical application.

4. Functions of the main natural active compounds of PDB

PDB contains a variety of chemical components, including flavonoids, terpenoids, organic acids, steroids and tannins. The structure backbones of the main components of PDB are shown in Fig. 3.

Flavonoids, which have different chemical structure subtypes, are one of the main active compounds in PDB, with many pharmacological and physiological activities. The total flavonoids content in PDB is approximately 20%. The two main types of flavonoids are conjugated glycosides and free forms. Terpenoids in PDB are mainly monoterpenes and triterpenes. The content of monoterpenes is lower than that of the triterpenes, and most of the triterpenes are oleanolic alkane, uranethane and their saponins. The main organic acids in PDB are phenolic acids and fatty acids. The steroids obtained from PDB are mainly beta-sitosterol and carotene. Tannins in PDB are mainly ellagic acid and its derivatives.

In a large majority of studies in which mouse and rat models were used, the active compounds from PDB have been found to exhibit a series of beneficial effects for the treatment of NAFLD. As such, it
was found that flavonoids improve lipid metabolism and IR, reduce oxidative stress, ER stress and inflammation in rodent models. In addition, flavonoids and organic acids were shown to regulate the intestinal microflora. The steroids and terpenoids from PDB also improved IR and lipid metabolism, respectively. The latter, also inhibited ER stress (Fig. 4).

5. Anti-NAFLD mechanisms of the natural active compounds of PDB

Table 4 summarizes the PDB active compounds that have been shown to improve NAFLD.

5.1. Improvement of lipid metabolism

The abnormal lipid metabolism during NAFLD involves synthesis, uptake and oxidation of FA, triglycerides (TG) synthesis, and very low density lipoprotein (VLDL) secretion. When carbohydrates are in excess, they are converted into FA by acetyl-CoA carboxylase, FAS and stearoyl-CoA desaturase and subsequently esterified to TG. The liver X receptors (LXRs) are multifunctional nuclear receptors that control lipid homeostasis. LXRs can be activated by glucose at physiological concentrations in the liver. Therefore, LXRs provide a transcriptional switch that integrates hepatic glucose metabolism and FA synthesis. Inhibition of LXRs transactivation may be beneficial for NAFLD. In addition, the mRNAs encoding enzymes in the biosynthetic pathway of FA can be regulated by sterol regulatory element binding protein-1c (SREBP-1c) that is a critical molecule involved in lipid synthesis. Adenosine 5’-monophosphate-activated protein kinase (AMPK) is known to regulate glucose and lipid metabolism, which plays vital roles in FAS and gluconeogenesis. Once AMPK is activated, the uptake of FA β-oxidation in the mitochondria is increased, with a concomitant increase of glucose uptake through the translocation of Glucose transporter type 4 (GLUT-4). In addition, peroxisomal proliferator-activated receptor α (PPAR-α) plays a central role in FA β-oxidation. The gene carnitine palmitoyl transferase 1/2 involved in FA β-oxidation is regulated by PPAR-α. Accumulating evidence suggests that several natural active ingredients from PDB play an important role in improving lipid metabolism, as discussed below.

5.1.1. Luteolin

Luteolin, a natural flavonoid, has been shown to have strong antioxidant and anti-inflammatory activities. Luteolin can improve hepatic steatosis by repressing hepatic TG accumulation and novel...
Table 2  Beneficial effects of Chinese medicinal formulas containing PDB in the treatment of patients.

| Disease                      | Chinese medicinal formula       | Composition of herbal mixture                                                                 | Ref. |
|------------------------------|--------------------------------|-------------------------------------------------------------------------------------------------|------|
| T2DM                         | Fanbaicao mixture              | PDB, Corn Silk                                                                                | 79   |
|                              | Fanbaicao decoction            | PDB, Rubus idaeus L, Astragalus mongholicus, Ophiopogon japonicus, Radix                       | 80   |
|                              |                                | Pseudostellariae, Dioscorea opposita Thunb, Polygonatum sibiricum, Salvia miltiorrhiza Bge, Corn Silk, Ilex pubescens Hook, Rehmannia glutinosa, Chinese wolfberry, Dendrobium nobile Lindl, Rehmannia glutinosa, Cornus officinalis |      |
| Jiulongjiangtang decoction   | Gentian, Astragalus mongholicus, Portia cocos, Salvia miltiorrhiza Bge, PDB, Atractylodes lancea, Agrimonia pilosa Ledeb, Pueraria lobata, Codonopsis pilosula, Rehmannia glutinosa, Rhizoma Dioscoreae, Schisandra chinensis, Anemarrhena asphodeloides Bunge, Cornus officinalis | 81   |
| Jiangtangzengmin decoction   | Pueraria lobata, Astragalus mongholicus, Codonopsis pilosula, Atractylodes macrocephala, PDB, Lotus leaf, Portia cocos, Salvia miltiorrhiza Bge, Coptis chinensis Franch, Licorice | 82,83 |
| Zengmin decoction            | Euonymus alatus (Thunb.) Sieb, PDB, Trichosanthis, Dioscorea opposita Thunb, Raw Astragalus, Coptis chinensis Franch, Anemarrhena asphodeloides Bunge, Laminaria, Asparagus root, Ophiopogon japonicus, Chinese wolfberry root-bark, Dendrobium nobile Lindl, Polygonatum odoratum | 84   |
| Yidaozengmin decoction       | Radix Bupleuri, Fructus aurantii, Coptis chinensis Franch, Codonopsis pilosula, Atractylodes macrocephala Koiz., Portia cocos, Lotus leaf, Salvia miltiorrhiza Bge, PDB, Pueraria lobata, Licorice | 85   |
| Xiaokekang No.2 decoction    | Atractylodes lancea, Atractylodes macrocephala, Pinellia ternata, Pericarpium Citri Reticulatae, Coptis chinensis, Scutellaria baicalensis, PDB, Radix Scrophulariae, Radix puerariae, Litchi seed | 86   |
| Qiyupingtang decoction       | Astragalus membranaceus, Cornus officinalis, Rehmannia glutinosa, Lilium brownies Thunb, Trichosanthis, Wolfberry, PDB, Cortex rehmanniae, Schisandra chinensis | 87   |
| Tegningtang decoction        | PDB, Salvia miltiorrhiza, Pangolin, Dalbergia odorifera, Achyranthes bidentata, Astragalus, Atractylodes macrocephala, Pueraria lobata, Sophora flavescens, Coptis chinensis, Bamboo shavings, Trichosanthis | 88   |
| Antang capsule               | Astragalus, Cornus officinalis, Salvia miltiorrhiza, PDB, etc. | 89   |
| Kuhuang capsule              | Bitter melon, Coptis, Pueraria, PDB | 90   |
| Baihuangjiangtang granule    | PDB, Raspberry, Astragalus membranaceus, Ophiopogon japonicus, Pseudostellaria heterophylla, Dioscorea opposita, Polygonatum, Salvia miltiorrhiza, Stigma maydis, Ilex pubescens, Medlar, Dendrobium, Rehmannia glutinosa, Cornus officinalis | 91   |
| Jiedufuyang decoction        | Honeysuckle, PDB, Coptis chinensis, Epimedium, Cynomorium songaricum, Morinda officinalis, Licorice | 92   |
| Yiqiyangyinhuoxue decoction  | Astragalus membranaceus, Epimedium, PDB, Radix paoniae alba, Radix rehmanniae, Fructus mume, Rhizoma atractylodes, Radix Scrophulariae, Radix puerariae, Radix salviae miltiorrhizae, Radix glycyrrhiza | 93   |
| Yiqiyangyingxingre decoction | Astragalus, Dioscorea opposita Thunb, Pueraria, Ophiopogon japonicus, Radix rehmanniae, Codonopsis pilosula, Coptis chinensis, PDB, Schisandra chinensis, Cortex rehmanniae, Anemarrhena asphodeloides, Cassia obtusifolia | 94   |
| Diabetic nephropathy         | Raw Astragalus, Salvia miltiorrhiza, PDB, Dioscorea opposita Thunb, Codonopsis pilosula, Leech, Radix rehmanniae, Peach kernel, Atractylodes macrocephala, Arctium lappa, Angelica sinensis, Rhubarb | 95,96 |
| Yiqijianpuhuayu decoction    | Raw Astragalus, Leech, Dioscorea opposita Thunb, Codonopsis pilosula, Radix rehmanniae, Rhizoma atractylodis macrocephala, Angelica sinensis, Salvia miltiorrhiza, Eupatorium adenophorum, Earthworm and rhubarb | 97   |

(continued on next page)
| Disease                              | Chinese medicinal formula              | Composition of herbal mixture                                                                 | Ref. |
|--------------------------------------|---------------------------------------|------------------------------------------------------------------------------------------------|------|
| Diabetic peripheral neuropathy       | Yiqihuoxue decoction                  | Raw Astragalus, Radix Codonopsis, **PDB**, Cornus officinalis, Chinese yam, Radix rehmanniae, Rhizoma atractylodismacrocephalae, Angelica sinensis, Salvia miltiorrhiza, **Eupatorium adenophorum**, peach kernel, **Safflower and rhubarb** | 98   |
| Diabetic limb arterial occlusion     | Tangshenkang mixture                  | Astragalus membranaceus, Codonopsis pilosula, Angelica sinensis, Radix paoniae rubra, Rhizoma Chuanxiong, Salvia miltiorrhiza, Peach kernel, **Leech, Rehmannia glutinosa, Cornus officinalis, Achyranthes bidentata, Raspberry, Euryale ferox seed, **PDB**, Honeysuckle, Licorice** | 99   |
| Chronic nephritis with proteinuria  | Fanbaicao capsule                     | **PDB**, Astragalus membranaceus, **Leech, Dioscorea opposita** | 100  |
| Chronic hepatitis B                  | Jiangbai decoction                    | PDB, Chinese wolfberry root-bark, Angelica tail, Astragalus, Peach kernel, Dragon, Radix paoniae rubra, **Ligusticum wallichii, Carthamus tinctorious, Achyranthes bidentata Lysimachia christinae, Hedyotis diffusa, PDB, Plantain, Tripterygium wilfordii, Cuscata, Cornus corni, Dried lotus, Cherry, Thicken, Salvia miltiorrhiza, **Motherwort, Astragalus, Portia cocos, Atractylodes** | 101  |
| Acute mastitis                       | Medicine of the yao nationality (no compound name) | Acanthopanax, Hypericum japonicum Thunb, Dicliptera chinensis, Ardisia mamilata Hance, Aralia elata, Hagen, Camellia, Sapium sebiferum, Blumea megacephala, Guidianhua, Selaginella uncinata(Desv.) spring, Melicope pteleifolia, Wild sesame, **PDB, Sedum sarmentosum, Abrus cantoniensis, Meizizhen, Acer davidii** | 102  |
| Bacterial dysentery                  | Potentilla discolor Bunge Yuliyan     | **PDB**, Radix pulsatillae, Radix paoniae rubra, Honeysuckle charcoal, Portulaca oleracea, **PDB**, Portulaca oleracea, Angelica sinensis, Radix paoniae rubra, Radix Aucklandiae, Radix glycyrrhiza | 103  |
| Idiopathic thrombocytopenic purpura  | Purpura mixture                       | Thistle, Thistle, Lotus leaf, Platycladus orientalis, Imperata cylindrica, Palm, Forsythia suspensa, Peony bark, **PDB, Bauhinia root (rhubarb), Gardenia jasminoides Ellis, Schizonepeta tenuifolia, Rehmannia glutinosa, Paonia lactiflora (stir fried with bran)** | 104  |
| Acute gouty arthritis                | Xiaozhongjiuwei powder (Mongolian medicine, external use) | Astragalus mongholicus, Angelica sinensis, Rehmannia glutinosa, Radix rehmanniae, Charred Radix Rubiae, Hairyvein agrimony, Alternanthera philoxeroides, Chinese wolfberry, Fructus Ligustri Lucidi, **PDB, Licorice, Rhizoma Cyperi, Jujube** | 105  |
| Epidemic parotitis                   | Habuder-9 (Mongolian patent medicine, external use) | **PDB**, Euphorbia, Rhabar, Turmeric, Aconitum kusnezoffii, Polygonatum odoratum, Turmeric, Acorus calamus, **Aconitum kusnezoffii** | 106  |
| Chronic prostatitis                  | Lebi-balazhuri powder (anal plug)     | **PDB**, Euphorbia, Rhabar, Rheum subrheum, Polygonatum odoratum, Acorus calamus, **Asparagus, Aconitum kusnezoffii** | 107  |
| Emphyrosis                           | Fanbaicao powder (external application) | **PDB**, Euphorbia, Rhabar, Rheum subrheum, Polygonatum odoratum, Acorus calamus, Turmeric, Asparagus, **Aconitum kusnezoffii** | 108  |
| Hemorrhoids                          | Zhining decoction (fumigation bath)   | Caecum, **PDB**, Verbena officinalis, Gallus chinensis, Sanguisorba officinalis, *Sophora japonica, Coptis chinensis, Honeysuckle, Artemisia anomala, Angelica sinensis, Angelica dahurica, Schizonepeta tenuifolia, Camphor, etc.* | 109  |

**PDB, Potentilla discolor Bunge; T2DM, type 2 diabetes.**
liver protection and anti-cancer effects. UA significantly inhibits the activity score by modulating lipid metabolism gene expression, below.

5.1.2. Ursolic acid (UA)
UA is the natural pentacyclic triterpenoid carboxylic acid, which has many medicinal properties, such as anti-tumorigenic, anti-obesity, anti-oxidative, anti-inflammatory, anti-fibrotic and anti-atherosclerotic properties. UA significantly inhibits the activity of LXRα response element by competitively binding to LXRα ligand binding region, which demonstrates that UA is a natural LXRα antagonist. In addition, UA reduces hepatic lipid contents through increasing AMPK phosphorylation. Another recent study showed that UA meaningfully reduces the degree of hepatic steatosis by down-regulating the expression levels of PPAR-α and carnitine palmitoyltransferase 1 A (CPT1A), which plays an essential role in the transport of FA into mitochondria for β-oxidation.

5.1.3. Oleanolic acid (OA)
OA is a natural triterpenoid compound, which widely exists in many plants. It has been demonstrated that OA plays a wide range of biological effects, including anti-oxidation, renal protection, liver protection and anti-cancer effects. One study in HFD-induced NAFLD model shows that the administration of OA significantly increases AMPK and CPT-1 levels, which decreases lipid accumulation and promotes the uptake of FA by mitochondria for β-oxidation. Another study shows that OA can sensitize cells to insulin and suppress the hormone-sensitive lipase, which inhibits lipolysis in adipose tissue and consequently decreases serum TGs and VLDL-C particles. OA also ameliorates hepatic oxidative stress and lowers the SREBP and intrahepatic TGs levels.

5.1.4. 3-Acetyloleanolic acid (3Ac-OA)
3Ac-OA is a derivative of oleanolic acid, which can significantly reduce body weight, liver weight and serum total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C) levels in HFD-fed rats by ameliorating hepatic lipid accumulation. In vitro, 3Ac-OA decreases intracellular levels of TC and TG and the number of lipid droplets in free fatty acids (FFA)-treated primary hepatocytes. Moreover, 3Ac-OA significantly increases the expression levels of GLUT-2 and LDL receptor, phosphorylated AMPK and protein kinase B (AKT) and glycogen synthase kinase 3β in the liver tissues of HFD-fed rats.

5.2. Improvement of IR
IR is one of the important pathogeneses of NAFLD. IR can lead to the increase of liver lipid synthesis and the inhibition of FA β-oxidation and lipolysis, which leads to hepatic steatosis. At present, homeostasis model assessment for IR (HOMA-IR) is the gold standard for measuring IR. HOMA-IR increases with the severity of NAFLD. In addition, studies show that Tumor necrosis factor-α (TNF-α) directly disrupts the role of intracellular calcium in beta cells and then induces IR. Accumulating evidence suggests that several natural active ingredients from PDB play an important role in IR in the development of NAFLD, as discussed below.

5.2.1. Quercetin
Quercetin, one of the most abundant flavonoids, is found naturally as glycosides, such as quercetin-3-O-β-rutinoside or quercetin-3-O-β-glucoside. Quercetin treatment decreases IR and NAFLD activity score by modulating lipid metabolism gene expression, cytochrome P450 2E1 dependent lipoperoxidation and related lipotoxicity, which reduces the intrahepatic lipid accumulation. Quercetin-3-O-β-glucoside can promote AKT phosphorylation in gastrocnemius muscles that are the most important tissue to determine whole-body insulin sensitivity. The activation of insulin signaling pathway induced by AKT may contribute to the reduction of plasma glucose concentration and IR.

5.2.2. Luteolin
Luteolin increases hepatic FA oxidation and decreases hepatic lipogenesis, which improves the hepatic insulin sensitivity and increases the insulin receptor substrate expression. Luteolin-7-O-glucoside (LUG) is one of the O-glycosides of luteolin. Luteolin and LUG can decrease serum fasting blood glucose.

### Table 3: Beneficial effects of Chinese medicinal formulas containing PDB in animal models.

| Disease model                  | Chinese medicinal formula                  | Composition of herbal mixture                        | Ref. |
|--------------------------------|--------------------------------------------|------------------------------------------------------|------|
| T2DM mice                      | Mixture of fanbaicao and dandelion         | PDB, Dandelion                                       | 117  |
|                                | Qiba mixture                               | Raw Astragalus, PDB                                  | 118  |
|                                | TCM for clearing heat and replenishing qi  | PDB, Raw Astragalus                                  | 119  |
| T2DM rats                      | Fanbaicao and shen mixture                 | PDB, Salvia miltiorrhiza, Astragalus, Schisandra chinensis, Trichosanthis | 120  |
|                                | Fanbaicao mixture                          | PDB, Semen Platycladus, Ginseng, Polygala tenuifolia, Schisandra chinensis | 121  |
| Diabetic nephropathy mice      | Tangshenping capsule                       | Astragalus tablets, Cooked ground yellow, Cornus, White flower snake tongue grass, PDB, Leech | 122  |
| Big-ear white rabbits with     | Water decoction of Potentilla discolor Bunge | PDB                                                  | 123  |
| Hyperlipidemia                 | Water decoction of Potentilla discolor Bunge | PDB                                                  | 124  |

PDB, Potentilla discolor Bunge; T2DM, type 2 diabetes.
5.2.3. Kaempferol
Kaempferol, one of the flavonoids, which is a subclass of flavonoids, has many medicinal properties such as anti-oxidative, anti-carcinogenic, anti-diabetic, antimicrobial and cardio-protective properties. Oral administration of kaempferol significantly improves FBG and decreases glucose tolerance in HFD-induced obese mice, which is associated with reduction of hepatic glucose production and improvement of whole-body insulin sensitivity. Kaempferol is an inhibitor of hepatic pyruvate carboxylase activity. It inhibits gluconeogenesis through suppressing pyruvate carboxylase and glucose-6 phosphatase activity. In addition, kaempferol also improves hepatic glucose metabolism by activating AKT and glucokinase. It has also been shown that kaempferol glycoside (KG) fractions reduce body weight, adipose tissue and TG levels in HFD-fed mice. KG treatment also decreases the levels of FBG and HbA1c and improves IR. In addition, KG decreases peroxisome proliferator-activated receptor-γ (PPAR-γ) and SREBP-1c expression levels, which is correlated with the decrease of adipose tissue accumulation and the improvement of lipid metabolism and IR.

5.2.4. Apigenin
Apigenin is a member of the flavone subclass of flavonoids present in fruits and vegetables. Previous research showed that apigenin can decrease serum TC, TG, LDL-C, FBG and fasting insulin levels, and increase high-density lipoprotein cholesterol levels in the HFD-induced NASH rats. In addition, apigenin can notably decrease HOMA-IR and increase PPAR-α and PPAR-γ levels in the liver. These results show that apigenin alleviates hepatic steatosis and inflammatory necrosis through improving IR, glucose tolerance and lipid metabolism.

5.2.5. β-Sitosterol
β-Sitosterol is a plant sterol, and its chemical structure is similar to cholesterol. β-Sitosterol has anti-diabetes, anti-cancer, anti-arthritis, hypolipidemic and hepatoprotective properties. It normalizes serum levels of glucose, insulin, lipids, oxidative stress markers and anti-oxidant enzymes in diabetic rats through the regulation of insulin receptor and GLUT-4.

5.3. Anti-oxidative and anti-inflammatory responses
Oxidative stress in the liver is one of the hits in the pathogenesis of NAFLD. The chronic inflammatory state of the liver is closely
associated with IR, inflammatory cytokines and hepatic steatosis. Neutrophils can produce ROS, subsequently activate stress kinases (e.g., ASK1 and p38 MAPK), and induce liver injury. CXCL1 or IL-8 can induce hepatic neutrophil infiltration and promote the progression of fatty liver to NASH in HFD-fed mice, which is mediated via the p47Phox-dependent production of ROS by neutrophils. By inducing hepatic metallothionein IL-22Fc is able to attenuate hepatic ROS production, stress kinase activation and the inflammatory functions of hepatocyte-derived EVs, and thereby ameliorates CXCL1-driven NASH. As described below, several PDB active ingredients also have anti-oxidative and anti-inflammatory properties.

5.3.1. Luteolin
Luteolin inactivates nuclear factor-κB and decreases the inflammatory levels of IL-6, Interleukin-1β (IL-1β) and TNF-α. Furthermore, hepatic ROS production is significantly attenuated by luteolin administration, which indicates that oral intake of luteolin exerts the anti-oxidant effects in the liver.

5.3.2. Rutin
Rutin is a natural flavonoid and has many biological functions, including anti-oxidative, anti-inflammatory, anti-cancer, neuroprotective and hepatoprotective functions. Rutin has also hypolipidemic and hepatoprotective effects in NAFLD. Rutin reduces the cellular malondialdehyde levels and increases the expression levels of anti-oxidant enzymes. It restores the superoxide dismutase activity, which inhibits the accumulation of lipids in liver cells and reduces oxidative damage simultaneously.

5.3.3. Apigenin
Apigenin has a variety of biological activities, such as anti-oxidative, anti-inflammatory, anti-apoptotic, anti-mutagenic and anti-tumorigenic properties. Apigenin can alleviate HFD-induced liver injury in mice by increasing insulin sensitivity, reducing liver lipid accumulation, improving hepatic steatosis and reducing macrophages recruitment. These protective effects may be correlated with the activation of NLRP3 inflammasome, the decreased expression of IL-1β and IL-18, the inhibition of xanthine oxidase activity and the reduction of ROS production. In addition, apigenin has been shown to ameliorate lipid metabolism and oxidative stress through regulating nuclear factor E2-related factor 2 (Nrf2) (a master regulator of lipid metabolism homeostasis and oxidative stress) and PPAR-γ. It has been confirmed that apigenin promotes the entry of Nrf2 into the nucleus, and thereby considerably activates Nrf2 to inhibit the expression of PPAR-γ.

5.4. Inhibition of endoplasmic reticulum (ER) stress
ER stress is a major contributor in the development of hepatic steatosis. ER is crucial for the formation of lipid droplets and is pivotal for VLDL assembly and the progression of hepatic steatosis. ER homeostasis is maintained through an adaptive mechanism termed the unfolded protein response. This adaptive mechanism is mediated by inositol-requiring transmembrane kinase/endoribonuclease 1α (IRE1α), which is responsible for producing spliced X-box binding protein 1 (XBPs1) and protein kinase R-like ER kinase, and activating transcription factor 6α. In addition, C/EBP homologous protein is a critical molecule involved in ER stress and ER stress-induced apoptosis. There is increasing evidence to suggest that several natural active compounds from PDB play a central role in endoplasmic reticulum stress in the development of NAFLD.

5.4.1. Quercetin
Quercetin can activate IRE1α and ameliorate hepatic steatosis and ER stress induced by high cholesterol. A study reports that quercetin reduces the levels of hepatic TG and TC and increases the levels of hepatic VLDL, and up-regulates XBPs1 expression in the HFD-fed rats. Additionally, microsomal TG-transfer protein complex expression is also increased by quercetin. Moreover, quercetin increases co-localization of lysosomes and lipid droplets, accompanied by the decreasing accumulation of autophagy related protein p62. Collectively, these findings demonstrate that quercetin plays anti-NAFLD effects by inducing the hepatic VLDL assembly and lipophagy through the IRE1α/XBP1s pathway.

5.4.2. UA
UA significantly reduces the liver weight, serum ALT/AST levels and hepatic steatosis in leptin receptor deficient diabetic

Figure 4 Functions of the main natural active compounds of PDB. Flavonoids improve lipid metabolism and IR, reduce oxidative stress and ER stress, and regulate the intestinal microflora. Organic acids regulate the intestinal microflora. The terpenoids improve lipid metabolism and inhibit endoplasmic reticulum stress. The steroids improve IR.
| Natural active compound | Chemical structure | Active ingredient content | Model | Mechanism of action | Ref. | PubChem CID |
|-------------------------|-------------------|--------------------------|-------|---------------------|------|-------------|
| Flavonoids | Quercetin | 0.1086 mg/g | HFD-induced NAFLD rats, FFA-induced HepG2, db/db mice | ↓ TC, TG | ↓ Microsomal TG-transfer protein complex, ↑ Co-localization of lysosomes with LDs | 131, 145 | 5280343 |
| | | | | ↑ VLDL | ↓ Accumulation of p62, ↑ IRE1α endonuclease activity, ↑ XBP1s, ↓ Lipid accumulation, ↓ Serum transaminase levels, ↓ Serum total bile acids | | |
| | | | | ↓ Histological alterations of liver | | |
| | | | | ↓ IL-1β, IL-6, and TNF-α in liver | | |
| | | | | ↑ FXR1/TGR5 signaling pathway | | |
| | | | | ↓ Glucose concentration in plasma, ↑ AKT phosphorylation | 132 | 5280804 |
| | Quercetin-3-O-β-glucoside | Sucrose-fed rats | | ↑ Body weight, ↓ FBG, HbA1c, ↓ Adipose tissue accumulation, ↓ TGs, ↑ Lipid metabolism, ↓ PPAR-γ and SREBP-1c | | 5280863 |
| | Kaempferol | 0.0611 mg/g | HFD-fed mice | ↓ TC | ↓ The abundance of lipid droplets, ↓ Lipid accumulation, ↓ Cellular malondialdehyde level, ↓ Superoxide dismutase activity, ↑ AMPK activity, ↑ Anti-oxidative enzymes, ↑ PPARα, CPT-1 and CPT-2, ↓ SREBP-1c, DGAT-1, DGAT-2, ↓ HMGCR, GPAT, FAS, ACC | 147, 148 | 5280805 |
| | Rutin | 0.555 mg/g | HFD-induced NAFLD mice, HepG2 cells | ↓ TC | ↓ Insulin sensitivity, ↓ Hepatic steatosis, ↓ Macrophages recruitment, ↓ IL-1β and IL-18, ↓ Xanthine oxidase(XO) activity, ↓ ROS production, ↑ NLRP3 inflammasome | 149, 150, 151 | 5280443 |
| | Apigenin | 0.114 mg/g | HFD-induced NAFLD mice, Hepa1-6 cells pre-treated with FFA | ↑ Insulin sensitivity | |

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| Compound          | Concentration | Cell Type                           | Effect                                                                                           |
|-------------------|---------------|-------------------------------------|-------------------------------------------------------------------------------------------------|
| Luteolin          | 0.04 mg/g     | db/db mice, HepG2 cells, primary hepatocytes | Novel lipid synthesis, PPAR-γ, TC, TGs, LDL-C, FBG, fasting insulin, HOMA-IR, HDL-C, glucose tolerance, hepatic inflammatory necrosis, PPAR-α and PPAR-γ (protein and mRNA expression) |
| Terpenoids        | 0.02436 mg/g  | T0901317-induced mice, HepG2 cells, intestinal cells, db/db mice, palmitate solution-treated LO2 cells | Hepatocyte lipid content, LXRα-SREBP-1c signaling pathway, AMPK phosphorylation, liver weight, ALT and AST, lipid accumulation, IRE1α activity, JNK phosphorylation, C/EBP homologous protein accumulation, PPARα, lipid β-oxidation, AMPK gene expression, GLUT-4 |
| Oleanolic acid    | 0.1086 mg/g   | High fructose diet-fed rats          | Lipid metabolism, AMPK gene expression, GLUT-4                                                                                                        |
| 3-Acetyloleanolic acid |             | HFD-induced NAFLD rats, FFA-treated primary rat hepatocytes | Body weight, liver weight, TC, TGs and LDL-C, GLUT-2, low-density lipoprotein receptor, AMPK phosphorylation, blood glucose, serum insulin, blood lipid, oxidative stress markers, anti-oxidant enzymes, insulin receptor, GLUT-4 |
| Steroids          |               | HepG2 cells, diabetic rats           | Blood glucose, serum insulin, blood lipid, oxidative stress markers, anti-oxidant enzymes, insulin receptor, GLUT-4 |
| Organic acids     |               | HFD-induced NAFLD mice              | Trimethylamine, Trimethylamine-N-oxide, Dimethylamine                                                                                               |

AKT, protein kinase B; AMPK, (AMP)-activated protein kinase; db/db mice, leptin receptor deficient diabetic mice; FAS, fatty acid synthase; FBG, fasting blood glucose; FFA, free fatty acid; FXR, farnesoid X receptor; GLUT-4, glucose transporter type 4; HbA1c, glycosylated hemoglobin; HFD, high-fat diet; HOMA-IR, homeostasis model assessment for IR; IRE1α, inositol-requiring transmembrane kinase/endoribonuclease 1α; LDL-C, low-density lipoprotein cholesterol; Nrf2, nuclear factor E2-related factor 2; PPAR-α, peroxisomal proliferator-activated receptor α; ROS, reactive oxygen species; SREBP-1c, sterol regulatory element binding protein-1c; TC, total cholesterol; TG, triglyceride; TGR5, Takeda G protein-coupled receptor 5; VLDL, very low density lipoprotein; XBP1s, X-box binding protein 1.
properties and anti-oxidative activities. GA, an endogenous plant phenol, has potent free radical scavenging activity. Furthermore, treatment of HFD-fed mice compared with the control group has been suggested to induce the development of NAFLD by multiple mechanisms. The intestinal barrier is maintained by the gut microbiota, including trimethylamine, kynurenine, and cysteine. For example, short chain fatty acids maintain the gut barrier and reduce pro-inflammatory cytokine secretion in the liver. The mechanisms by which BAs contribute to the development of NAFLD involve two major receptor molecules: the nuclear farnesoid X receptor (FXR) (mainly activated by primary BAs) and the Takeda G protein-coupled receptor 5 (TGR5) (mainly activated by secondary BAs). Activation of FXR reduces hepatic inflammation and maintains the intestinal barrier by inhibiting LPS-stimulated nuclear factor-κB (NF-κB) activation. Moreover, choline acquired through the diet can be further metabolized by the microbiome from trimethylamine into trimethylamine-N-oxide. Trimethylamine-N-oxide has been suggested to induce the development of NAFLD by multiple mechanisms, such as aggravating hepatic IR, increasing adipose tissue inflammation and reducing the levels of BAs produced by enzymes. In recent years, studies have shown that several natural active ingredients from PDB play an important role in regulating intestinal flora in the course of NAFLD progression. Those active ingredients are discussed below.

5.5. Regulation of intestinal microflora

The intestinal microflora and their metabolites, including bile acids (BAs), branched-chain amino acids and tryptophan catabolites, regulate the intestinal homeostasis and may contribute to the pathogenesis of NAFLD. The metabolites exhibit multiple effects on the development of NAFLD through saccharolytic and proteolytic fermentation. For example, short chain fatty acids maintain the gut barrier and reduce pro-inflammatory cytokine secretion in the liver. The mechanisms by which BAs contribute to the development of NAFLD involve two major receptor molecules: the nuclear farnesoid X receptor (FXR) (mainly activated by primary BAs) and the Takeda G protein-coupled receptor 5 (TGR5) (mainly activated by secondary BAs). Activation of FXR reduces hepatic inflammation and maintains the intestinal barrier by inhibiting LPS-stimulated nuclear factor-κB (NF-κB) activation. Moreover, choline acquired through the diet can be further metabolized by the microbiome from trimethylamine into trimethylamine-N-oxide. Trimethylamine-N-oxide has been suggested to induce the development of NAFLD by multiple mechanisms, such as aggravating hepatic IR, increasing adipose tissue inflammation and reducing the levels of BAs produced by enzymes. In recent years, studies have shown that several natural active ingredients from PDB play an important role in regulating intestinal flora in the course of NAFLD progression. Those active ingredients are discussed below.

5.5.1. Quercetin

Quercetin can revert the gut microbiota imbalance and the linked endotoxemia-mediated TLR-4 pathway activation, which results in the inhibition of inflammamson response and reilum stress pathway activation and the deregulation of lipid metabolism gene expression. Quercetin significantly reduces serum transaminase levels and T2DM-induced liver histological characteristics. In addition, quercetin restores the levels of superoxide dismutase, catalase and glutathione, and reduces total BAs levels and lipid accumulation in the liver of db/db mice. In vitro, quercetin eliminates lipid droplets and restores the up-regulated TC and TG levels. Mechanistic studies have shown that quercetin activates the FXR/TGR5 signaling pathway that is involved in the regulation of T2DM-induced lipid metabolism during NAFLD.

5.5.2. Gallic acid (GA)

GA, an endogenous plant phenol, has potent free radical scavenging properties and anti-oxidative activities. Lower levels of methylamine-associated metabolites including trimethylamine, trimethylamine-N-oxide and dimethylamine are found in GA treatment HFD-fed mice compared with the control group. GA is able to reduce the elevation of choline metabolism in the gut microflora present in HFD-fed mice and as such improve hepatic steatosis.

6. Challenges and suggestions

The application of TCM for the treatment of NAFLD has been reported in many Asian countries including China, India and Japan. However, the clinical effects of TCM for the treatment of NAFLD have not been yet recognized by regulatory agencies such as the U.S. Food and Drug Administration. Clinical trials for the evaluation of the safety and efficacy of PDB as a potential anti-NAFLD therapeutic are still necessary for regulatory acceptance. In this paper we investigated the mechanisms by which the natural active compounds of PDB may improve NAFLD using experimental models. Yet, clinical data, in which the mode-of-action of the therapeutic effects of natural active compounds of PDB are described, are still missing. Moreover, pharmacokinetic data of the PDB compounds, such as drug dose variance and absorbance rates cannot be extrapolated from animal models and need also to be determined in patients during clinical trials.

7. Summary

The prevalence of NAFLD is reaching pandemic proportions, and since the pathogenesis of this disease is very complex, there are currently no approved effective drugs for its treatment. Therefore, it is urgent to develop novel efficient therapeutic and preventative strategies for NAFLD. More and more studies are paying attention to TCM. PDB has been known since ancient times for its curative properties. In this paper, we provide an overview of the current knowledge of the pathogenesis of NAFLD, and summarize the anti-NAFLD properties of PDB, providing the underlying mechanisms of its natural active compounds. Luteolin, UA, OA, 3Ac-coumaric acid, rutin and GA were found to ameliorate NAFLD characteristics. Interestingly, these compounds exert their anti-NAFLD effects through different mechanisms, including improving lipid metabolism and IR, reducing oxidative stress and inflammation, inhibiting ER stress, and regulating intestinal microflora. These beneficial effects of the natural active compounds of PDB support the notion that PDB can be considered as a potential novel candidate for the treatment and prevention of NAFLD. As such, the PDB natural active compounds may represent new sources for the development of new drugs or dietary supplements against NAFLD.

However, some questions remain to be addressed. On one hand, a systematic meta-analysis of the available publications about traditional Chinese medicines containing PBD still needs to be conducted. On the other hand, the hepatotoxicity and nephrotoxicity induced by PDB also needs investigation. The increase of well-designed preclinical and clinical studies to investigate the therapeutic effects of TCM, will hopefully validate the benefits of PDB as a therapeutic agent for the treatment of NAFLD in the future.

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**Author contributions**

Man Li, Yueqiu Gao and Robim M. Rodrigues: proposition proposal, design and final revision; Longshan Ji and Qian Li: organizational framework and construction, paper drafting; Yong He: revision and analysis; Xin Zhang and Zhenhua Zhou: collected data and provided materials; Yating Gao, Miao Fang, and Zhuo Yu: revision.

**Conflicts of interest**

The authors declare no conflicts of interest.

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