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Progress in the study of ameliorative effects of medicinal and edible plants based on various active ingredients on non-alcoholic fatty liver disease

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ABSTRACT: Nonalcoholic fatty liver disease (NAFLD) is a chronic fatty liver disease whose core mechanism lies in obesity-induced insulin resistance, adipose tissue dysfunction, accumulation of free fatty acids in the liver, and concomitant dysbiosis of the intestinal flora. In recent years, some of the active ingredients of food and drug homologous plants have significantly improved NAFLD. This paper focuses on food and medicine homologous plants with the ability to improve NAFLD. The active substances of food and medicine homologous active substances to improve NAFLD are mainly classified into five categories: polysaccharides, polyphenols, flavonoids, terpenoids and others, and their sources and categories, active substances and extraction methods are summarized and analyzed for their mechanisms of action on NAFLD. It aims to provide meaningful data and references for the study and application of food and medicine homologous plants in the treatment of NAFLD.

Keywords: food and medicinal plants; active substances; extraction methods; NAFLD

1. Introductiona

Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic liver condition, affecting approximately 30% of the global population (Pan et al., 2023) . Compared with the normal population, NAFLD patients had a 93% increase in all-cause mortality, which increased with the severity of the disease; NAFLD patients with cirrhosis had a 3.79 times greater risk of death, and those with simple steatosis, also had a 71% greater risk of death compared with the normal population (Simon et al., 2021). NAFLD begins with the accumulation of fat in the liver, a stage that can be caused by genetics, insulin resistance and bad habits, with increasing fat, cholesterol regulation and cellular damage increases, leading to the formation of a fatty liver, followed by persistent inflammation, accumulation of lipocytes and extracellular matrix, etc. which can lead to hepatic fibrosis and cirrhosis (Ahmad et al., 2019), triggering liver damage、liver

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encephalopathy and hydroperitoneum in the liver and other additional Diseases (Figure 1). With the deepening of research, the determination of NAFLD no longer relies solely on the exclusion of alcohol or other liver damage factors, but takes metabolic dysfunction as the core diagnostic basis, emphasizing the direct correlation of metabolic abnormalities such as obesity, insulin resistance or type 2 diabetes mellitus (Lin et al., 2020). Therefore, the concept of metabolism-associated fatty liver disease (MAFLD) was formally proposed in 2020. MAFLD focuses on metabolic function and puts more emphasis on the driving role of metabolic disorders in disease progression, which improves the precision of disease identification and also promotes the shift of treatment strategies from pure liver management to comprehensive metabolic interventions. Although there are some differences in diagnostic criteria between NAFLD and MAFLD, both have excessive liver fat deposition (hepatocellular steatosis >5%) as the core pathological feature, which is highly correlated with metabolic disorders and metabolic complications, and their pathophysiological mechanisms still highly overlap with NAFLD in terms of the core factors, such as obesity and chronic inflammation (Chalasani et al., 2018; Kaya & Yilmaz, 2021). Therefore, research on the improvement of NAFLD in the effects remain valid for MAFLD. Currently, pharmacological treatments are the primary ap (Kaya & Yilmaz, 2021)proach for managing NAFLD (Babu et al., 2021). However, traditional pharmacological interventions often demonstrate limited efficacy and are accompanied by adverse side effects. Consequently, there is a growing interest in identifying safe and effective strategies for the management of NAFLD that minimize side effects.

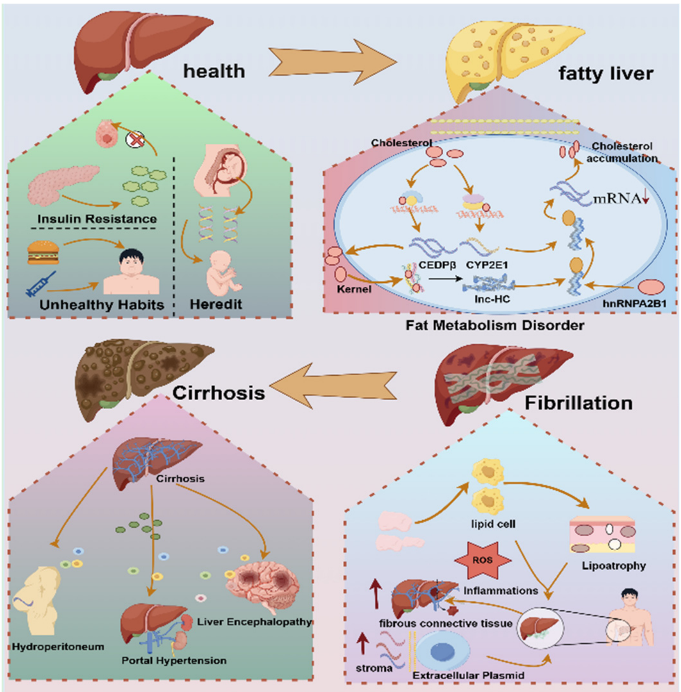


Figure 1. Evolution of NAFLD (Created by figdraw: https://www.figdraw.com)

With the ongoing exploration of novel therapeutic approaches and treatments with minimal side effects, the potential of food and medicine homologous plants for disease management has gained increasing recognition (Guo et al., 2023). To date, the Health Commission of the People's Republic of China has documented 101 plants classified as both food and medicine (http://www.nhc.gov.cn/). Active components were extracted from food and medicine homologous plants (flowers, leaves, stems and roots) by ultrasound and microwave, and revealed that these components have a broad application potential in lipid-lowering (Gupta & Jain, 2022), antidiabetic effects (Bach et al., 2019), blood glucose regulation (Gong et al., 2020), cardiovascular disease improvement (Ma et al., 2023), and the treatment of NAFLD (Liu et al., 2017) , and the main methods of action are shown in Figure 2.

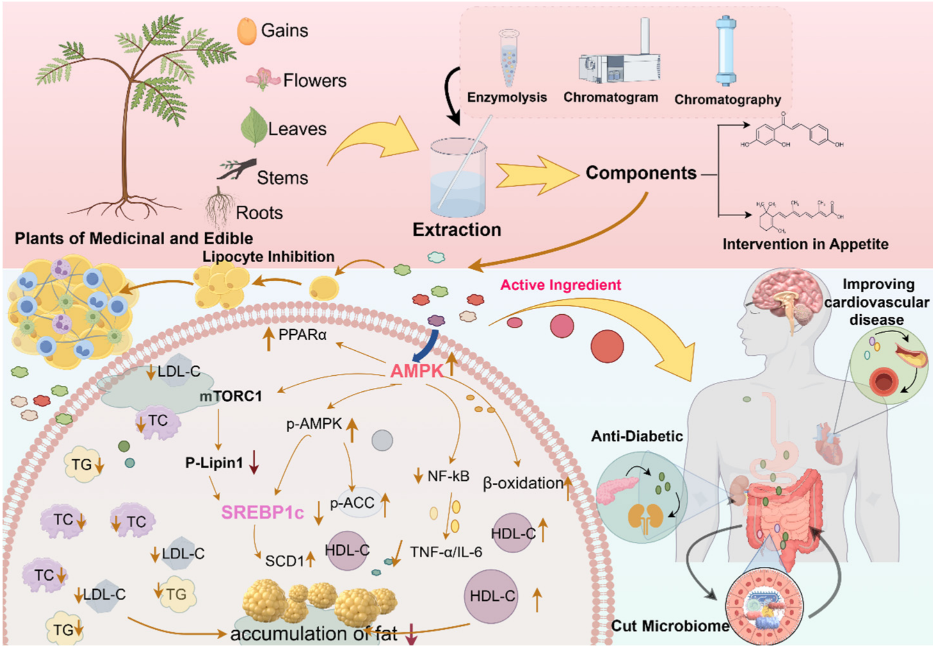


Figure 2. Extraction of active substances from food and medicine plants and their main effects (Created by figdraw: https://www.figdraw.com)

In addition, compared with common plants, food and medicine homologous plants have clear nutritional and medicinal properties, and the safety and functional specificity of their active ingredients have been verified through long-term consumption and modern research, whereas common plants are usually used only as a food source or have not been systematically exploited for their pharmacological potential. The application of food and medicine homologous plants should follow the dosage and compounding principles of “food and medicine” to avoid excessive toxicity and ensure the synergistic effect of the functional components (Sun et al., 2024), whereas common plants lack such systematic specifications. In terms of the mechanism of action of the active ingredients, there are significant differences between food and medicine homologous ingredients and traditional drugs. Traditional drugs (e.g., statins or insulin sensitizers) mostly target a single target (Lagunas-Rangel et al., 2024) (e.g., HMG-CoA reductase or PPARγ receptor), which can easily lead to drug resistance or metabolic side effects; whereas, herbal homologous ingredients synergistically act through multi-target, multi-pathway networks, such as hawthorn polysaccharides regulating Lipid metabolic pathways, to enhance fatty acid oxidation as a whole to improve NAFLD (Fan et al., 2025). In addition, traditional medications focus on acute symptom control, whereas homoeopathic ingredients emphasize the importance of ensuring one's health through a balanced intake of different food items (Law & Au, 2025), and thus homoeopathic ingredients are conducive to a more favorable health regimen.

Although the research on the active substances of food and medicine homologous plants has matured, there is no systematic review on the summary of food and medicine homologous plants with active substances to improve NAFLD and the mechanism of action to improve NAFLD. Through searching Google Scholar, ScienceDirect, and Web of Science, we found that 35 food and medicine plants contain bioactive substances and have preventive and ameliorative effects on NAFLD. Therefore, this paper systematically categorizes these plants and their active ingredients, and discusses the extraction methods of active substances and the effects of active substances (flavonoids, polyphenols, polysaccharides, terpenoids) on NAFLD diseases, to provide a reference for the improvement of NAFLD by using natural active substances, and to provide theoretical guidance for the development of functional products for the prevention and regulation of NAFLD.

2. Sources and classification of food and medicine homologous for improving NAFLD

2.1 Rootstocks

The main food and medicine homologous rhizomes that improve NAFLD include *Houttuynia cordata* Thunb., *Angelica sinensis* (Oliv.) Diels, *Polygonatum sibiricum* Delaroche, *Glycyrrhiza uralensis* Fisch., *Alpinia officinarum* Hance, *Zingiber officinale* Roscoe, *Dioscorea opposita* Thunb., *Curcuma longa* L., *Codonopsis pilosula* (Franch.) Nannf., *Cinnamomum cassia* (L.) J.Presl, *Gastrodia elata* Blume and *Pueraria montana* var. *lobata* (Willd.) Sanjappa & Pradeep (Figure 3). Among these, the active substances from six rhizomes—*Curcuma longa* L*.*, *Alpinia officinarum* Hance, *Houttuynia cordata* Thunb*.*, *Glycyrrhiza uralensis* Fisch*.*, *Dioscorea opposita* Thunb*.*, *Gastrodia elata* Blume—primarily exhibit anti-inflammatory, antioxidant properties, and the ability to regulate gut microorganisms. These substances improve NAFLD primarily by modulating signaling pathways, including those associated with total cholesterol (TC), triglycerides (TG), phosphorylated AMP-activated protein kinase (p-AMPK), and sterol regulatory element-binding protein 1 (SREBP1), as well as by influencing blood lipid levels. The primary active substances of four plants—*Angelica sinensis* (Oliv.) Diels*, Polygonatum sibiricum* Delaroche*, Codonopsis pilosula* (Franch.) Nannf.*and Pueraria montana* var. *lobata* (Willd.) Sanjappa & Pradeep—are polysaccharides. These polysaccharides play significant roles in regulating the immune system and lowering cholesterol levels. The key signaling pathways involved in the regulation of NAFLD include fatty acid synthase (FAS), peroxisome proliferator-activated receptor alpha (PPARα), and acetyl-CoA carboxylase (ACC). Gingerol is the main ingredient in *Zingiber officinale* Roscoe, which can be converted into gingerols, gingerones and other substances (Kausar et al., 2021). *Cinnamomum cassia* (L.) J.Presl has demonstrated effectiveness in regulating lipids and modulating blood lipid levels, among other benefits. *Cinnamomum cassia* (L.) J.Presl has been shown to be effective in regulating lipids and modulating blood lipid levels, among other things, and the active ingredients in both plants ameliorate fat accumulation and liver injury mainly by regulating the expression of lipogenic genes such as PPARγ, SREBP-1c, and LXR.

Figure 3. Homologous food and medicine plants for the improvement of NAFLD

2.2 Leaf

Currently, the main leaves of food and medicine homologous plants that can improve NAFLD include *Morus alba* L., *Eucommia ulmoides* Oliv., *Ginkgo biloba* L., *Perilla frutescens* (L.) Britton and *Taraxacum mongolicum* Hand.-Mazz. (Figure 3). It is notable that the active substances of food and medicine homologous plants in the leaf group are mainly composed of polyphenol flavonoids, followed by terpenoids and α-linolenic acid. These active substances exhibit high activities in reducing fat accumulation, anti-inflammatory, and antioxidant effects. Among various natural remedies, *Morus alba* L. (Peng et al, 2018), *Taraxacum mongolicum* Hand.-Mazz. (Schütz et al, 2006) and *Eucommia ulmoides* Oliv. (Kobayashi et al., 2011) primarily ameliorate NAFLD by modulating the expression lipid metabolism and inflammatory signaling pathways. Furthermore, Ginkgolide B, a constituent of *Ginkgo biloba* L., exhibits a protective effect on cardiomyocytes and alleviates inflammatory responses and liver injury predominantly by regulating the expression of inflammatory proteins, including cyclooxygenase-2 (Cox-2) and the p65 subunit of NF-κB. The primary component of perilla oil, α-linolenic acid, exhibits beneficial effects on NAFLD through PPARβ and the PI3K/AKT/mTOR signaling pathways, among others.

2.3 Flower

Lonicera japonica Thunb., *Chrysanthemum × morifolium* (Ramat.) Hemsl., *Gardenia jasminoides* J.Ellis and *Crocus sativus* L. are floral food and medicine homologous that exhibit beneficial effects on NAFLD (Figure 3). *Lonicera japonica* Thunb., *Chrysanthemum × morifolium* (Ramat.) Hemsl. and *Gardenia jasminoides* J.Ellis are rich in polyphenol flavonoids, which have remarkable efficacy in anti-inflammatory, antioxidant and lipid-lowering (Koo et al., 2004; Zhuang et al., 2023), and improve NAFLD mainly through SREBP1, AMPK and PPAR signalling pathways. *Crocus sativus* L. is abundant in carotenoids and terpenoids, compounds that exhibit hypolipidemic and hypoglycemic properties (Xing et al., 2021). The active ingredient crocin, in particular, ameliorates NAFLD primarily by diminishing inflammatory responses and inhibiting the expression of very low-density lipoprotein (VLDL) lipase.

2.4 Gains

Citrus medica var. *sarcodactylis*, *Morus alba* L., *Sesamum indicum* L., *Citrus × aurantium* 'Chenpi', *Senna tora* (L.) Roxb., *Hippophae rhamnoides* L., *Chaenomeles speciosa* (Sweet) Nakai, *Crataegus pinnatifida* Bunge, *Lycium barbarum* L., *Coix lacryma-jobi* var. *ma-yuen* (Rom.Caill.) Stapf and *Phyllanthus emblica* L. (Figure 3) are eleven fruiting food and medicine homologous plants with a great potential for improving NAFLD. Among them, the active substances of *Morus alba* L.and *Citrus × aurantium* 'Chenpi'. are mainly flavonoid compounds with antioxidant and anti-inflammatory effects, which mainly improve NAFLD by regulating the SREBP-1 signalling pathway. The active ingredients of *Citrus medica* var. *sarcodactylis*, *Senna tora* (L.) Roxb and *Coix lacryma-jobi* var. *ma-yuen* (Rom.Caill.) Stapf are mostly polyphenol flavonoids, which improve NAFLD mainly through AMPK and CPT1 pathway expression. clitorin, an active substance in *Chaenomeles speciosa* (Sweet) Nakai (Cominguez et al., 2022), and chlorogenic acid, epicatechin, and hyperoside, active substances in *Crataegus pinnatifida* Bunge (Han et al., 2016), all ameliorate NAFLD mainly through PPARα and SREBP signaling pathways. *Lycium barbarum* polysaccharide (Zhang et al., 2020) and Coriolagin reduce inflammatory factor accumulation and alleviate liver injury mainly by modulating inflammation-related pathways such as NRF-1 and TFAM. In addition, sesamin, the main active substance in *Sesamum indicum* L, ameliorated NAFLD mainly through signalling pathways such as P-IRS1307 and P-IKK (Yang et al., 2018). *Hippophae rhamnoides* L. is abundant in flavonoids, vitamins, phytosterols, and essential fatty acids (Suryakumar & Gupta, 2011), which exhibit antioxidant (Upadhyay et al, 2010) and anti-obesity properties (Wang et al, 2021). These compounds primarily enhance the management of NAFLD by modulating blood lipid levels and regulating fat accumulation.

2.5 Fungus

Wolfiporia cocos (F.A.Wolf) Ryvarden & Gilb. and *Ganoderma lucidum* (Curtis) P.Karst. have been extensively studied for their active ingredients as traditional materials that food and medicine homologous (Figure 3). The main components of *Wolfiporia cocos* (F.A.Wolf) Ryvarden & Gilb. are polysaccharide compounds (Qian et al., 2018), which are considered safe for clinical applications and do not exhibit acute effects (Wang et al., 2013). *Wolfiporia cocos* polysaccharides reduce inflammatory responses and slow down oxidative stress in the liver mainly through the inflammations signalling pathway. *Ganoderma lucidum* (Curtis) P.Karst. as a traditional Chinese herbal medicine its *ganoderma lucidum* polysaccharide is one of the main active substances of *ganoderma lucidum* (Boh et al., 2007) , which has the effect of protecting the liver and so on (Peng et al., 2023). *Ganoderma lucidum* polysaccharides mainly reduce lipid accumulation and slow down liver injury through SREBP1 and FASN signalling pathways, thus improving NAFLD.

3. Efficient methods for extracting active substances

3.1 Negative-pressure cavitation extraction

Negative-pressure cavitation extraction is the continuous introduction of liquid-solid system through negative pressure generated cavitation to enhance the turbulence, collision and mass transfer between the extraction solvent and the solid matrix, which can effectively destroy the plant tissues and release the biomolecules such as polysaccharides. When the solid-liquid ratio was 4:13, the temperature was 64.8℃, the extraction time was 53 min, the homogenisation time was 70 s, and the negative pressure was -0.068 Mpa, the polysaccharide extraction rate was 16.74% (Jiao et al., 2014). Secondly, the flavonoids (baicalein, wogonoside) extracted from *Scutellaria baicalensis Georgi* membranaceus were extracted under the conditions of 80 mesh size, 40 mL/g solid-liquid ratio, 75% ethanol aqueous solution as the extraction solvent, 60 min extraction time and -0.07 MPa vacuum, and the negative-pressure cavitation technique had a good extraction efficiency in comparison with other conventional extraction methods (Dong et al., 2011).

3.2 Low eutectic solventsv extraction

Low eutectic solvents (DES) are a class of liquids formed by mixing hydrogen-bond donors and hydrogen-bond acceptors in a certain ratio, which have the advantages of environmental protection and sustainability. In recent years, low eutectic solvent method is mainly used for the extraction of small molecules (e.g., polysaccharides) in food processes and is commonly combined with solid-liquid extraction, liquid-liquid extraction and high-intensity focused ultrasound (HIFU) to improve the efficiency of extraction of small molecules (Gao et al., 2024). Extraction of *Wolfiporia cocos* polysaccharides by DES consisting of choline chloride and oxalic acid at a molar ratio of 1:2 (choline chloride: oxalic acid) and 100°C for 15 min resulted in a *Wolfiporia cocos* polysaccharide extraction rate of 46.24% ± 0.13%, which is 10 times higher than that of the water extraction (Zhang et al., 2020). The yield of flavonoids extracted from *Polygonatum sibiricum* Delaroche was 25.4 mg/g, which was 8 times higher than that of ethanol extraction, at a molar ratio of betaine-acetic acid of 1:4, a water content of 30%, a solid-liquid ratio of 1:100 g/mL, an extraction temperature of 50°C, and an extraction time of 30 min (Zhang et al., 2022).

3.3 Ultrasonic extraction

Ultrasonic extraction method utilizes ultrasonic cavitation and shear force to accelerate the leaching of plant active ingredients and thus extract the active ingredients. The method does not require heating and helps to protect thermally unstable components from thermal decomposition. The most critical factor in ultrasound is the frequency of the ultrasound, which has been shown to be between 20 and 120 kHz for the extraction of bioactive compounds from natural products. The ultrasound-assisted ethanol extraction method at a temperature of 40°C, ultrasonic power of 150 W and an ethanol-to-water ratio of 4:1 (v/v) resulted in a high total phenolic content (275.8 mg of gallic acid equivalent/100 g FW), flavanone concentrations (70.3 mg of naringin and 205.2 mg of hesperidin/100 g FW), and an extraction rate of 10.9% from the *Citrus × aurantium* 'Chenpi' (Khan et al., 2010). The extraction of triterpenoids from *Ganoderma lucidum* reached 0.38% under the conditions of aqueous ethanol (50%, v/v) as extraction solvent, ultrasonic power of 210 W, extraction temperature of 80°C, liquid-solid ratio of 50 mL/g, and extraction time of 100 min (Zheng et al., 2020).

3.4 Microwave-assisted extraction

Microwave is an electromagnetic wave with a frequency of 300MHz to 3×10^5MHz, under the action of high-frequency electromagnetic field, its polarity orientation will change with the change of the external electric field, resulting in the movement of molecules and mutual friction effect, so that the active ingredients are effectively leached out. Research has shown that the maximum yield of flavonoids from *Perilla frutescens* (L.) Britton is achieved through dual extraction under conditions of 600 W microwave power, a solvent-to-material ratio of 1:16.5, an irradiation time of 23 minutes, and a pH of 8.4 (Shao et al, 2012). phenolic compounds, such an flavonoids are susceptible to various factors such as temperature and time. Therefore, when using microwave extraction for active compounds, it is essential to select optimal operational conditions and extraction processes to achieve the highest extraction yield of the target bioactive substances.

3.5 Supercritical fluid extraction

Supercritical fluid extraction primarily utilizes supercritical fluids as solvents to extract specific components from liquids or solids for the purpose of separation. Under supercritical extraction conditions, the flavonoid content and purity of *Ginkgo biloba* L. reached 1.342 mg/g and 35.9%, respectively, while the purity of the produced flavonoid extract was 30.3% (Liu et al., 2015). After extracting *Chrysanthemum* × *morifolium* (Ramat.) Hemsl. at 200 atmospheres and 40°C for 30 min, the recovery rate of the flavonoid apigenin was found to be 71.4% (Scalia et al., 1999). A comparison between supercritical fluid extraction of *araxacum mongolicum* Hand.-Mazz. and traditional extraction methods using n-hexane and ethanol showed that the concentration of triterpenoids was higher in the supercritical extracts than in those obtained through traditional extraction methods (Kristó et al., 2001). Furthermore, the extraction efficiency of supercritical fluid extraction was more than double that of steam distillation, while the extraction time was reduced by approximately half (Zhang et al., 2022).

3.6 Enzymatic

Enzymatic method is an environmentally friendly extraction method, which utilizes the selectivity and specificity of enzymes to destroy pectin and fibers in plants so that flavonoid can be fully released. The flavonoid extraction rate of *Ginkgo biloba* L. after Penicillium decursum cellulase treatment reached 28.3 mg/g , which was 31% higher than the pre-optimized condition and 102% higher than the enzyme-free condition (Shuo et al., 2011). In addition, *Morus alba* L. was treated by pectinase to increase the extraction rate of kuromanin chloride and quercetin (Kim et al., 2021). The extraction rate of *Scutellaria baicalensis Georgi* polysaccharides was increased by more than 250% with the assistance of glucose oxidase compared with no enzyme treatment, and the extracted polysaccharides had good antioxidant activity (Chen et al., 2014).

4. Active components of food and medicine homologous plants in the improvement of NAFLD

4.1 Polysaccharides

Polysaccharides are usually composed of multiple monosaccharides with high molecular weight, mainly distributed in plant roots, stems and leaves, and have various effects such as antioxidant and immunomodulatory (Chen et al., 2022). There are many types of polysaccharides with large differences in molecular weight, structure and function. Studies have shown that the main components of *Angelica sinensis* (Oliv.) Diels polysaccharides are mannose, rhamnose, glucuronic acid, galactose, arabinose and xylose (Ma et al., 2020). Among them, mannose, rhamnose, galactose, arabinose and xylose have been found to be more effective in anti-inflammation (Yang et al., 2019). Therefore, *Angelica sinensis* (Oliv.) Diels polysaccharides can attenuate lipoatrophy and improve lipid levels in obese mice, inhibit the expression of SCD1 and GPAT4 and the expression of ERRα in the liver of NAFLD mice, and increase the expression of the enzyme CPT1A and hepatic ERRα (Luo et al., 2023). *coix lacryma* polysaccharides exhibit hypoglycemic effects (Chiang et al., 2020). Supplementation with 3% ethanol extract (rich in polysaccharides) and 10% water extract (also rich in polysaccharides) from *Coix lacryma-jobi* var. *ma-yuen* (Rom.Caill.) Stapf can improve fasting blood glucose, insulin levels, glucose tolerance, and HOMA-I elevation induced by a high-fat diet, as well as improve lipid levels and potentially offer therapeutic effects against atherosclerosis (AI). In addition, it also reduced the expression of inflammatory genes as well as serum GOT and GPT levels as well as regulated the expression of genes related to lipid metabolism, suggesting that the ethanol and aqueous extracts of *Coix lacryma-jobi* var. *ma-yuen* (Rom.Caill.) Stapf have an ameliorative effect on NAFLD.

4.2Phenolic Compounds

4.2.1 Flavonoids

Flavonoids are a significant class of natural compounds characterized by a basic structure comprising a heterocyclic pyran ring linked to two phenyl rings via a central three-carbon chain, forming a C6-C3-C6 carbon skeleton (Chen et al., 2023). In plants, flavonoids primarily exist in free form or as glycosides bound to sugars. They are distributed across various plant organs, particularly in flowers, leaves, roots, stems, and fruits, and have been extensively studied due to their notable antioxidant activity and free radical scavenging abilities. Research has shown that puerarin possesses effects against cardiovascular diseases (Zhou et al., 2014). After puerarin administration, there was a significant reduction in serum levels of TG and TC in mice, along with an increase in the levels of SOD, GSH-Px, and CAT in the liver. In addition, Puerarin not only reduced the expression of genes such as Acacb and Apob100, and increased the levels of Cpt1a, Pparα, Mttp, and Pnpla2 genes (Zhou et al., 2022), but also enhanced the leptin receptor mRNA expression and the levels of P-JAK2/P-STAT3, which reduced lipid accumulation (Zheng et al., 2009). The extracts from *Morus alba* L. contain compounds such as cyanidin 3-O-glucoside and pelargonidin 3-O-glucoside, which can reduce levels of LDL cholesterol and upregulate LDLR and HMGCR expression (Chung et al., 2021). The flavonoid compound Cyanidin-3-O-glucoside found in *Lonicera japonica* Thunb. significantly modulates blood lipid and creatinine levels, reduces MDA and hepatic G6Pase levels, and increases levels of GSH, CAT, and SOD (Chun et al., 2018). Additionally, it enhances the content of exocrine zymogen granules and restores the activity of hepatic glucose kinase (GK) to normal levels. With advancements in technology, the research and application prospects of flavonoids warrant further exploration and development. The application of flavonoids in the field of NAFLD is expected to become increasingly widespread, bringing more benefits to human health.

4.2.2 Polyphenols

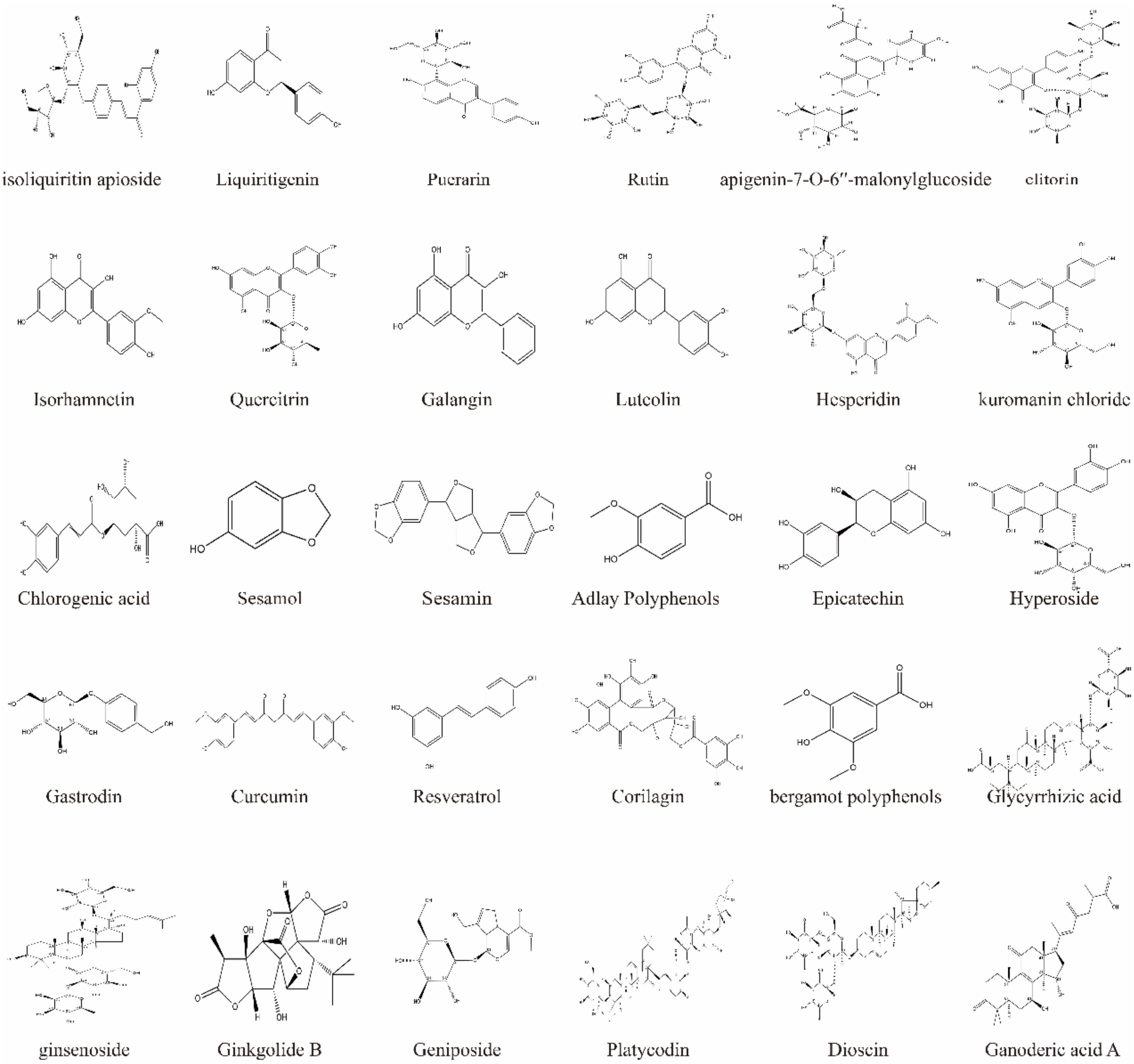
Polyphenols are a class of secondary metabolites widely found in plants, characterized by multiple phenolic hydroxyl groups connected by covalent or ester bonds to form aromatic rings. Due to their unique chemical structures and biological activities, polyphenols are abundant and diverse in plants. Polyphenols including phenolic acids, tannins and many other types, have a wide range of biological activities, and their antioxidant effects can prevent NAFLD caused by oxidative stress damage. It was found that chlorogenic acid in *Morus alba* L. could significantly reduce body weight, decrease fat accumulation, lower serum biochemical indices (TC , TG, LDL-C, ALT) and liver biochemical indexes, increase SOD expression and lipocalin level and PPAR-α and CPT-1 expression in rats (Peng et al., 2018). The phenolic compounds in *Crataegus pinnatifida* Bunge primarily include chlorogenic acid, epicatechin, and hyperoside (Han et al., 2016). These compounds have been shown to reduce liver damage and cellular apoptosis in mice, resulting in decreased activities of ALT, AST, and alkaline phosphatase (ALP), as well as lowered levels of TNF-α, interleukin-1 (IL-1), and interleukin-6 (IL-6). Additionally, they increase antioxidant enzyme activity and the expression of peroxisome PPARα, while lowering blood lipid levels and apolipoprotein B (Apo-B) levels, thereby effectively improving NAFLD. Curcumin not only promoted the expression of CYP3A protein and CYP7A protein, decreased the expression of LXRα and SREBP-1c, and inhibited the level of SREBP-1 in mouse liver (Yan et al., 2018), but also enhanced the expression of LC3-Atg7 and Bcl2/BAX, suggesting the ability to increase the formation of autophagy and inhibit apoptosis in cells (Lee et al., 2020), thus improving NAFLD.

4.3 Terpenoids

Terpenoids are mainly polymerized by isoprene unit, according to the different number of polymerization unit, terpenoids can be divided into monoterpenes, sesquiterpenes, diterpenes and other different categories (Yao & Liu, 2023). Geniposide is mainly a terpene active substance extracted from *Gardenia jasminoides* J.Ellis, which is able to improve hepatic steatosis by lowering the liver index and lipid levels, inhibit the expression of cytochrome P4502E1, and increase the level of insulin resistance and the expression of PPARα (Ma et al., 2011). Gardenia glycosides inhibited the expression of SREBP-1c, hepatic LXR, lipoprotein lipase (LPL), increased CPT activity, down-regulated MDA, and up-regulated SOD and Gpx levels. It also reversed the translocation of Bax to the lysosome and the appearance of histone B in the lysosome, and increased the activities of the lysosomal enzymes α-galactosidase, α-mannosidase and acid phosphatase (Lee et al., 2020; Nam et al,, 2014). Terpenoids extracted from food and medicine homologous plants exert ameliorative effects on NAFLD through different mechanisms.

4.4 Other compounds

The compounds found in *Senna tora* (L.) Roxb., including emodin and chrysophanol (anthraquinone compounds), lutein, crocetin, cinnamaldehyde, glycyrrhizin coumarin, gingerol, chicoric acid, maslinic acid from *Crataegus pinnatifida* Bunge, and perilla oil, each play a role in improving NAFLD. Emodin, among others, is significant for maintaining hepatic homeostasis by influencing hepatic enzyme and protein levels and reducing liver coefficients (Meng et al., 2019; Tzeng et al., 2013). Lutein has been shown to lower TNF-α levels and blood lipids, which may help ameliorate metabolic disorders caused by dyslipidemia (Lee et al., 2019). Crocetin reduces serum indices and exhibits anti-inflammatory properties, potentially functioning through the modulation of inflammatory factor networks (Parsi et al., 2020; Xu et al., 2021). Cinnamaldehyde alleviates body weight in obese mice, possibly related to the regulation of energy metabolism pathways (Dai et al., 2023). Glycyrrhizin coumarin reduces hepatic fat accumulation, likely intervening in critical aspects of hepatic lipid metabolism (Zhang et al., 2016; Zhang et al., 2020). Gingerol addresses NAFLD primarily by regulating hepatic gene expression and modulating gut microbiota (Tzeng et al., 2015; Wang et al., 2022). Chicoric acid regulates blood lipid and inflammation-related proteins, which is beneficial for improving hepatic inflammatory status and lipid metabolism (Ding et al., 2020). Maslinic acid modulates mRNA and protein expression, potentially affecting cellular proliferation, differentiation, and apoptosis (Li et al., 2022). Perilla oil influences the mRNA expression related to lipogenesis, contributing to the transcriptional regulation of lipid formation (Bae et al., 2020). In summary, bioactive compounds such as polyphenols, flavonoids, and terpenoids (Figure 4) provide diverse insights into the research and treatment of fat accumulation and metabolism in NAFLD through various molecular mechanisms. This exploration aids in a deeper understanding of disease pathogenesis and the development of novel therapeutic strategies.



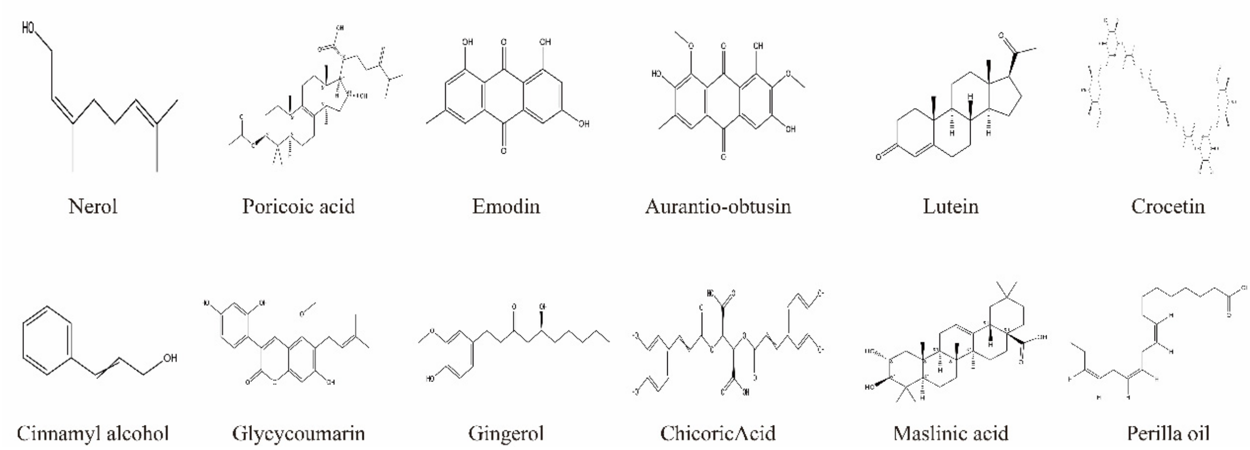


Figure. 4. Active constituents of food and medicine homologous plants for the improvement of NAFLD

5. Mechanisms of active components from food and medicine homologous in improving NAFLD.

5.1 Improvement of blood lipid levels

Blood lipids refer to lipid substances in the blood, primarily including cholesterol, triglycerides, LDL-C, and HDL-C. Studies have indicated a significant association between abnormal blood lipid levels and the incidence of NAFLD, particularly highlighting that elevated TG levels are strongly correlated with an increased risk of developing NAFLD (Scorletti et al., 2015). Therefore, monitoring and managing blood lipid levels is crucial for the prevention and treatment of NAFLD.Puerarin polysaccharide possesses lipid-lowering (Rao et al., 2020) and blood glucose-lowering properties (Qian et al., 2020). The low molecular weight *Pueraria lobata* polysaccharide RPP-2 with α-D-1,3-glucan as the main chain (Li et al., 2023) and the fructose, glucose and mannose polysaccharides of *Polygonatum sibiricum* Delaroche (Liu et al., 2022), Rutin (El-Shial et al., 2023), Apigenin-7-O-6-malonylglucoside (Li et al., 2023), Anthocyanidin 3-O-glucoside (Yang & Jo, 2018), Isorhamnetin (Guo et al., 2021), and Forsythia polyphenols (Musolino et al., 2020) were able to improve the levels of blood lipids (TC, TG, and LDL-C and HDL-C) and reduce liver injury and liver fat accumulation. In addition *Polygonatum sibiricum* Delaroche polysaccharides also increased SOD and GSH levels and decreased MDA levels in the liver, suggesting some improvement in oxidative stress injury. In addition, the ability of puerarin to lower blood lipid levels was superior to that of puerarin alone when acting in conjunction with total flavonoids and total saponins, and was able to significantly reduce the degree of liver swelling and improve NAFLD (Dong et al., 2024)

5.2 Reducing the inflammatory response

Inflammatory responses play a crucial role in the onset and progression of NAFLD. In NAFLD, the liver's innate immune function is disrupted, leading to an imbalance between pro-inflammatory and anti-inflammatory cytokines. This dysregulated inflammatory response is characterized by elevated levels of transcription factors induced by insulin resistance, such as NF-κB, and various inflammatory cytokines (Malaguarnera et al., 2009). Inflammasomes, which are complexes composed of multiple proteins, can activate inflammatory responses by releasing mature IL-1β and IL-18, thereby exerting inflammatory effects

(Buzzetti et al,, 2016). Using *Wolfiporia cocos* polysaccharide to intervene in NAFLD mice reduced steatohepatitis (Ye et al., 2022), decreased the expression of CD11b and TLR4 in the inflammations signaling pathway, inhibited macrophage infiltration, and reduced the accumulation of CCL3 and CCR1B (Tan et al., 2022), further suggesting that *Wolfiporia cocos* polysaccharide improves NASH by regulating the NF-κB/CCL3-CCR1 axis, thereby effectively preventing NAFLD. The main components of *Lycium barbarum* polysaccharides are mannose and glucose (Zhang et al., 2022), which can increase cell viability and reverse abnormal oxidative stress by inhibiting mitochondria-mediated apoptotic pathways and correcting cell cycle progression (Zhang et al., 2021). Additionally, Isoliquiritin apioside (Luo et al., 2023) inhibits HT-DNA-induced IRF3 phosphorylation and IFN-β secretion and expression of the GAS-STING pathway, thereby suppressing inflammatory factor expression in cells. Hesperidin (Yang et al., 2022), epicatechin (Wu et al., 2017), and resveratrol (Wu et al., 2023) have all been shown to alleviate inflammation and oxidative stress, improve insulin resistance, and restore the inhibitory protein IκBα, thereby reducing NF-κB activity and mitigating liver injury (Li et al., 2014). Additionally, ginsenoside Rg1 (Hou et al., 2020)and platycodin (Choi et al., 2017) can promote the expression of carnitine acyltransferases, inhibit lipid peroxidation levels, and reduce the expression of pro-fibrotic and pro-inflammatory cytokines, further suppressing the nuclear translocation of NF-κB p65 and the degradation of IκBα. Ginkgolide B has also been shown to decrease the expression of JNK and caspase proteins associated with lipotoxic apoptosis, as well as the expression of inflammation-related proteins such as Cox-2, NF-κB and p65 (Jeong et al., 2017; Yang et al., 2020). Collectively, these findings highlight the significant role of inflammatory responses in the onset and progression of NAFLD. The enhanced activity of inflammatory cells and inflammasomes, along with the lipid metabolic dysregulation induced by inflammation, are key factors driving the transition of NAFLD towards an inflammatory state.

5.3 Reducing oxidative stress

Oxidative stress is a significant regulatory mechanism in NAFLD, involving an imbalance between the production of ROS and cellular antioxidant defense mechanisms, which leads to cellular damage and disease progression. The role of oxidative stress in NAFLD is highly complex and involves multiple pathways. Firstly, dysregulation of lipid metabolism results in lipid accumulation in the liver, which subsequently affects mitochondria, the endoplasmic reticulum, and other oxidases, leading to alterations in insulin sensitivity and changes in the expression and activity of key lipid metabolic enzymes (Chen et al., 2020; Karkucinska et al., 2022). Liquiritigenin has been shown to enhance the expression of SOD and GSH in liver tissues, inhibiting the increase of reactive oxygen species. It has been demonstrated that liquiritigenin can mitigate inflammatory responses and oxidative stress, thereby improving antioxidant enzyme activity and alleviating liver injury (Gou et al., 2020). The ethanolic extract of *Sesamum indicum* L. containing sesamol and sesamolin significantly increased GSH, vitamin C37 and NRF2 levels, enhanced GSH-Px, SOD, CAT and SOD activities, decreased malondialdehyde and NO levels, thus reducing hepatic oxidative stress and decreasing the expression of P-JNK1, phosphorylated nuclear factor NF-κB p65, P-IRS1307 and

P-IKK (Yang et al., 2018). Corilagin increased SOD, GSH-/Px, CAT levels and upregulated genes related to mitochondrial biological responses such as NRF1, NRF2 and TFAM (Zhang et al., 2020). In conclusion, natural constituents such as glycyrrhizin, sesamol and corilagin have demonstrated potent hepatoprotective effects by enhancing antioxidant enzyme activities, down-regulating ROS production, restoring mitochondrial function, reducing hepatic lipid accumulation, and inhibiting inflammation, revealing new perspectives on their potential therapeutic use as NAFLD therapeutics.

5.4 Regulation of hepatic metabolic levels through the AMPK signaling pathway

AMP-activated protein kinase (AMPK) serves as a critical energy sensor and holds a prominent position and wide influence in the field of NAFLD research, particularly in the context of cellular energy homeostasis imbalance. This signaling cascade finely regulates multiple aspects of lipid metabolism, insulin resistance, and fatty acid oxidation, making it a primary target for intervention strategies in NAFLD (Cai et al., 2024; Loeffelholz et al., 2021). Bioactive components derived from food and medicine homologous activate the AMPK signaling pathway, leading to the phosphorylation of downstream effectors such as ACC and hormone-sensitive lipase (HSL), which directly inhibit fatty acid synthesis and accelerate the rate of fatty acid β-oxidation, significantly reducing hepatic lipid accumulation (Fang et al., 2022; Smith et al., 2016). Additionally, AMPK can induce autophagic flux to eliminate damaged mitochondria and abnormally accumulated lipid droplets, further alleviating oxidative stress and inflammatory responses. By regulating the expression of AMPK signaling pathways, it is possible to improve the progression of NAFLD. Research has shown that *Ganoderma lucidum* polysaccharides downregulate the expression of SREBF1 and ACCα proteins while increasing the phosphorylation of AMPK and ACC, as well as the ex--pression of CPT-1, thereby inhibiting the expression of lipogenesis-related genes SREBP1 and FASN (JIA et al., 2016; Yuan et al., 2020). Additionally, compounds such as quercitrin (Kang & Koppula, 2015), luteolin (Davaatseren et al., 2013), hesperidin (Lee et al., 2020), and dioscin not only activate the AMPK signaling pathway to inhibit the expression of genes including SCD-1, HMG-R, GPAT, and ACC, but also further improve lipid profiles and reduce oxidative stress. Porinic acid not only activated the AMPK pathway to inhibit hepatic steatosis, activated downstream phosphorylation at the Thr172 site, and induced Acc phosphorylation at, also regulates lipid metabolism levels, and decreased the expression of the endoplasmic reticulum stresses GRP78, CHOP, XBP1c, and p-PERK (Kim et al., 2019). In summary, the AMPK-mediated signaling pathway is regulated by bioactive compounds derived from food and medicine, inhibiting lipogenesis, promoting lipolysis, and exerting anti-inflammatory effects. Natural products such as Ganoderma lucidum polysaccharides and quercitrin activate AMPK, downregulate lipid synthesis, and promote lipid metabolism, demonstrating significant research value and application prospects in the improvement of NAFLD.

5.5 Regulates lipid metabolism

Sterol regulatory element-binding proteins (SREBPs) play a crucial role in the regulation of cholesterol synthesis and fatty acid metabolism by activating the expression of genes involved in cholesterol and fatty acid synthesis. Peroxisome proliferator-activated receptors (PPARs) include three types: PPARα, PPARβ, and PPARγ, which play key roles in various biological processes such as energy metabolism and inflammatory responses (Mirza et al., 2019). There is a close relationship between SREBPs and PPARs in lipid metabolism. In hepatic cells, the activation of PPARα can inhibit the activity of SREBP-1c, thereby reducing lipid synthesis and accumulation (Qin et al., 2016). Conversely, the activation of SREBP-1c promotes fatty acid and cholesterol synthesis, while PPARγ activation enhances adipocyte differentiation and insulin sensitivity (Sankaran et al., 2021). Therefore, investigating the relationship between PPARα and SREBP-1c is a critical step in understanding the development and progression of NAFLD. Studies have shown that kaempferol (Tang et al., 2022) and clitorin (Divina et al., 2021) promote lipid metabolism in the liver by regulating the expression of SREBP, PPARs and CCAAT/ C/EBPα in mice, and increase the expression of PPARα, CPT1, and adenosine monophosphate-activated protein kinase genes in liver tissues, which reduces the accumulation of fats in the liver, thus ameliorating NAFLD. Galangin (Zhang et al., 2020), Adlay polyphenols (Ma et al., 2022), Gastrodin (Ahmad et al., 2019) and Ganoderic acid A (Liu et al., 2020) could increase the PPARα level and regulate the expression of adipose-regulated genes such as SREBP1c and FAS in the model group. In addition, nerolidol improved liver tissue condition by regulating the SREBP2 gene and decreasing cholesterol synthesis (Givian et al., 2020), thus regulating the expression of lipid metabolism genes in NAFLD in which the regulation of these genes is of particular importance.

5.6 Regulation of intestinal microorganisms

Gut microorganisms play an important role in the development of NAFLD by regulating lipid metabolism, inflammatory response and gut barrier function. Studies have shown that dysbiosis of intestinal flora is closely related to the development of NAFLD, and specific flora members and metabolites may influence lipid accumulation and inflammatory responses in the liver through the “gut-liver axis” (Liu et al., 2022). Glycyrrhizic acid, the main active substance in Glycyrrhiza glabra, was able to reduce the body weight of hyperlipidemia-induced mice, had a restorative effect on the Chao index of gut microorganisms, altered the structure of the gut microbiota in the hyperlipidemia group, increased the relative abundance of *Streptococcus alimentarius*, and decreased the abundance of *Helicobacter lachryonii* as well as the transport and metabolism pathways of carbohydrates, which suggests that glycyrrhizic acid regulates the NAFLD in a similar way as the modulation of gut microbiota in rats (Wang et al., 2022). In addition, both glycyrrhizin and isoglycyrrhizin increased the proportion of *Lactobacillus* and *Faecalibaculum*, but glycyrrhizin decreased the relative abundance of *Coriobacteriaceae UCG-002, GCA-900066575*, while isoglycyrrhizin decreased the relative abundance of *Erysipelatoclostridium* (Liu et al., 2025). Studies have shown that *Lactobacillus* can reduce the negative effects of obesity (Lim et al., 2025), and the relative abundance of *Coriobacteriaceae UCG-002* is positively correlated with lipid levels (Liu et al., 2023). Dioscin can regulate Bas metabolism through hepatic FXR-SHP and intestinal FXR-FGF15 pathways and has therapeutic effects on the gut microorganism Clostridium difficile (Yan et al., 2023).

In conclusion, the active ingredients of food and medicine homologous improved NAFLD from six aspects such as improving blood lipid levels, slowing down oxidative stress, and regulating lipid metabolism levels, and their main mechanisms of action are shown in Figure 5, which has positive significance for the improvement and treatment of NAFLD.

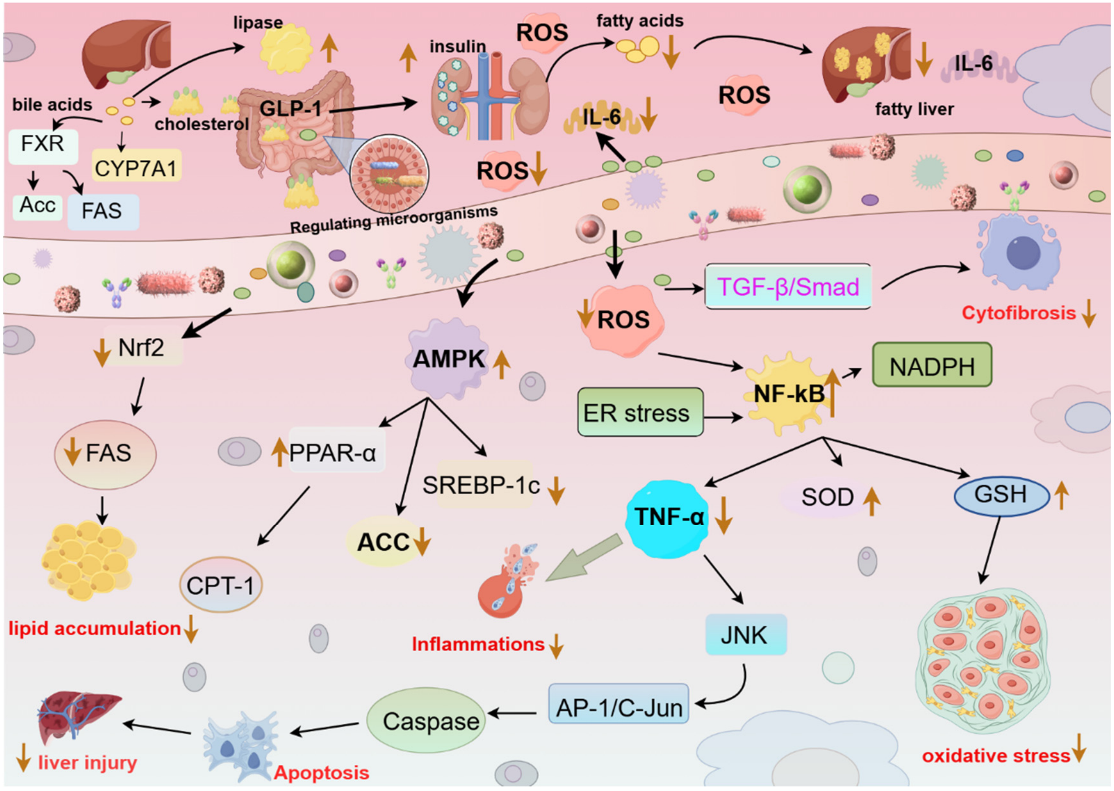


Figure 5. Main mechanisms of action of active substances of homologous food and medicine origin (Created by figdraw: https://www.figdraw.com)

6. Conclusion

Bioactive compounds from food and medicine homologous plants hold significant potential for improving NAFLD. NAFLD has long been recognized as a chronic liver condition. Although traditional pharmacological therapies can improve certain indicators associated with NAFLD, they may also increase the burden on the liver and are often accompanied by side effects. Consequently, phytochemicals derived from food and medicine homologous sources are considered low-cost and safe therapeutic strategies. Polysaccharides, polyphenols, flavonoids and terpenoids are the main active ingredients in food and medicine homologous plants, which are mainly found in the roots, stems, leaves, flowers and fruits of food and medicine plants. Among the food and drug homologous active ingredients polysaccharides, polyphenol flavonoids and terpenoids are the main active ingredients, which are mainly found in the roots, stems, leaves, flowers and fruits of food and drug homologous plants. However, the study of food and medicine homologous plants contains a variety of factors, such as plant species, extraction methods, dosage and time, etc., which may have an impact on them. A single statistical method may not be sufficient to comprehensively analyze the interactions among these factors, so it is of great significance to use multivariate statistical methods, including multiple regression analysis, principal component analysis, partial least squares discriminant analysis, etc., to comprehensively evaluate the interactions and overall effects of multiple factors on the content of active ingredients in food and medicine homologous plants. In addition, the pathogenesis of NAFLD encompasses several aspects, and several aspects should be considered when developing an effective treatment regimen while ensuring that food and drug homologous active substances improve NAFLD. First, the concentration of active compounds that improve NAFLD in food and medicinal herbs is relatively low; thus, optimizing extraction methods to enhance the yield of active compounds is essential for large-scale production. Furthermore, research on the efficacy of bioactive compounds from food and medicine homologous herbs is currently limited to cellular and animal studies. Future efforts should focus on conducting large-scale clinical trials to validate the effectiveness and safety of these bioactive components in the treatment of NAFLD. Such studies will provide stronger evidence for clinical applications and help determine parameters such as the appropriate scope, usage methods, dosage, and treatment duration.In addition, considering the multifactorial pathogenesis of NAFLD, it is essential to employ modern biotechnological and molecular biological approaches to investigate the action targets and molecular mechanisms of effective components in food and medicine homologous resources from multiple angles. Finally, a comprehensive prevention and treatment strategy for NAFLD should be developed, taking into account its multifactorial and multi-mechanistic nature, as well as the interconnections between different organs. Particularly, personalized treatments should be tailored based on individual physiological characteristics, selecting suitable bioactive components from food and medicine homologous resources for targeted therapy. In the future, the development of bioactive components from food and medicine homologous resources can serve as adjunctive therapeutic approaches, complementing traditional pharmacological treatments to enhance therapeutic efficacy. Particularly, modern food processing technologies can be leveraged to create novel dietary products and specialized medical foods that are rich in components aimed at preventing and treating NAFLD. Moreover, through the extraction, concentration, purification and other processes of food and drug ingredients, to improve the content and bioavailability of the active ingredients, to enhance the efficacy of the product. In summary, addressing NAFLD presents a significant challenge, and research and development of food and medicine homologous resources can offer new perspectives, methods, and a solid material foundation for the prevention and treatment of non-alcoholic liver injury. This endeavor holds considerable positive and important implications for public health.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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