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REVIEW

Herbal medicines and nonalcoholic fatty liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD), which is characterized by excessive fat accumulation in the liver of patients who consume little or no alcohol, becomes increasingly common with rapid economic development. Long-term excess fat accumulation leads to NAFLD and represents a global health problem with no effective therapeutic approach. NAFLD is considered to be a series of complex, multifaceted pathological processes involving oxidative stress, inflammation, apoptosis, and metabolism. Over the past decades, herbal medicines have garnered growing attention as potential therapeutic agents to prevent and treat NAFLD, due to their high efficacy and low risk of side effects. In this review, we evaluate the use of herbal medicines (including traditional Chinese herbal formulas, crude extracts from medicinal plants, and pure natural products) to treat NAFLD. These herbal medicines are natural resources that can inform innovative drug research and the development of treatments for NAFLD in the future.

Key words: Herbal medicines; Nonalcoholic fatty liver disease; Natural product; Traditional Chinese medicines; Review

Core tip: Herbal medicines have gained popularity as potential therapeutic agents for the prevention and treatment of nonalcoholic fatty liver disease (NAFLD), due to their high efficacy and low side effects. This review introduces traditional Chinese herbal formulas, crude extracts from medicinal plants, and pure natural products as new treatments for NAFLD.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is rapidly becoming a serious global health problem as the prevalence of obesity and type 2 diabetes mellitus (T2DM) rises[1,2]. The term NAFLD refers to a spectrum of liver diseases, ranging from hepatic steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis, specifically in patients who do not consume excessive amounts of alcohol[3-5]. NAFLD is present in up to one-third of the population, affects all ages and ethnicities, and is the second leading cause of death in the general population[6,7]. At present, the high prevalence and negative pathological consequences of NAFLD represent a significant economic burden for many countries. However, up to now, there is no effective procedure to treat the disease[8-10]. The primary therapeutic approach is to recommend healthy lifestyle strategies that are focused on reducing body weight and increasing insulin sensitivity, including dietary and exercise regimens. Although these strategies are effective in randomized controlled trials, they have limited impact on the incidence and severity of NAFLD at the population level, due to poor patient compliance[11-13].

NAFLD is believed to be an essential component of the liver metabolic syndrome, including insulin resistance, obesity, hyperlipidemia, dyslipidemia, and hypertension[14-16] (Figure 1). Although the activity of plasma transaminase enzymes can serve as an early indicator of liver damage, NAFLD cannot be accurately diagnosed with routine blood tests[17,18]. Liver biopsy, accompanied by histological staining and NAFLD activity score, is the standard for NAFLD diagnosis, however, in clinical practice, its use is limited due to invasiveness[19]. In the past 10 years, the association between NAFLD and other chronic diseases, such as chronic liver disease, cardiovascular disease, and T2DM, has been a major focus of NAFLD research[20,21]. Additionally, increasing attention has also focused on NAFLD-related chronic kidney disease[22]. There is also emerging evidence that NAFLD is linked to other chronic diseases, including sleep apnea, colorectal cancer, osteoporosis, psoriasis, and various endocrinopathies[23]. Hence, there is a huge demand to explore effective approaches to NAFLD treatment.

Due to the key role of lipid accumulation in NAFLD progression, inhibition of lipid accumulation is a major focus of anti-NAFLD drug development. A variety of anti-NAFLD agents are currently in preclinical development. Additionally, metformin, statins, and fibrates, are currently being tested as NAFLD treatments in clinical trials. However, these drugs have significant adverse side effects, including enhanced risk of infection and osteoporosis[24-26]. Hence, novel treatment candidates with high efficacy and minimal side effects are urgently demanded for the treatment of NAFLD[27-30].

Traditional Chinese medicines (TCM) are abundant sources of biologically active substances that can be applied to prevent human diseases[31-34]. Currently, an increasing number of studies have focused on herbal extracts or natural products, and many of these studies have discovered herbal products with potent effects against NAFLD[35,36]. Thus, herbal medicines are promising candidate drugs for the treatment of NAFLD. The primary aim of this paper is to systematically review the available herbal medicines (including traditional Chinese herbal formulas, crude extracts from medicinal plants, and pure natural products) for the treatment of NAFLD.

UNDERLYING MECHANISMS OF HERBAL MEDICINES AGAINST NAFLD

Due to the current lack of effective therapies, there is a great need to identify dietary approaches to NAFLD prevention and treatment. Evidence from cells and animal studies suggests that many drugs can protect NAFLD and its progression in steatosis. Traditional medicines can prevent NAFLD through a variety of mechanisms, including: (1) depressing lipogenesis through down-regulating sterol regulatory element-binding protein 1c (SREBP-1c); (2) increasing β-fatty acid (FA) oxidation by up-regulating peroxisome proliferator activated receptor α (PPARα); (3) increasing insulin sensitivity and depressing oxidative stress through increased antioxidant levels *via* nuclear factor-erythroid 2-related factor 2 (Nrf2); and (4) inhibiting activation of inflammatory pathways (Figure 2). Activation of the AMPK/SIRT-1 signaling pathway is the common trigger that regulates all of these molecular processes in recent insights. Nevertheless, more experiments are needed to verify this hypothesis. Moreover, indirect anti-inflammatory and anti-oxidative effects of TCM may also help to improve the symptoms of NAFLD.

TRADITIONAL CHINESE HERBAL FORMULAS

Currently, the use of a traditional Chinese herbal formula is in a dialectical trial to assess its efficacy as an NAFLD treatment method. A traditional Chinese herbal formula consists of two or more appropriate medicinal plants for discretionary use that are selected in accordance with the composition principles of proper compatibility[37]. The formula contains complex chemical constituents with multi-level and multi-target pharmacological activity[38,39]. The traditional Chinese herbal formula prescription consists of four parts: Monarch, Minister, Assistant, and Guide. The Monarch drug, also known as the main drug, is intended to provide the major therapeutic effect to treat the main disease or principal syndrome[40]. The Minister drug, also known as the official medicine adjuvant, strengthens the effect of the auxiliary gentleman medicine drug to treat the main disease or primary

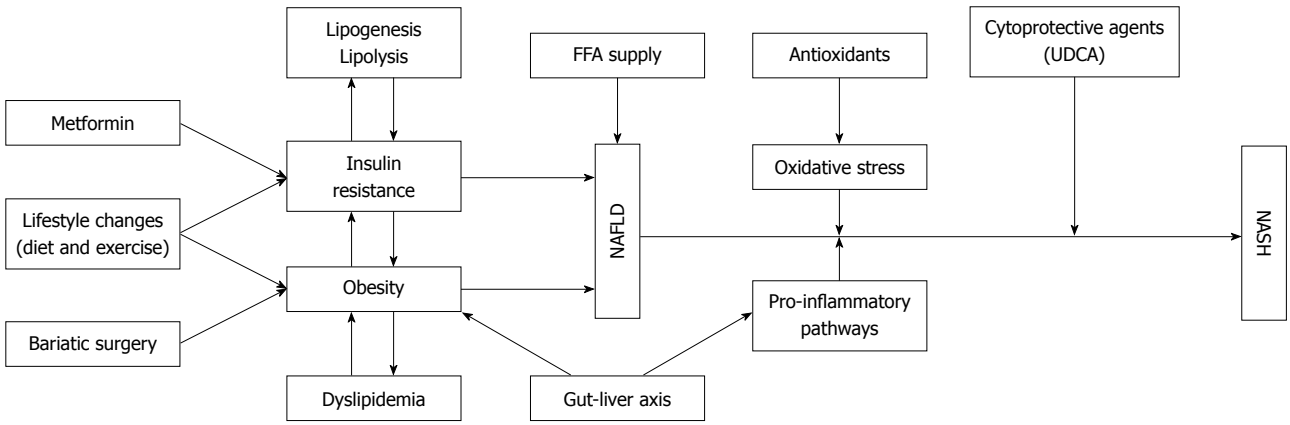


Figure 1 Schematic representation of the pathogenetic mechanism-based nonalcoholic fatty liver disease. NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; FFA: Free fatty acid.

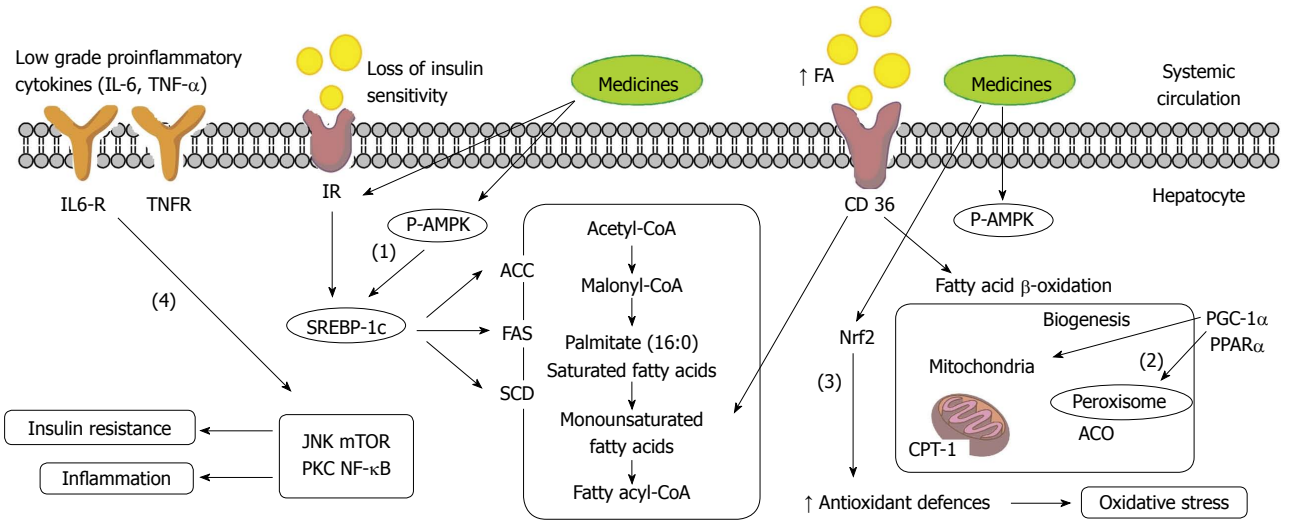


Figure 2 Underlying mechanisms of herbal medicines for the treatment of nonalcoholic fatty liver disease. Medicines may prevent cellular damage in hepatocytes associated with NAFLD through different mechanism of action including: (1) depressing lipogenesis through down-regulating sterol regulatory element-binding protein 1c (SREBP-1c); (2) increasing β-fatty acid (FA) oxidation by up-regulating peroxisome proliferator activated receptor α (PPARα); (3) increasing insulin sensitivity and depressing oxidative stress through increased antioxidant levels *via* nuclear factor-erythroid 2-related factor 2 (Nrf2); and (4) inhibiting activation of inflammatory pathways. TNFR: TNFα receptor; IL6-R: IL-6 receptor; IR: Insulin receptor; CD36: Cluster of differentiation 36/FA translocase; p-AMPK: Phosphorylated AMP-activated protein kinase α; ACC: Acetyl-CoA carboxylase; FAS: Fatty acid synthase; SCD: Stearoyl-CoA desaturase; GPAT: Glycerol-3-phosphate acyltransferase; CPT-1: Carnitine palmitoyl transferase 1; ACO: Acyl-CoA oxidase; PGC-1: PGC1α: PPARγ coactivator-1α; JNK: c-Jun N-terminal kinase; PKC: Protein kinase C; mTOR: Mammalian target of rapamycin.

syndrome. The Assistant drug either indirectly treats the primary disease by assisting the Monarch and Minister drugs, or directly treats secondary syndromes. The Guide drug acts as a messenger drug that leads other drugs to the site of disease[41,42]. Traditional Chinese herbal formulas are developed according to traditional theory, which guides the selection of appropriate medicines according to prescription principles, and determines the dosage and usage of each medicine[43].

Many traditional Chinese herbal formulas are reported to have significant anti-NAFLD effects. One famous traditional Chinese herbal formula, Yinchenhao Decoction (YCHD), first recorded in the "Shen Nong's Herbal Classic", has been used in treatment of gallbladder and liver diseases for centuries. YCHD consists of three medicinal plants: *Artemisia capillaris* (Thunb), *Gardenia jasminoides* (Ellis), and *Rheum palmatum* (L)[44]. Recent studies have reported that YCHD can reduce the accumulation of hepatic fat, enhance adiponectin secretion, increase endothelial progenitor cell proliferation, and increase PPAR-γ expression, which is probably responsible for the therapeutic effect of YCHD on NAFLD[45,46]. Another well-known traditional Chinese herbal formula, Qushi Huayu Decoction (QSHYD), consists of five kinds of medicinal plants: *Artemisia capillaris* (Thunb), *Polygonum cuspidatum Sieb. et Zucc.*, *Hypericum japonicum* (Thunb), *Curcuma Longa L,* and *Gardenia jasminoides* (Ellis)[47]. QSHYD can effectively reverse elevated levels of free fatty acid and total triglycerides (TG), and also can improve hepatic steatosis and inflammation[48]. Furthermore,

QSHYD may inhibit fat deposition and inflammation through multiple signaling pathways[49,50]. Apart from these, other traditional Chinese herbal formulas (Table 1), including Danning Tablet[51], Sini San[52], Ganzhixiao Decoction[53], Tangzhiqing Decoction[54], Hugan Qingzhi tablet[55], Cigu Xiaozhi Pill[56], BaiHuJia RenShen Decoction[57], LiGan ShiLiuBaWei San[58], Gegenqinlian Decoction[59], Lingguizhugan Decoction[60] and Huanglian Jiedu Decoction[61] are also effective treatments for NAFLD.

Although academic journals have reported the benefits of many traditional Chinese herbal formulas in NAFLD therapy, there are several issues to note in these recent studies. The efficacy of these drugs is not clear, due to the limitations of the existing non-invasive techniques that are clinically used to assess the extent of inflammation and liver steatosis[62]. Furthermore, the impact of pharmacodynamic interactions between these formulas and other medications should be evaluated further. The molecular targets of these drugs and the signaling transduction pathways involved remain unknown, which further complicates clinicians' ability to predict how these formulas may interact with other medicines[63,64]. Molecular targets for drug interactions are generally more difficult to predict the pharmacokinetic interactions. All of the issues mentioned above retard the scientific progress of TCM formulas in treating NAFLD.

CRUDE EXTRACTS FROM MEDICINAL PLANTS

Compared with traditional Chinese herbal formulas, the use of crude extracts from medicinal plants represents a fusion of modern pharmaceutical technology with traditional medicine. In this treatment approach, traditional medicinal materials are processed into purified bioactive compounds by leaching, clarification, filtration, evaporation, or other methods of extraction[65]. Extraction of compounds from Chinese herbal medicines is one approach to discover novel drugs. The extraction of active compounds is also important for enhancing our understanding of traditional Chinese medicine[66,67]. After extraction and separation, crude extracts have higher purity, are easy to administer, and can be subjected to quality control[68,69]. Thus, use of crude extracts from medicinal plants to treat NAFLD is a feasible approach.

Many crude extracts from medicinal plants have significant anti-NAFLD effects. *Polygonum hypoleucum* (Ohwi) is the dry root of leguminous plants belonging to the genus *Pueraria*, which is recorded in the "Treatise on Febrile Diseases". It has been used to treat cancer, arthritis, and nephritis[70]. Extract of *P. hypoleucum* contains the chemicals epicatechin, emodin, epicatechin-3-O-gallate, catechin and procyanidin B2P[71]. *P. hypoleucum* can also inhibit acetyl-CoA carboxylase (ACC) activity, which plays a key role in FA metabolism. Inhibiting ACC expression has been demonstrated to prevent high-fat diet (HFD)-induced NAFLD and hepatic ischemia-reperfusion (IR)[72-74]. *Artemisia Sacrorum* Ledeb (ASL) is a TCM used to treat multiple liver diseases. Ethanol extract from ASL can attenuate hepatic lipid accumulation *via* activating adenosine 5'-monophosphate-activated protein kinase (AMPK) in human HepG2 cells[75]. Besides promoting AMPK and ACC phosphorylation, ethanol extract from ASL down-regulates expression of the lipogenesis gene SREBP-1c, and also decreases the expression of target genes of SREBP-1c, including FA synthase (FAS) and stearoyl-coenzyme A desaturase 1. Conversely, EE also increases the expression of lipolytic genes, including PPAR-α and cluster of differentiation 36 (CD36)[76]. Other herbal extracts (shown in Table 2) from Chinese blueberry[77], *Hibiscus sabdariffa* L.[78], red grapes[79], grape skin[80], coffee[81], Roiboos (*Aspalathus linearis*)[82], Lotus root[83], hawthorn leaf[84], araliaelata[85], rubus aleaefolius[15], neomangiferin[86] and tea[87] are also effective in treating NAFLD.

On the other hand, extracting bioactive compounds from medicinal plants can be problematic. For example, many active compounds, especially water - insoluble compounds, may be lost during extraction in organic solvents. Furthermore, extraction solvents may react with active ingredients, or high temperatures during extraction may degrade labile compounds[88,89]. However, breakthroughs in science and technology could overcome these shortcomings in the future.

PURE NATURAL PRODUCTS

The term "pure natural products" refers to clear chemical structures that are different from traditional Chinese medicine formulas and crude extracts[90,91]. Pure natural products are derived from medicinal plants through extraction, separation, and purification[92]. Many pure natural products, including flavonoids, alkaloids, polysaccharides, volatile oils, quinones, terpenes, coumarins, lignans, saponins, cardiac glycosides, phenolic acids, and amino acids, have been found to have significant therapeutic benefits against NAFLD[93].

Flavonoids

Flavonoids are compounds with a common basic structure of 15 carbons (C6-C3-C6)[94]. Flavonoids found in plants usually combine with sugar to form glycosides, however some remain in free-state (aglycone) form. There is growing evidence that flavonoids (or related compounds) have therapeutic effects on cancer and other chronic diseases, including cardiovascular disease, T2DM, and NAFLD, at least in part through immunomodulatory, anti- inflammatory, and antioxidant properties[95].

Quercetin (Figure 3A) is a well-known flavonoid that has a wide variety of biological functions. This flavonol is reported to have beneficial effects on lipid

Table 1 List of Chinese herbal formulas for the treatment of nonalcoholic fatty liver disease

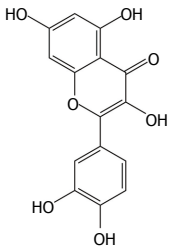
Formula	Composition	Mechanisms	Ref.
Yinchenhao Decoction	*Artemisia capillaries* Thunb. *Gardenia jasminoides* Ellis *Rheum palmatum* L.	↓PPARγ expression	[46]
Qushi Huayu Decoction	*Artemisia capillaries* Thunb. *Rhizoma polygoni* Cuspidati *Hypericum japonicum* Thunb *Rhizoma curcumae* Longae *Gardenia jasminoides* Ellis	↓SCD1, ↓FAS, ↓ACAT, ↑CPT expression ↓Lipid droplets and inflammatory infiltration ↓TNFα	[50]
Danning Tablet	*Rheum palmatum* L. *Polygonum cuspidatum* Sieb.et Zucc. *Citrus reticulata* Blanco *Curcuma rcenyujin* Y. *Crataegus pinnatifida* Bunge	↓Fat mass ↓ALT level	[51]
Sini San	*Bupleurum scorzonerifolium* Willd *Paeonia lactiflora* Pall *Fructus aurantii* Immaturus *Glycyrrhiza uralensis* Fisch	↓ALT, ↓AST level ↓Steatosis	[52]
Ganzhixiao Decoction	*Artemisia capillaries* Thunb. *Rhizoma polygoni* Cuspidati *Radix bupleuri* Chinensis	↓ALT, ↓TG, ↓IHCL level ↑CT value ratio	[53]
Cigu Xiaozhi Pill	Sagittaria sagittifolia *Alisma plantago-aquatica* Linn *Crataegus pinnatifida* Bunge *Salvia miltiorrhiza* Bge *Steleophaga plancyi* Boleny *Pinellia ternata* Breit	↓ALT, ↓AST level ↓TC, ↓TG level	[56]
Tangzhiqing Decoction	*Paeonia veitchii* Lynch *Morus alba* L. *Lotus leaf* Tea *Salvia miltiorrhiza* Bge. *Grataegus pinnati fida* Bge.	↓TC, ↓TG level ↓LDL-C, ↓HDL-C level ↓Fat mass ↓MDA level	[54]
Hugan Qingzhi Tablet	*Alisma orientalis* Juzep *Crataegus pinnatifida* Bunge *Typha orientalis* C. Presl *Nelumbo nucifera* Gaertn *Panax pseudoginseng* var. notoginseng	↓ALT, ↓AST level ↓TC, ↓TG level ↓IL-6, ↓P65	[55]
BaiHuJia RenShen Decoction	*Anemarrhena asphodeloides* Bunge *Radix Glycyrrhizae* Preparata *Oryza sativa* L. Gypsum Fibrosum *Panax ginseng* C. A. Mey.	↑p-AMPK level ↓SCD1, ↓FAS, ↓ACAT, ↑CPT expression	[57]
LiGan ShiLiuBaWei San	*Punica granatum* L. *Cinnamomum tamala* Nees *Alpinia katsumadai* Hayata *Piper longum* Linn *Carthamus tinctorius* L. *Amomum tsao-ko* Crevost et Lemaire *Zingiber oj-jicinale* Rosc *Myristica fragrans* Houtt.	↓ALT, ↓AST level ↓TC, ↓TG, ↓FFA, ↓MDA level ↑PPARα expression	[58]
Gegenqinlian Decoction	*Pueraria omeiensis* Wang *Scutellaria baicalensis* Georgi *Coptis chinensis* Franch *Glycyrrhiza uralensis* Fisch	↓LDL-C, ↓HDL-C level ↓PPARγ	[59]
Lingguizhugan Decoction	*Smilax ocreafa* A. *Cinnamomum tamala* Nees *Rhizoma atractylodis* macrocephalae *Glycyrrhiza uralensis* Fisch	↓TC, ↓TG, ↓LDL-C	[60]
Huanglianjiedu Decoction	*Coptis chinensis* Franch *Scutellaria baicalensis* Georgi *Heteropogon contortus* P. *Gardenia jasminoides* Ellis	↓TC, ↓TG, ↓LDL-C, ↓HDL-C leve	[61]

Table 2 List of crude extracts from medicinal plants for the treatment of nonalcoholic fatty liver disease

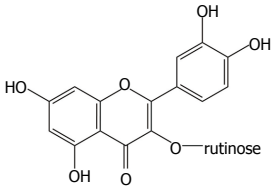
Crude extract	Model	Mechanisms	Ref.
Polyphenols extract from Chinese blueberry	HepG2 cells	↓TG ↓Inflammatory	[73]
Polyphenols extract from *Hibiscus sabdariffa* L.	BALB/c normal liver cells	↓Death cell ↓p-JNK, ↓Bax, ↓tBid expression ↓MDA, ↑GSH levels ↑CAT activity	[74]
Polyphenols extract from red grapes	Male Wistar rats (HFD)	↓Steatosis, ↓TG ↑SIRT-1, ↑p-ACC level	[75]
Polyphenols extract from grape skin	C57BL/6J mice (HFD)	↓Hepatic cholesterol ↓ChREBP, ↓PPARγ, ↓SCD1 ↓FAS, ↓ACAT, ↑PPARα, ↑CPT expression ↑β-oxidation, FAS, ME activity ↓Leptin, ↑adiponectin, ↓NEFA	[76]
Polyphenols extract from Coffee	Male Wistar rats (HFD)	↓ALT plasma, ↑GSH/GSSG ratio, ↓MDA ↓Lipid droplets and inflammatory Infiltration ↓TNFα ↑PPARα and Adipo R2 expression ↑FRAP in serum ↑IL-4 and IL-10 ↓IL-1a and IL-1b	[77]
Polyphenol extract from *Aspalathus linearis* Roiboos	Male C57BL/6J (HFD)	↓Steatosis, ↓TG ↓Macrophage infiltration ↓Cholesterol and NEFA in serum ↑p-AMPK level ↑FAS level	[78]
Polyphenolic extract from Lotus root	Male db/db mice	↓Liver weight ↓TG level ↓FAS and ME activity	[79]
Polyphenol extract from *Hibiscus sabdariffa* L.	Male C57BL/6J mice (HFD)	↓Body weight ↓TG, ↓Steatosis ↓Adipocyte size in adipose tissue ↓Insulin resistance ↓miR-103, ↓miR-107 and ↑miR-122 expression in liver ↓FAS, ↑p-AMPK levels ↓SREBP-1c expression	[72]
Flavonoids extract from Hawthorn leaf	Male Sprague Dawley rats (HFD)	↓ALT, ↓AST, ↓TC, ↓TG, ↓FFA, ↓FAS, ↑p-AMPK levels ↑PPARα, ↓SREBP-1c expression	[80]
Total aralosides extract from araliaelata	ApoE$^{-/-}$ mice (HFD)	↓IL-6, ↓TNFα, ↓P65, ↓p-JNK expression	[81]
Rubus aleaefolius	Male Sprague Dawley rats (HFD)	↓TC, ↓TG, ↓FFA, ↓SCD1, ↓FAS, ↓ACAT, ↑CPT expression	[82]
Neomangiferin	Male Sprague Dawley rats (HFD)	↓TC, ↓TG, ↓MDA, ↑SOD, ↑PPARα, ↑CPT, ↓FATP2, ↓ACSL1 expression	[83]
Deepure Tea	C57BL/6J mice (HFD)	↓SCD1, ↓FAS, ↑p-AMPK levels ↑p-ACC level ↓SREBP-1c expression	[84]

accumulation, inflammation, fibrosis, nitrosative/oxidative stress, and insulin resistance associated with NAFLD[96]. Previously, studies showed that quercetin reduces lipid accumulation in primary hepatocytes in obese mice fed a high-fat diet, through regulation of mitochondrial oxidative metabolism. Therefore, quercetin is a useful dietary additive for reducing obesity-induced hepatosteatosis[97,98].

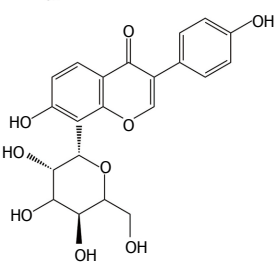
Rutin (Figure 3B), a glycoside of quercetin, is found in many foods such as red wine, apples and onions. Panchal *et al*[99] first proved that rutin can decrease adiposity, improve insulin sensitivity, and reduce cardiac remodeling and liver injury in HFD rats[100]. Consistently, in a successive study, rutin effectively inhibited palmitate-induced macrophage activation and reduced liver fat by suppressing transcription of



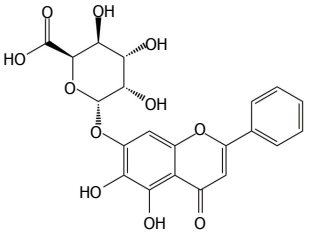
(A) Quercetin



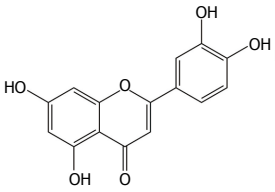
(B) Rutin



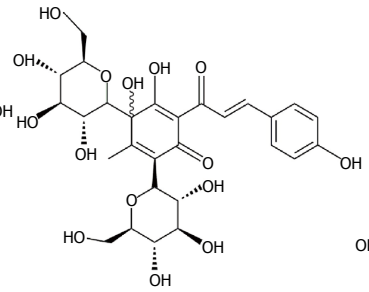
(C) Puerarin



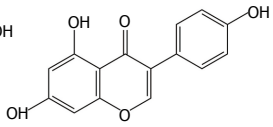
(D) Baicalin



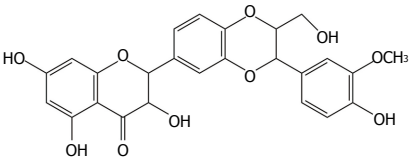
(E) Luteolin



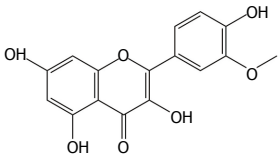
(F) Hydroxysafflor yellow A



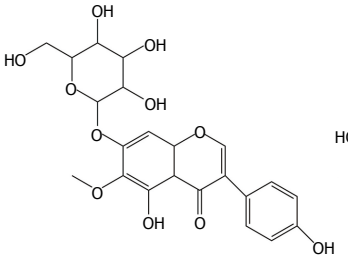
(G) Genistein



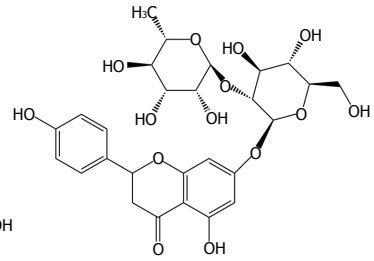
(H) Silybin



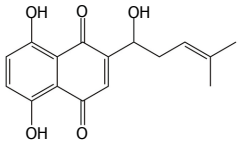
(I) Isorhamnetin



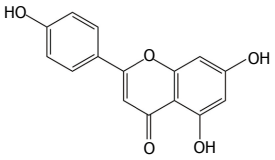
(J) Iridin



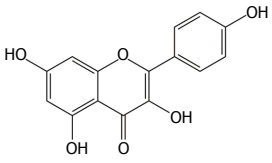
(K) Naringin



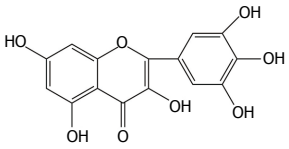
(L) Shikonin



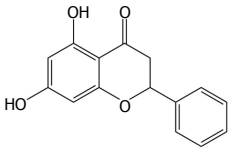
(M) Apigenin



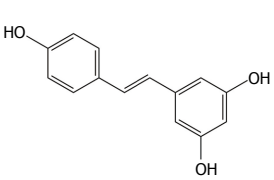
(N) Kaempferol



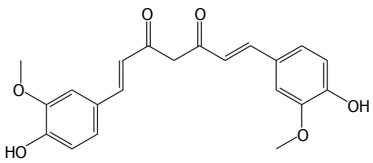
(O) Myricetin



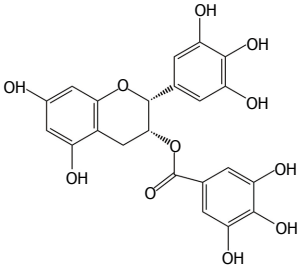
(P) Pinocembrin



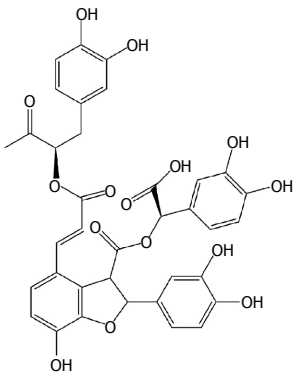
(Q) Resveratrol



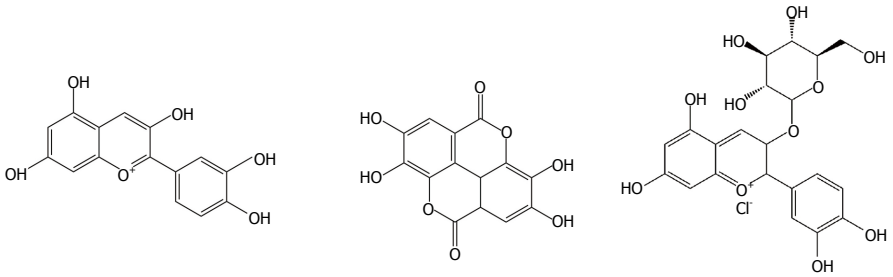
(R) Curcumin



(S) EGCG



(T) Salvianolic acid B



(U) Anthocyanidin (V) Ellagic acid (W) Cyanidin-3-glucoside

Figure 3 Chemical structures of flavonoids and polyphenols for the treatment of nonalcoholic fatty liver disease.

SREBP-1c and CD36 in the liver[101]. Recently, troxerutin was also shown to reduce liver steatosis and improve metabolic syndrome-related pathology in mice fed a high-fat diet, by suppressing oxidative stress-mediated NAD depletion and stimulating fat oxidation[99]. Other flavonoids, including pueraria[102], baicalein[103], luteolin[104], hydroxysafflor yellow A[105], genistein[106,107], silybin[108], isorhamnetin[109], iridin[110], naringin[111], shikonin[112], apigenin[113], kaempferol[114], myricetin[115], and pinocembrin[116] (Figure 3C-P), also play significant roles in the treatment of NAFLD.

Polyphenols

Polyphenols are a group of phenolic compounds from plants. Phenolic compounds are present in a large amount in cereals, vegetables, fruits, and beverages including red wine, coffee and tea[117]. Polyphenols have strong antioxidant effects, and are commonly known as "the seventh kind of nutrient." How well polyphenols exert antioxidant properties hinges on (1) the extent of their phase 1 and 2 bio-transformation; (2) the amount of conjugated products formed during the absorption of the gastrointestinal tract; and (3) the formation of conjugated products mainly absorbed in the liver[118].

Resveratrol (Figure 3Q) is contained in red grapes, *Fructus Mori*, *Arachis hypogaea* Linn. and *cacao*[119,120]. Two seminal studies show the positive effects of resveratrol on metabolic health and aging by activating AMPK and silent mating type information regulation 2 homolog 1 (SIRT1)[121,122]. Further studies suggest that resveratrol can reduce fat accumulation, even in the absence of weight loss. Resveratrol decreases liver fat accumulation through different mechanisms, including decreased lipogenesis and increased FA oxidation[123-126]. In addition, resveratrol has been shown to reduce lipid peroxidation by promoting the Nrf2-dependent antioxidative response in high fructose fed rats[127] and improving dysbiosis in the gut microbiome, which is induced by HFD. The proportion of resveratrol to the growth of the thick walled bacterial strain of the fungus, which was reduced by the growth of *Lactobacillus* and bacteria, was decreased[128]. Nevertheless, two clinical trials show that the results are contradictory. After 8 wk, the liver fat accumulation and insulin sensitivity showed no improvement compared to the men on 3000 mg of resveratrol. What's more, no change was observed in the plasma antioxidant activities. Importantly, this study reported that resveratrol supplements increased plasma liver enzyme levels, which showed hepatic stress[129,130]. However, in a trial, the signature of the liver enzyme with inflammatory cytokines was shown to improve in 50 patients with NAFLD treated with resveratrol 500 mg for 12 wk, although the antioxidant effect was not reported[131].

Curcumin (Figure 3R), responsible for the yellow colour of the plant *Curcuma Longa* L, is extracted from curry and spice. Its antioxidant properties are widely studied in liver metabolism[132]. Curcumin has also been studied for NASH and metabolic pathologies. Leclercq *et al*[133] showed that curcumin improves liver injury by inhibiting nuclear factor-kappa B (NF-κB) activation, which in turn inhibits the expression of NF-κB target genes, including intercellular cell adhesion molecule-1, cyclooxygenase-2, and monocyte chemotactic protein 1. Vizzutti *et al*[134] later extended that curcumin can reduce alpha-smooth muscle actin a level in the NASH mice and can reduce the production of reactive oxygen species and tissue inhibitor of metalloproteinases-1 secreting activated hepatic stellate cells. While some dietary supplements containing curcumin are commercially available, it should be emphasized that case-reports and case series provide insufficient clinical evidence to draw firm conclusions. Polyphenols including techin-3-gallate[135], salvianolic acid B[136], anthocyanidin[137], ellagic acid[138] and cyanidin-3-glucoside[139] (Figure 3S-W) also play significant roles in the treatment of NAFLD.

Terpenoids

Terpenoids are compounds with molecular formulas containing multiple hydrocarbon isoprene units and their oxygenated derivatives. These oxygenated derivatives can be alcohols, aldehydes, ketones, carboxylic acids or esters. Terpenoids exist widely in the nature, and are the main components of some plant essence, and pigment resins[140]. Terpenoids have many physiological activities including acting as an expectorant, relieving cough, expelling wind, inducing sweating, acting as an insecticide, and reducing pain

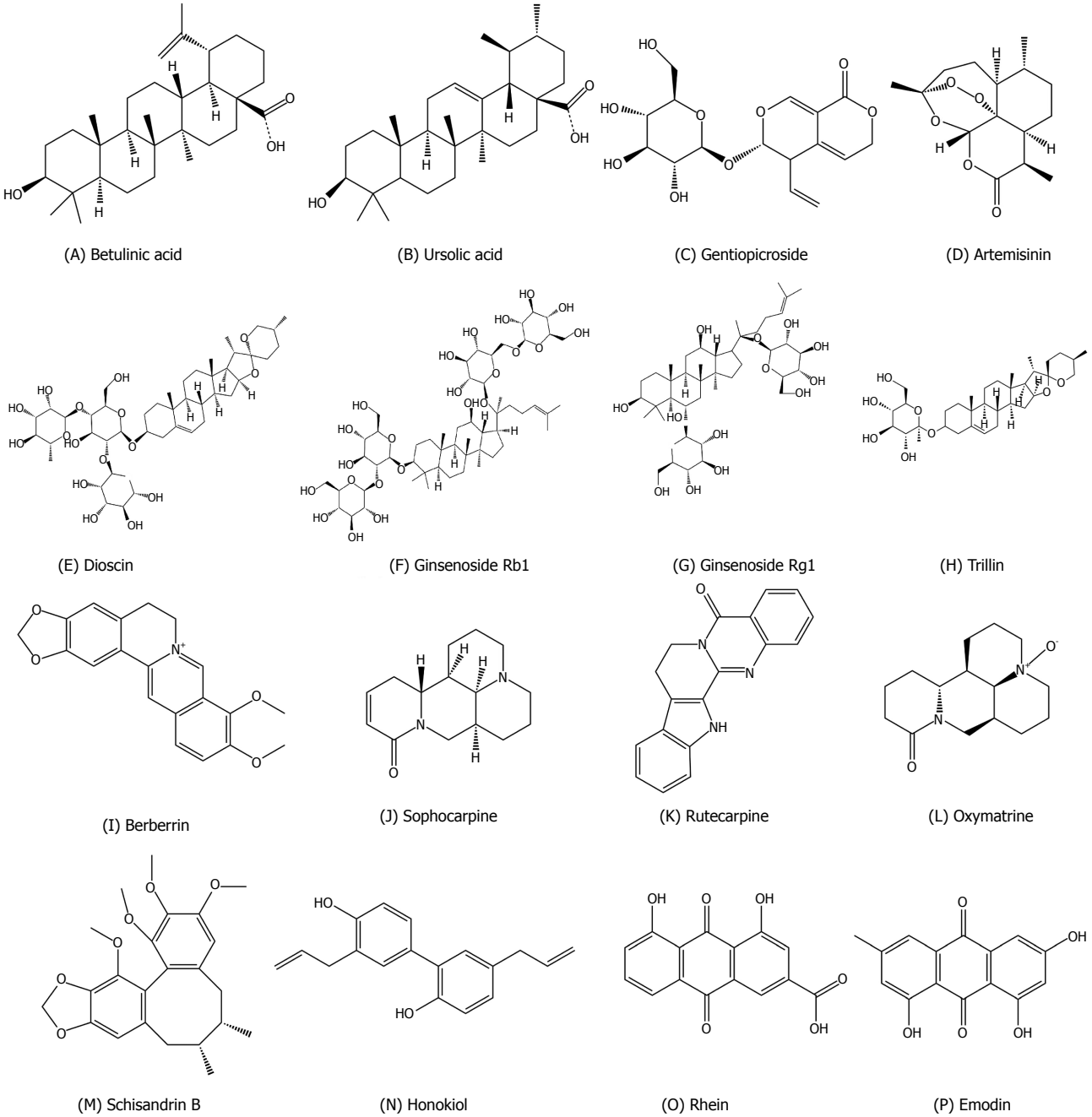


Figure 4 Chemical structures of other kinds of pure natural products for the treatment of nonalcoholic fatty liver disease.

(analgesia)[141].

Betulinic acid (Figure 4A) is a pentacyclic triterpene found in many plants, especially *Betula*. Betulinic acid can be converted from its precursor, betulin. Betulinic acid plays a significant role in reducing hepatic lipid accumulation through modulation of the AMPK-SREBP signaling pathway[142]. Mice fed an HFD for a three-week period exhibit severe fat accumulation in the liver, significant reductions in hepatic AMPK phosphorylation, and increased activation of SREBP1. Betulinic acid activates AMPK by activating an upstream kinase, calmodulin-dependent protein kinase kinase. Betulinic acid also suppresses mammalian target of rapamycin and S6 kinase-mediated activation of SREBP1 in a human hepatoma cell line, primary rat hepatocytes, and liver tissue of Institute of Cancer Research mice fed an HFD. Treatment with betulinic acid inhibits HFD-induced changes in nuclear SREBP1 activation and consequent hepatic TG accumulation[143]. Other terpenoids, such as ursolic acid[144], gentiopicroside[145] and artemisinin[146] (Figure 4B-D), also play significant roles in the treatment of NAFLD.

Saponins

Saponins are glycoside aglycones of three terpenoids or spirostane compounds, mainly found in terrestrial plants[147]. The primary active ingredients in many Chinese traditional herbs, such as *Panax ginseng* (C. A.

Mey.), *Polygala tenuifolia* (Willd.), *Glycyrrhiza uralensis* (Fisch), and *Platycodon grandiflorus* (Jacq.) A. DC., are saponins. Some saponins also have anti-bacterial, anti-pyretic, and anti-cancer activities[148,149].

Dioscin (Figure 4E) is a natural steroid saponin widely found in various herbs[150]. Previous studies have demonstrated that dioscin has anti-tumor[151], anti-hyperlipidemic[152], and anti-fungal activities[153]. Studies have shown that dioscin can gradually reduce the weight, but not suppress appetite or increase physical activity in obese mice. Oral administration of dioscin reduces blood lipid levels, improves fat accumulation in the liver, decreases liver cholesterol and FA and triglyceride deposition through inhibition of FAS, promotes FA beta oxidation, reduces oxidative stress and inflammation, and regulates the MAPK signaling pathway and autophagy[154]. Other saponins such as ginsenoside Rb1[155], ginsenoside Rg1[156] and trillin[157] (Figure 4F-H) also play significant roles in the treatment of NAFLD.

Alkaloids

Alkaloids are a group of nitrogenous organic compounds present in nature. They are widely found in dicotyledons. They have many pharmacological activities, such as anti-bacterial, anti-inflammatory, analgesic, anti-tumor, and anti-fungal actions[158,159]. A large number of studies have indicated that alkaloids have significant effects on NAFLD.

Berberine (Figure 4I) is isolated from the herb *Coptis chinensis* Franch. and widely used to treat diarrhea and other inflammatory diseases in China[160]. Recent studies have proved a new therapeutic function of berberine in metabolic disorders, including obesity and diabetes[161,162]. Berberine can be used as a cholesterol lowering drug, through a unique mechanism distinct from statins[163]. These studies suggested a potential therapeutic activity of berberine for NAFLD. Liver gene expression profile analysis showed that high fat diet induced hepatic steatosis in rats led to global changes in gene expression, and treatment with berberine reversed this process. Several modules of berberine-regulated genes, including abundant long non-coding RNAs (lncRNAs), were identified by bioinformatics analysis. Among these berberine-regulated genes, we found that the lncRNA MRAK052686 and its associated gene Nrf2 are implicated in the pathogenesis of NAFLD[164]. Hence, the study provides a new insight into the mechanism of the pharmacological action of berberine in the prevention and treatment of NAFLD. Other alkaloids such as sophocarpine[165], rutecarpine[166] and oxymatrine[167] (Figure 4J-L) also play significant roles in protecting against NAFLD.

Other pure products have been showed to be effective in the treatment of NAFLD, including schisandrin B[168], honokiol[169], rhein[170] and emodin[171] (Figure 4M-P). TCM are worthy of further study. This review only summarizes a drop in the bucket, and more Chinese medicines that are useful for the treatment of NAFLD will come to light in the future.

CONCLUSION

NAFLD, the main cause of chronic hepatic disease, is essentially a condition of over-nutrition, and the effective treatments are limited. Thus, it is very important to search ways to prevent and treat NAFLD. In this review, the experimental evidence has suggested that a number of herbal medicines can prevent steatosis and NAFLD through various underlying mechanisms. However, more convincing experiments are needed to confirm this hypothesis. What's more, the indirect anti-inflammatory and antioxidant effects of TCM also play an important role in the treatment of NAFLD. But so far, the results of clinical studies are limited and tend to show a subtle influence in comparison with animal models. Further studies on the use of dietary doses of Chinese herbal medicines in rodents and human subjects are necessary.

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