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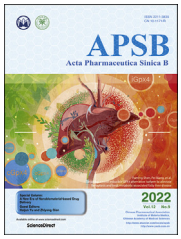

REVIEW

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

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Anti-oxidative;

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

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Anti-inflammatory;
Lipid metabolism;
Insulin resistance;
Endoplasmic reticulum stress;
Intestinal microflora

metabolism and reversal of insulin resistance. In this review, we summarize potential therapeutic effects of TCM formulas for the treatment of NAFLD, focusing on the medicinal properties of natural active compounds from PDB and their underlying mechanisms. We point out that PDB can be classified as a novel candidate for the treatment and prevention of NAFLD.

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[4–6]. 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[7]. 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[8]. 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[9]. 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[10]. 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, diarrhoea and diabetes mellitus[11]. 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[12,13]. The comprehensive inter-tissue crosstalk between the liver, the intestine, adipose tissue, and the nervous system plays a role in the development of NAFLD[14,15]. Also, the liver immune microenvironment, and particularly macrophages and neutrophils are involved in lipid accumulation and inflammation during NAFLD[16] (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 gastro-intestinal anatomy and pH[17]. 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)[18].

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[14]. 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[22].

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[23]. In addition, extracellular vesicles (EVs) released from hepatocytes contribute to key processes involved in the pathogenesis and progression of NAFLD[24–26]. The EVs can promote the expression of proinflammatory cytokines and polarize hepatic macrophages to the proinflammatory (M1) phenotype[27–29]. Mixed-lineage kinase 3 induces lipid-treated hepatocytes to release EVs containing C−X−C motif chemokine ligand 10 to recruit macrophages[30]. Moreover, EVs can contribute to hepatic recruitment of monocyte-derived macrophages[31], which results in inflammation[32]. The identification of the pivotal molecules associated with the dynamic

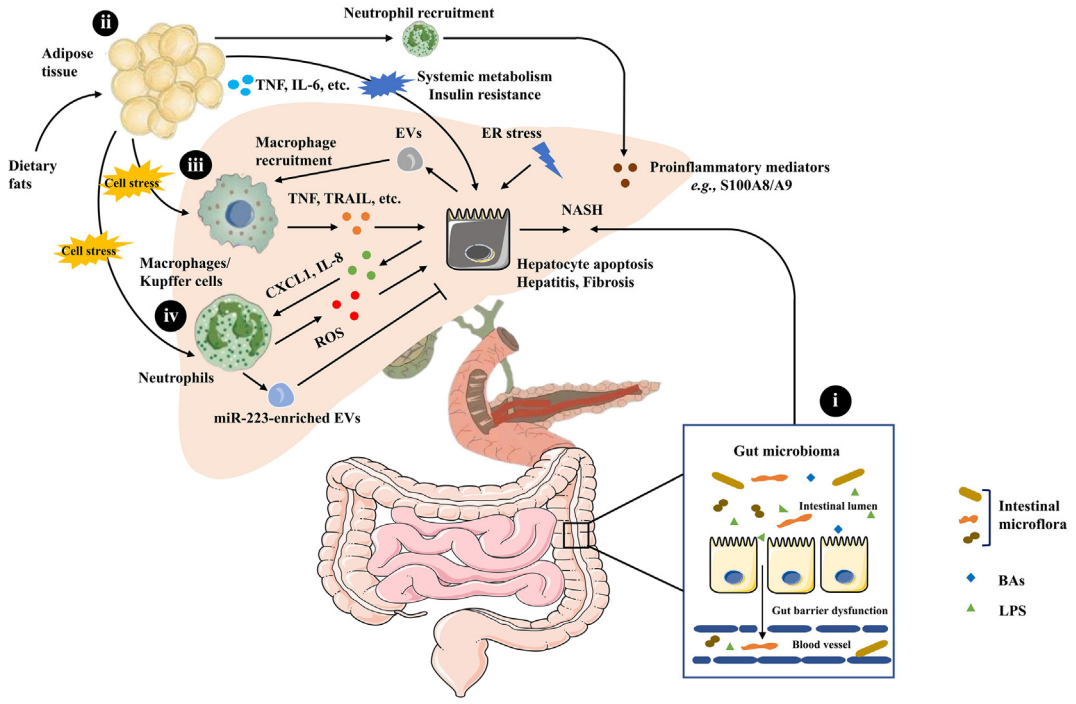


Figure 1 Pathogenesis of NAFLD: inter-tissue crosstalk between the liver, the intestine, and adipose tissue. (i) Gut barrier dysfunction and disruption of barrier integrity cause translocation of bacteria or bacterial products into the blood circulation, resulting in liver inflammation and the progression towards NASH. (ii) The intricate crosstalk between adipose tissue and the liver contributes to the progression of NAFLD. (iii) KCs produce TNF, TRAIL and FAS ligands through phagocytosis of apoptotic bodies, which subsequently promotes hepatocyte apoptosis, causing hepatitis and fibrosis. EVs released from hepatocytes contribute to hepatic recruitment of monocyte-derived macrophages. (iv) The up-regulation of hepatic chemokines CXCL1 and IL-8 and resulting infiltration of neutrophils are hallmarks of NASH.

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[33]. 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[34−36]. 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[37].

In addition, neutrophil-specific microRNA-223 (miR-223) is elevated in hepatocytes and limits NASH progression in obese mice[38]. This elevation of miR-223 in hepatocytes 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[39].

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[40].

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[41]: (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)*[42,43], simiao powder *(Cheng Fang Bian Du)*[44], sanziyangqin decoction *(Han Shi Yi Tong)*[45]; (ii) formulas for relieving liver and regulating qi: xiaochaihu decoction (*Shang Han Lun*)[46], chaihushugan powder (*Jingyue Complete Library*)[47−49]; (iii) formulas for clearing heat, promoting dampness and dispersing knot: dachaihu decoction

Table 1 Treatment principles and effects of the classical TCM formulas for the treatment of NAFLD.

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 CDAA-fed 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 ↑ Adiponection ↓ SREBP-1c, FAS	42, 43
	Simiao powder (SMS)	HFHS-induced NAFLD mice	↓ *Acly*, *Fas*, *Acc*, *Scd1* ↓ IL-1β, NLRP-3 ↓ The biosynthesis of fatty acids ↑ Insulin secretion pathway ↑ Gut microbiota composition	44
	Sanziyangqin decoction (SZYQT)	HFD-induced NAFLD mice	↓ Hepatosteatosis ↓ TNF-α ↓ Inflammatory cell infiltration in liver tissues ↑ Insulin resistance ↑ p-AKT; ↓ apoptosis	45
Relieve liver and regulate Qi	Xiaochaihu decoction (XCHT)	Patients with NAFLD	↑ Lipid metabolism	46
	Chaihushugan powder (CHSGS)	HFD-induced NAFLD/NASH rats High fat and sugar emulsion-induced NAFLD rats	↓ 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	47, 48, 49
Clear heat, promote dampness and disperse knot	Dachaihu decoction (DCHT)	Patients with NAFLD High-fat high-fructosediet-induced NAFLD rats	↓ TNF-α, TGF-β, NF-κB, TLR4	50, 51
	Yinchenhao decoction (YCHT)	HFD-induced NASH rats	↓ TNF-α	52
Promote blood circulation and dissipate blood stasis	Taohongsiwu decoction (THSWT)	HFHC-induced NAFLD mice	↓ Hepatic lipid accumulation ↓ C/EBPα, PPARγ, *p*AMPK; ↑ IRS-1, pAKT ↓ The ratio of BAX to BCL-2 expression	53
Warm Yang and invigorate spleen	Chaihulizhong decoction (CHLZT)	HFD-induced NAFLD rats A long chain fat emulsion-treated HepG2 cells	↑ AMPKα, PPAR-γ; ↓ ACC-α, p-ACC-α, SREBP2, HMGR	54
	Lingguizhugan decoction (LGZGT)	HFD-induced NAFLD rats HFD-induced NAFLD mice	↓ GS, ACC, SREBP-1c, HMGCR ↑ PYGL activity	55, 56, 57

			↓ Hepatosteatosis	
			↑ Insulin resistance;	
			↑ Oxygen consumption rate	
			↓ The expression and protein abundance of lipogenic genes in the liver	
			↑ Gut microbiota	
	Fuzilizhong decoction (FZLZT)	HFD-induced NAFLD rats	↑ IL-10, IFN-α, IFN-β	58
			↑ p53 signaling; ↓ PPARγ signaling	
	Sini powder (SNS)	Stress-induced NAFLD rats	↓ Psychological stress	59, 60, 61
		HFD-induced NAFLD mice	↓ TNF-α	
			↑ Gut microbiota	
		HFD-induced NAFLD rats	↓ CPT1B, rno-miR-138-5*p*	62
	Ganjianglingzhu decoction (GJLZT)			

HFD, high-fat diet; CDAA, choline-deficient amino acid-defined diet; HFHS, high fat/high sucrose diet; HFHC, high-fat and high-cholesterol diet; TLR4, toll-like receptor 4; TRAF6, TNF receptor associated factor 6; SREBP-1c, sterol regulatory element binding protein-1c; FAS, fatty acid synthase; *Acly*, ATP citrate lyase; *Acc*, acetyl-CoA carboxylase; *Scd1*, stearoyl-CoA desaturase 1; IL-1β, interleukin-1β; NLRP-3, NLR family containing pyrin domain protein 3; p-AKT, phospho-protein kinase B; TNF-α, tumor necrosis factor-α; CASPASE-1, cysteinyl aspartate specific proteinase; p38 MAPK, mitogen activated protein kinases with molecular weight of 38 kD; TGF-β, transforming growth factor-β; PPAR-γ, peroxisome proliferator-activated receptor-γ; C/EBPα, CCAAT/enhancer binding proteins alpha; IRS-1, insulin receptor substrate 1; BAX, protein of BCL2 associated x; BCL-2, B-cell lymphoma-2; SREBP2, sterol regulatory element binding protein-2; HMGR, 3-hydroxy-3-methyl glutaryl coenzyme A reductase; GS, glycogen synthase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; PYGL, glycogen phosphorylase liver type; IL-10, interleukin-10; IFN-β, interferon-β; CPT1B, carnitine palmitoyltransferase.

(*Treatise on Febrile Disease*)[50,51], yinchenhao decoction (*Shang Han Lun*)[52]; (iv) formulas for promoting blood circulation and dissipating blood stasis: taohongsiwu decoction (*The Golden Mirror of Medicine*)[53]; (v) formulas for warming yng and invigorating spleen: chaihulizhong decoction *(Shang Han Lun)*[54], lingguizhugan decoction (*Jin Gui Yao Lue*)[55–57], fuzilizhong decoction *(San Yin Ji–Bing Zheng Fang Lun)*[58], sini powder *(Shang Han Lun)*[59–61], ganjianglingzhu decoction (*Jin Gui Yao Lue*)[62]. The regulatory effects and relevant mechanisms of the classical formulas of TCM treating NAFLD are shown in Table 1[42–62] and Fig. 2.

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 major acupoints[63]. 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[64–66]. In addition, acupuncture has been shown to ameliorate NAFLD by regulating lipid metabolism[67–70], improving IR[71] and ER stress[70,72,73], alleviating oxidative stress[68,74], inhibiting the expression of inflammatory cytokines[68,69,75], and alleviating steatosis, necrosis and inflammatory cell infiltration of liver tissue in NAFLD rat model. Furthermore, acupuncture can alleviate bullous steatosis of liver tissue[76–78], and the expansion and disorder of rough endoplasmic reticulum[73] 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[79–116] (patient clinical data) and Table 3[117–124] (animal models), 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 chemiczal components, including flavonoids, terpenoids, organic acids, steroids and tannins[125]. 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[126]. The total flavonoids content in PDB is approximately 20%[127]. The two main forms of flavonoids are conjugated glycosides and free forms. Terpenoids in PDB are mainly monoterpenes and triterpenes[10]. The content of monoterpenes is lower than that of the triterpenes, and most of the triterpenes are oleanolic alkane, urethane and their saponins[128]. The main organic acids in PDB are phenolic acids and fatty acids[10]. The steroids obtained from PDB are mainly beta-sitosterol and carotene[129]. Tannins in PDB are mainly ellagic acid and its derivatives[130].

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[131–139]. In addition, flavonoids and organic acids were shown to regulate the intestinal microflora[131,137,140]. The steroids and terpenoids from PDB also improved IR[141] and lipid metabolism[142,143], respectively. The latter, also inhibited ER stress[143] (Fig. 4).

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

Table 4[131–135,140,142–155] 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[156]. 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[157]. Therefore, LXRs provide a transcriptional switch that integrates hepatic glucose metabolism and FA synthesis[158]. 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 transferase1/2 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[159]. Luteolin can improve hepatic steatosis by repressing hepatic TG accumulation and novel

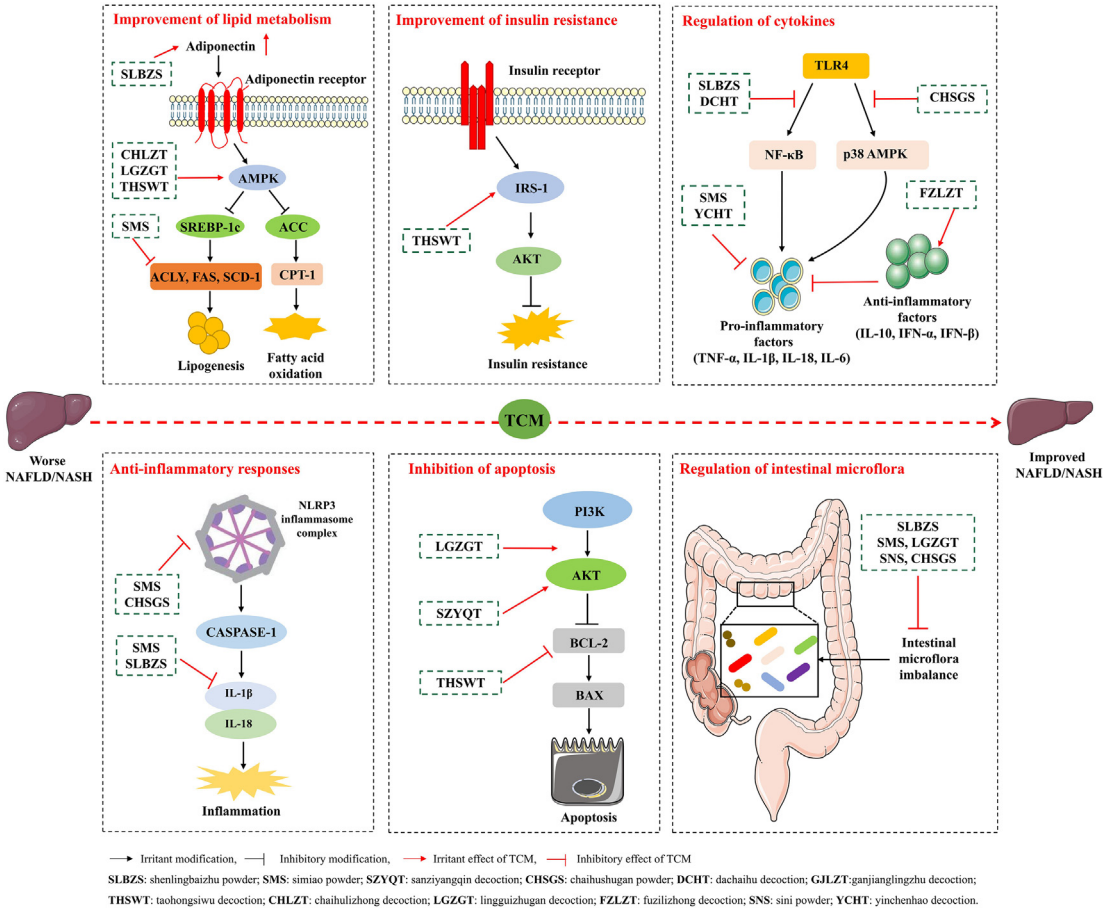


Figure 2 Mechanisms of the classical TCM formulas for the treatment of NAFLD. The classical formulas of TCM exhibit a series of beneficial effects for the treatment of NAFLD, including improvement of lipid metabolism and IR, regulation of cytokines, anti-inflammatory responses, inhibition of apoptosis, and regulation of intestinal microflora.

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 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*	80
	Jiulongjiangtang decoction	Gentian, *Astragalus mongholicus*, *Poria cocos*, *Salvia miltiorrhiza* Bge, **PDB,** *Atractylodes lancea*, *Agrimonia pilosa* Ledeb, *Pueraria lobata*, *Codonopsis pilosul, 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, *Poria cocos*, *Salvia miltiorrhiza* Bge, *Coptis chinensis* Franch, Licorice	82,83
	Zengmin decoction	*Euonymus alatus* (Thunb.) Sieb, **PDB,** Trichosanthin, *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* Koidz, *Poria 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 browmies* Thunb, Trichosanthin, Wolfberry, **PDB**, Cortex rehmanniae, *Schisandra chinensis*	87
	Tangniaoning decoction	**PDB,** *Salvia miltiorrhiza*, Pangolin, *Dalbergia odorifera*, *Achyranthes bidentata*, *Astragalus*, *Atractylodes macrocephala*, *Pueraria lobata*, *Sophora flavescens*, *Coptis chinensis*, *Bamboo shavings*, Trichosanthin	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 paeoniae alba, Radix rehmanniae, Fructus mume, Rhizoma atractylodes, Radix Scrophulariae, Radix puerariae, Radix salviae miltiorrhizae, Radix glycyrrhiza	93
	Yiqiyangyinqingre 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	Yiqijianpihuayu decoction	Raw *Astragalus*, *Salvia miltiorrhiza*, **PDB**, *Dioscorea opposita* Thunb, *Codonopsis pilosula*, Leech, Radix rehmanniae, Peach kernel, *Atractylodes macrocephalae*, *Arctium lappa*, *Angelica sinensis*, *Rhubarb*	95,96
	Yiqihuayu decoction	Raw *Astragalus*, Leech, *Dioscorea opposita* Thunb, *Codonopsis pilosula*, **PDB**, Radix rehmanniae, Rhizoma atractylodis macrocephalae, *Angelica sinensis*, *Salvia miltiorrhiza*, *Eupatorium adenophorum*, Earthworm and rhubarb	97

(*continued on next page*)

Table 2 (*continued*)

Disease	Chinese medicinal formula	Composition of herbal mixture	Ref.
	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
	Tangshenkang mixture	*Astragalus membranaceus*, *Codonopsis pilosula*, *Angelica sinensis*, Radix paeoniae rubra, Rhizoma Chuanxiong, *Salvia miltiorrhiza*, Peach kernel, Leech, *Rehmannia glutinosa*, *Cornus officinalis*, *Achyranthes bidentata,* Raspberry, *Euryale ferox* seed, **PDB**, Honeysuckle, Licorice	99
Diabetic peripheral neuropathy	Fanbaicao capsule	**PDB**, *Astragalus membranaceus*, Leech, *Dioscorea opposita* Thunb	100
Diabetic limb arterial occlusion	Fandihuanwu decoction	**PDB**, Chinese wolfberry root-bark, Angelica tail, *Astragalus*, Peach kernel, Dragon, Radix paeoniae rubra, *Ligusticum wallichii*, *Carthamus tinctorious*, *Achyranthes bidentata*	101, 102
Chronic nephritis with proteinuria	Jiangbai decoction	*Lysimachia christinae*, *Hedyotis diffusa*, **PDB**, Plantain, *Tripterygium wilfordii*, *Cuscuta*, *Cornus corni*, Dried lotus, Cherry, Thicken, *Salvia miltiorrhiza*, Motherwort, *Astragalus*, *Poria cocos*, *Atractylodes*	103, 104
Chronic hepatitis B	Medicine of the yao nationality (no compound name)	*Acanthopanax*, *Hypericum japonicum* Thunb, *Dicliptera chinensis*, *Ardisia mamillata* Hance, *Aralia elata*, Hugen, Camellia, *Sapium sebiferum*, *Blumea megacephala*, Guidianhuo, *Selaginella uncinata*(Desv.) spring, *Melicope pteleifolia*, Wild sesame, **PDB**, *Sedum sarmentosum*, *Abrus cantoniensis*, Meizizhen, *Acer davidii*	105
Acute mastitis	Fanbaicao decoction	**PDB**, *Taraxacum mongolicum*, Purslane, Geranium, *Plantago asiatica*, *Polygonum sibiricum*, *Dianthus Superbus*, *Angelica dahurica*, *Bupleurum chinense*, *Achyranthes bidentata*, *Cyperus*, *Elsholtzia splendens*, *Isatis indigotica*	106
Bacterial dysentery	*Potentilla discolor* Bunge	**PDB**	107
	Yuliyin	Radix pulsatillae, Radix paeoniae rubra, *Honeysuckle charcoal*, *Portulaca oleracea*, **PDB**, *Portulaca oleracea*, *Angelica sinensis*, Radix paeoniae rubra, Radix Aucklandiae, Radix glycyrrhiza	108
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*, *Paeonia lactiflora* (stir fried with bran)	109, 110
	Zhixuexiaoban decoction	*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	111
Acute gouty arthritis	Xiaozhongjiuwei powder (Mongolian medicine, external use)	*Euphorbia pekinensis*, **PDB**, *Polygonatum odoratum*, Turmeric, *Acorus calamus*, *Aconitum kusnezoffii*, Asparagus, Rheum subrheum, Rhubarb	112
Epidemic parotitis	Habuder-9 (Mongolian patent medicine, external use)	**PDB**, *Euphorbia*, *Rhubarb*, Turmeric, *Aconitum kusnezoffii*, *Polygonatum*, *Polygonatum odoratum*, *Acorus calamus*, Asparagus	113
Chronic prostatitis	Lebi-balazhuri powder (anal plug)	**PDB**, *Euphorbia*, Rhubarb, Rheum subrheum, *Polygonatum*, *Acorus calamus*, Turmeric, Asparagus, *Aconitum kusnezoffii*	114
Empyrosis	Fanbaicao powder (external application)	**PDB**	115
Hemorrhoids	Zhining decoction (fumigation bath)	Caecum, **PDB**, *Verbena officinalis*, *Galla chinensis*, *Sanguisorba officinalis*, *Sophora japonica*, *Coptis chinensis,* Honeysuckle, *Artemisia anomala*, *Angelica sinensis*, *Angelica dahurica*, *Schizonepeta tenuifolia*, Camphor, etc.	116

PDB, *Potentilla discolor* Bunge; T2DM, type 2 diabetes.

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
	Qibai mixture	Raw *Astragalus*, **PDB**	118
	TCM for clearing heat and replenishing qi	**PDB**, Raw *Astragalus*	119
T2DM rats	Fanbaicaodanshen mixture	**PDB**, *Salvia miltiorrhiza*, *Astragalus*, *Schisandra chinensis*, Trichosanthin	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 hyperlipidemia	Water decoction of *Potentilla discolor* Bunge	**PDB**	123
Hyperlipidemia rats	Water decoction of *Potentilla discolor* Bunge	**PDB**	124

PDB, *Potentilla discolor* Bunge; T2DM, type 2 diabetes.

lipid synthesis in leptin receptor deficient diabetic (*db/db*) mice, which is correlated with the inhibition of LXR-SREBP-1c signaling pathway. In HepG2 cells and primary hepatocytes[134], luteolin inhibits LXR activation and thus reduces the accumulation of TGs. In addition, luteolin indirectly activates Sirt1/AMPK pathway by up-regulating nicotinamide phosphoribosyl transferase expression levels, subsequently increasing β-oxidation and inhibiting lipogenesis[136].

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[141,160]. 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[142]. 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[143].

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[161−163]. One study in HFD-induced NAFLD model shows[153] 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[164]. OA also ameliorates hepatic oxidative stress and lowers the SREBP and intrahepatic TGs levels[164].

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[154]. *In vitro,* 3Ac-OA decreases intracellular levels of TC and TG and the number of lipid droplets in free fatty acids (FFA)-treated primary rat 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[154].

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[165,166]. 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[130]. Quercetin-3-*O*-β-glucoside can promote AKT phosphorylation in gastrocnemius muscles that are the most important tissue to determine whole-body insulin sensitivity[132]. The activation of insulin signaling pathway induced by AKT may contribute to the reduction of plasma glucose concentration and IR[132].

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[167]. Luteolin-7-*O*-glucoside (LUG) is one of the *O*-glycosides of luteolin. Luteolin and LUG can decrease serum fasting blood glucose

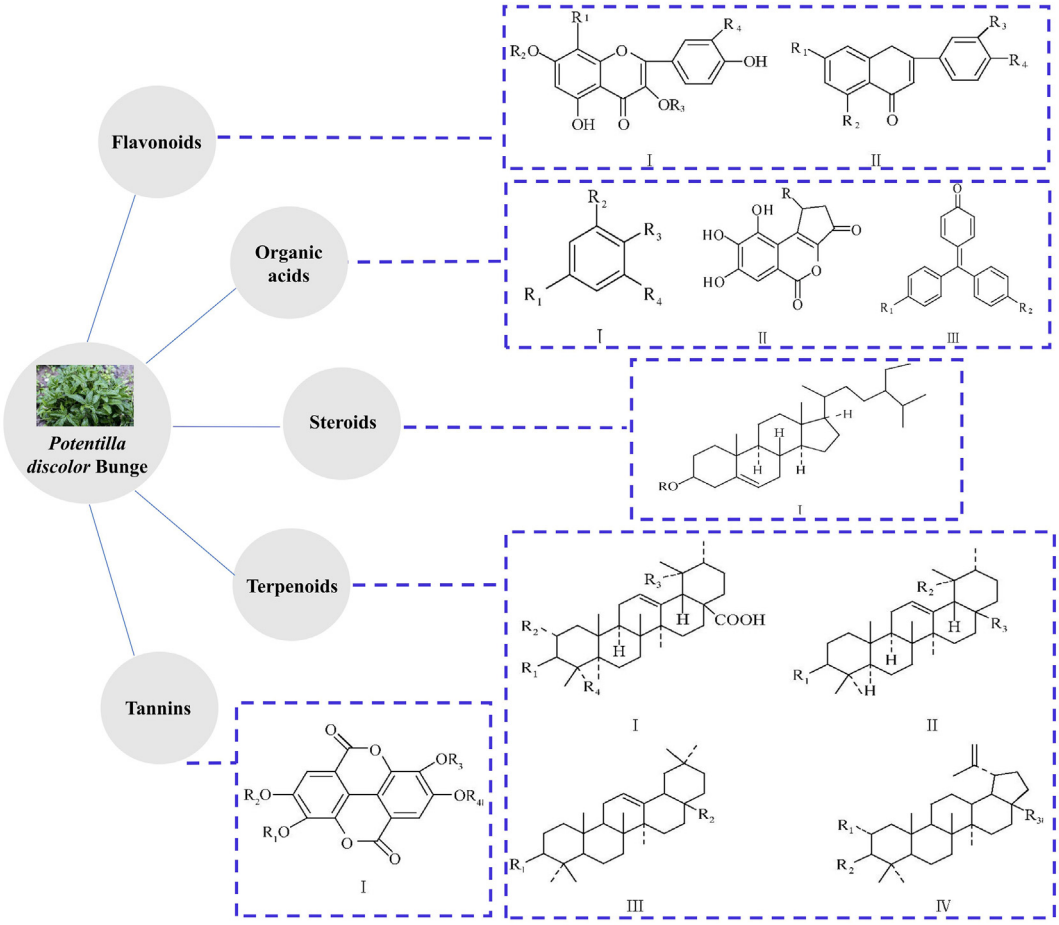


Figure 3 Structure backbones of the main components of PDB.

(FBG), glycosylated hemoglobin (HbA1c), insulin levels and HOMA-IR index in the spontaneous T2DM mouse model[135]. Luteolin and LUG significantly decrease SREBP-1c levels in the liver[135]. The activity of FAS, which is positively correlated with TG levels, is notably lower in the luteolin and LUG groups than in the control group[135]. Besides, luteolin and LUG notably reduce TNF-α levels in serum and liver[135].

5.2.3. *Kaempferol*

Kaempferol, one of the flavonols, which is a subclass of flavonoids, has many medicinal properties such as anti-oxidative, anti-carcinogenic, anti-diabetic, antimicrobial and cardio-protective properties[168]. 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[138]. Kaempferol is an inhibitor of hepatic pyruvate carboxylase activity[133]. It inhibits gluconeogenesis through suppressing pyruvate carboxylase and glucose-6 phosphatase activity[133]. 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[133]. 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[133].

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[151]. 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[151].

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[155]. 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[141].

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

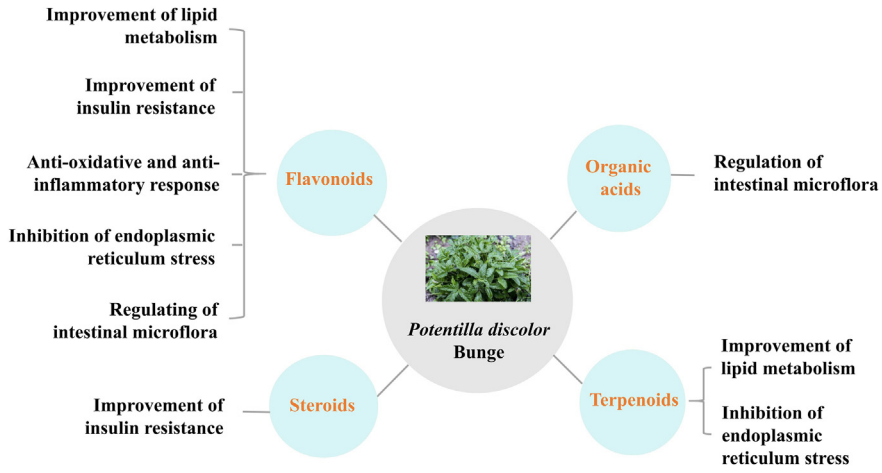


Figure 4 Functions of the main natural active compounds of PDB. Flavonoids improve lipid metabolism and IR, reduce oxidative stress and ER stress, and regulate the intestinal microflora. Organic acids regulate the intestinal microflora. The terpenoids improve lipid metabolism and inhibit endoplasmic reticulum stress. The steroids improve IR.

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[169]. 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[37]. 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[136]. 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[139].

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[170–173]. Rutin has also hypolipidemic and hepatoprotective effects in NAFLD[147,148]. Rutin reduces the cellular malondialdehyde levels and increases the expression levels of anti-oxidant enzymes[147]. It restores the superoxide dismutase activity, which inhibits the accumulation of lipids in liver cells and reduces oxidative damage simultaneously[148].

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[172,174–177]. Apigenin can alleviate HFD-induced liver injury in mice by increasing insulin sensitivity, reducing liver lipid accumulation, improving hepatic steatosis and reducing macrophages recruitment[149]. 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[149]. 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[150]. 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[150].

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 (XBP1s) and protein kinase R-like ER kinase, and activating transcription factor 6α[178]. In addition, C/EBP homologous protein is a critical molecule involved in ER stress and ER stress-induced apoptosis[178]. 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.

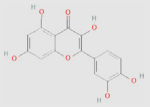
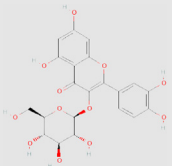
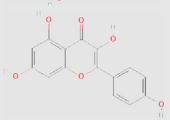
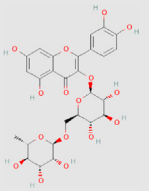
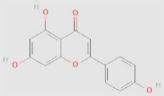
5.4.1. *Quercetin*

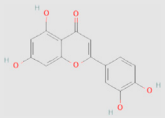
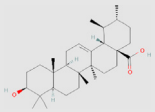
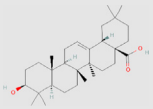
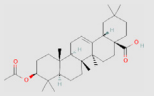
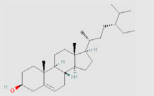
Quercetin can activate IRE1α and ameliorate hepatic steatosis and ER stress induced by high cholesterol[179,180]. A study reports that quercetin reduces the levels of hepatic TG and TC and increases the levels of hepatic VLDL, and up-regulates XBP1s expression in the HFD-fed rats[145]. Additionally, 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[145]. Collectively, these findings demonstrate that quercetin plays anti-NAFLD effects by inducing the hepatic VLDL assembly and lipophagy through the IRE1α/XBP1s pathway[145].

5.4.2. *UA*

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

Table 4 Anti-NAFLD mechanisms of natural active compounds of PDB.

Natural active compound		Chemical structure	Active ingredient content	Model	Mechanism of action	Ref.	PubChem CID
Flavonoids	Quercetin		0.1086 mg/g[144]	HFD-induced NAFLD rats FFA-induced HepG2 *db/db* mice	↓ TC, TG ↑ VLDL ↑ Microsomal TG-transfer protein complex ↑ Co-localization of lysosomes with LDs ↓ Accumulation of p62 ↑ IRE1α endonuclease activity ↑ XBP1s ↓ Lipid accumulation ↓ Serum transaminase levels ↓ Serum total bile acids ↑ Lipid distribution, lipid profiles ↓ Histological alterations of liver ↓ IL-1β, IL-6, and TNF-α in liver ↑ FXR1/TGR5 signaling pathway	131, 145	5280343
	Quercetin-3-*O*-β-glucoside			Sucrose-fed rats	↓ Glucose concentration in plasma ↑ AKT phosphorylation	132	5280804
	Kaempferol		0.0611 mg/g[144]	HFD-fed mice	↓ Body weight ↓ FBG, HbA1c ↓ Adipose tissue accumulation ↓ TGs ↑ Lipid metabolism ↓ PPAR-γ and SREBP-1c	133	5280863
	Rutin		0.555 mg/g[146]	HFD-induced NAFLD mice HepG2 cells	↓ 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
	Apigenin		0.114 mg/g[144]	HFD-induced NAFLD mice Hepa1-6 cells pre-treated with FFA	↑ Insulin sensitivity ↓ Hepatic steatosis ↓ Macrophages recruitment ↓ IL-1β and IL-18 ↓ Xanthine oxidase(XO) activity ↓ ROS production ↑ NLRP3 inflammasome	149, 150, 151	5280443

					↑ *Nrf2* ↓ 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)		
	Luteolin		0.04 mg/g[146]	*db*/*db* mice HepG2 cells Primary hepatocytes from spontaneous type 2 diabetes mellitus model KK-A^y mice	↓ Novel lipid synthesis ↑ Glycogen storage ↓ LXR-SREBP-1c signaling pathway ↓ FBG, HbA1c, HOMA-IR, TGs in serum and liver ↓ SREBP-1c mRNA expression in liver ↓ FAS activity ↓ Serum TNF-α and TNF-α mRNA expression in liver	134, 135	5280445
Terpenoids	Ursolic acid		0.02436 mg/g[152]	T0901317-induced mice HepG2 cells Intestinal cells *db*/*db* mice palmitate solution-treated LO_2 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	142, 143	64945
	Oleanolic acid			High fructose diet-fed rats	↑ Lipid metabolism ↑ AMPK gene expression ↑ GLUT-4	153	10494
	3-Acetyloleanolic acid			HFD-induced NAFLD rats FFA-treated primary rat hepatocytes HepG2 cells	↓ Body weight, liver weight, TC, TGs and LDC-C ↑ GLUT-2 ↑ Low-density lipoprotein receptor ↑ AMPK phosphorylation	154	151202
Steroids	β-Sitosterol			Diabetic rats	↓ Blood glucose, serum insulin, blood lipid, oxidative stress markers, anti-oxidant enzymes ↑ Insulin receptor, GLUT-4	155	222284
Organic acids	Gallic acid		0.1086 mg/g[144]	HFD-induced NAFLD mice	↓ Trimethylamine ↓ Trimethylamine -*N*-oxide ↓ Dimethylamine	140	370

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.

mice (*db*/*db* mice). Moreover, it also decreases lipid accumulation in LO_2 cells exposed to palmitic acid[143]. In addition, UA treatment inhibits the hyperlipidemia-induced IRE1α activation, JNK phosphorylation and C/EBP homologous protein accumulation in the livers of *db*/*db* mice and cultured hepatocytes[143]. Furthermore, UA treatment normalizes the down-regulated protein levels of PPAR-α, which plays a central role in FA β-oxidation. These results suggest that UA improves NAFLD by increasing lipid β-oxidation and inhibiting ER stress[143].

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[181]. 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)[182,183]. Activation of FXR reduces hepatic inflammation and maintains the intestinal barrier by inhibiting LPS-stimulated nuclear factor-κB activation[184]. Moreover, choline acquired through the diet can be further metabolized by the microbiome from trimethylamine into trimethylamine-*N*-oxide[185]. 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[186]. 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 inflammasome response and reticulum stress pathway activation and the deregulation of lipid metabolism gene expression[137]. 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[131]. *In vitro*, quercetin eliminates lipid droplets and restores the up-regulated TC and TG levels. Mechanistic studies have shown that quercetin activates the FXR1/TGR5 signaling pathway that is involved in the regulation of T2DM-induced lipid metabolism during NAFLD[131].

5.5.2. *Gallic acid (GA)*

GA, an endogenous plant phenol, has potent free radical scavenging properties and anti-oxidative activities[187–189]. 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[140]. 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[140].

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 therapeutical 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-OA, quercetin, kaempferol, apigenin, β-sitosterol, rutin and GA were found to ameliorate NAFLD characteristics. Interesting, 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 therapeutical effects of TCM, will hopefully validate the benefits of PDB as a therapeutical 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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