



Review Article

# The food and medicinal homological resources benefiting patients with hyperlipidemia: categories, functional components, and mechanisms

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**Abstract:** Hyperlipidemia is a kind of lipid metabolism disease, whose pathogenesis is complex and diverse, mainly related to abnormal glucose and lipid metabolism, as well as insulin resistance and other characteristics. Because of their low toxic and side effects along with clear medicinal effects, the food and medicinal homological resources are widely used in the regulation of blood lipids in recent years. The State Administration for Market Regulation website and various databases have been searched for the use of food and medicinal homological materials in functional food products, the categories and frequency in food and medicinal homological resources, the lipid-lowering active ingredients and their mechanisms. The results showed that 53 kinds of food and medicinal homological resources were used to regulate blood lipids, of which *Crataegus pinnatifida* Bge., *Cassia obtusifolia* L., *Nelumbo nucifera* Gaertn., *Morus alba* L. and *Pueraria lobata* (Willd.) Ohwi were used most frequently. The main active ingredients are triterpenes and their glycosides, flavonoids, alkaloids and polysaccharides, etc., they regulated blood lipid levels and cholesterol metabolism by activating AMPK and PPAR $\gamma$ .

**Keywords:** hyperlipemia; food and medicinal homological; State Administration for Market Regulation; functional components; mechanism

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## 1 Introduction

Hyperlipidemia is a metabolic disease caused by a disorder of lipid metabolism in the body and characterized by one or more abnormalities of total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein in the blood<sup>[1]</sup>. Clinically, it can be divided into four categories: Hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, and low-density lipoprotein. Hyperlipidemia is closely related to the progression of diseases such as type 2 diabetes, hypertension, nonalcoholic fatty liver disease, and atherosclerosis<sup>[2-4]</sup>. Currently, statins and fibrates are commonly used in clinical practice for the treatment of hyperlipidemia, but they can cause severe side effects and high drug dependence<sup>[5,6]</sup>.

It has been a consensus that diet is important to health, especially the adjustment of sub-health and the prevention of diseases. More and more attention has been paid to the prevention

and treatment of cardiovascular diseases through diets, such as the Mediterranean diet, low-glycan diet and medicinal diet. The concept of food and medicine homology (FMH) derived from the ancient Chinese *Huangdi's internal classic*, who combined the functions of food and medicine scientifically so that it can be used both as a food and a medicine<sup>[7,8]</sup>. Recently, it has been found that their chemical components can regulate fat metabolism, promote insulin secretion, change gut microbiota, promote the growth of beneficial flora, and improve energy metabolism<sup>[9,10]</sup>. In addition, various functional foods made from FMH resources have been used to prevent or improve hyperlipidemia and its related complications which show significant therapeutic effects and fewer side effects<sup>[11]</sup>. Therefore, these products have become the first choice for people to regulate daily blood lipids. According to the State Administration for Market Regulation (SAMR) website, FMH resources such as *Crataegus pinnatifida* Bge., *Cassia obtusifolia* L., and *Pueraria lobata* (Willd.) Ohwi have become the

main raw materials for blood-regulating in functional food, but their active components and mechanisms are still unclear.

Here, the frequencies and categories of raw materials in functional foods used in the market were analyzed, and the functional components and mechanisms were summarized, which provides a theoretical basis for the research of functional foods to regulate blood lipids.

## 2 The food and medicine homology resources for the regulation of blood lipids

### 2.1 The categories and frequencies of food and medicine homology resources used to regulate blood lipids recognized by SAMR

The database of SAMR (<https://www.samr.gov.cn>) was searched with "hypolipidemic" as the keyword, which retrieved 226 items of lipid-regulating functional foods containing FMH resources in September 2022. Among them, different dosage forms of the same functional food were considered as one, and only the main raw material was included in accordance with the *Catalogue of Substances for Both Food and Traditional Chinese Medicine* issued in 2018. Table 1 shows the categories and frequencies of FMH resources used in functional foods.

**Table 1** Frequencies of FMH resources used in functional foods

| Medical materials                             | Frequencies | Medical materials                           | Frequencies |
|-----------------------------------------------|-------------|---------------------------------------------|-------------|
| <i>Crataegus pinnatifida</i> Bge.             | 96          | <i>Platycodon grandiflorus</i>              | 3           |
| <i>Pueraria lobata</i> (Willd.) Ohwi          | 71          | <i>Glycyrrhiza uralensis</i>                | 3           |
| <i>Cassia obtusifolia</i> L.                  | 48          | <i>Gastrodia elata</i>                      | 2           |
| <i>Nelumbo nucifera</i> Gaertn.               | 48          | Mulberry                                    | 2           |
| <i>Ganoderma Lucidum</i> Karst                | 25          | <i>Pseudocydonia sinensis</i>               | 2           |
| <i>Morus alba</i> L.                          | 22          | <i>Sophora japonica</i>                     | 2           |
| <i>Astragalus membranaceus</i> (Fisch.) Bunge | 15          | <i>Codonopsis pilosula</i> (Franch.) Nannf. | 2           |
| <i>Lycium chinense</i> Miller                 | 15          | <i>Perilla frutescens</i>                   | 1           |
| <i>Hippophae rhamnoides</i>                   | 14          | <i>Coix lacryma-jobi</i>                    | 1           |
| <i>Panax quinquefolius</i>                    | 11          | <i>Allium macrostemon</i>                   | 1           |
| <i>Panax ginseng</i>                          | 10          | <i>Ptyas dhumnades</i>                      | 1           |
| <i>Chrysanthemum morifolium</i>               | 9           | <i>Persica vulgaris</i>                     | 1           |
| <i>Curcuma longa</i> Linn.                    | 8           | <i>Ziziphus jujuba</i>                      | 1           |
| <i>Poria cocos</i> (Schw.) Wolf (Poria).      | 7           | <i>Cinnamomum cassia</i>                    | 1           |
| <i>Eucommia ulmoides</i>                      | 7           | <i>Taraxacum mongolicum</i>                 | 1           |
| <i>Angelica sinensis</i>                      | 5           | <i>Siraitia grosvenorii</i>                 | 1           |
| <i>Polygonatum odoratum</i>                   | 4           | <i>Ecklonia kurome</i>                      | 1           |
| <i>Dioscorea opposita</i>                     | 4           | <i>Lonicera japonica</i>                    | 1           |
| <i>Polygonatum sibiricum</i>                  | 4           | <i>Zingiber officinale</i>                  | 1           |
| <i>Gardenia jasminoides</i>                   | 3           | <i>Eucommia ulmoides</i>                    | 1           |
| <i>Phyllanthus emblica</i>                    | 3           | <i>Lophatherum gracile</i>                  | 1           |
| <i>Raphanus sativus</i>                       | 3           | <i>Piper longum</i>                         | 1           |

Among the 226 kinds of functional foods, there were 44 categories of FMH resources. Among them, 6 FMH resources appeared more than 20 times, including *Crataegus pinnatifida* Bge. (96), *Pueraria lobata* (Willd.) Ohwi (71), *Cassia obtusifolia* L. (48), *Nelumbo nucifera* Gaertn. (48), *Ganoderma Lucidum*

Karst (25), and *Morus alba* L. (22), of which *C. pinnatifida* is the most common one.

### 2.2 The categories and frequencies of food and medicine homology resources with lipid-regulating effects

We searched the literature using "dyslipidemia", "herbs" and "traditional Chinese medicine" or "hyperlipidemia", "herbs" and "traditional Chinese medicine (TCM)" and excluded the repeated and review articles. A total of 191 publications were identified, including 37 species of FMH resources. Among them, eight species of FMH resources appeared more than 20 times, including *C. pinnatifida* (103), *P. cocos* (66), *Cassia obtusifolia* L. (56), *Astragalus membranaceus* (37), *Glycyrrhiza uralensis* (34), *Angelica sinensis* (Oliv.) Diels (21), *Persica vulgaris* (20), and *Nelumbo nucifera* Gaertn. (20). Among them, *C. pinnatifida* was the most frequently used plant. The results are shown in Table 2.

**Table 2** Frequency of use of medicinal and FMH resources in the literature

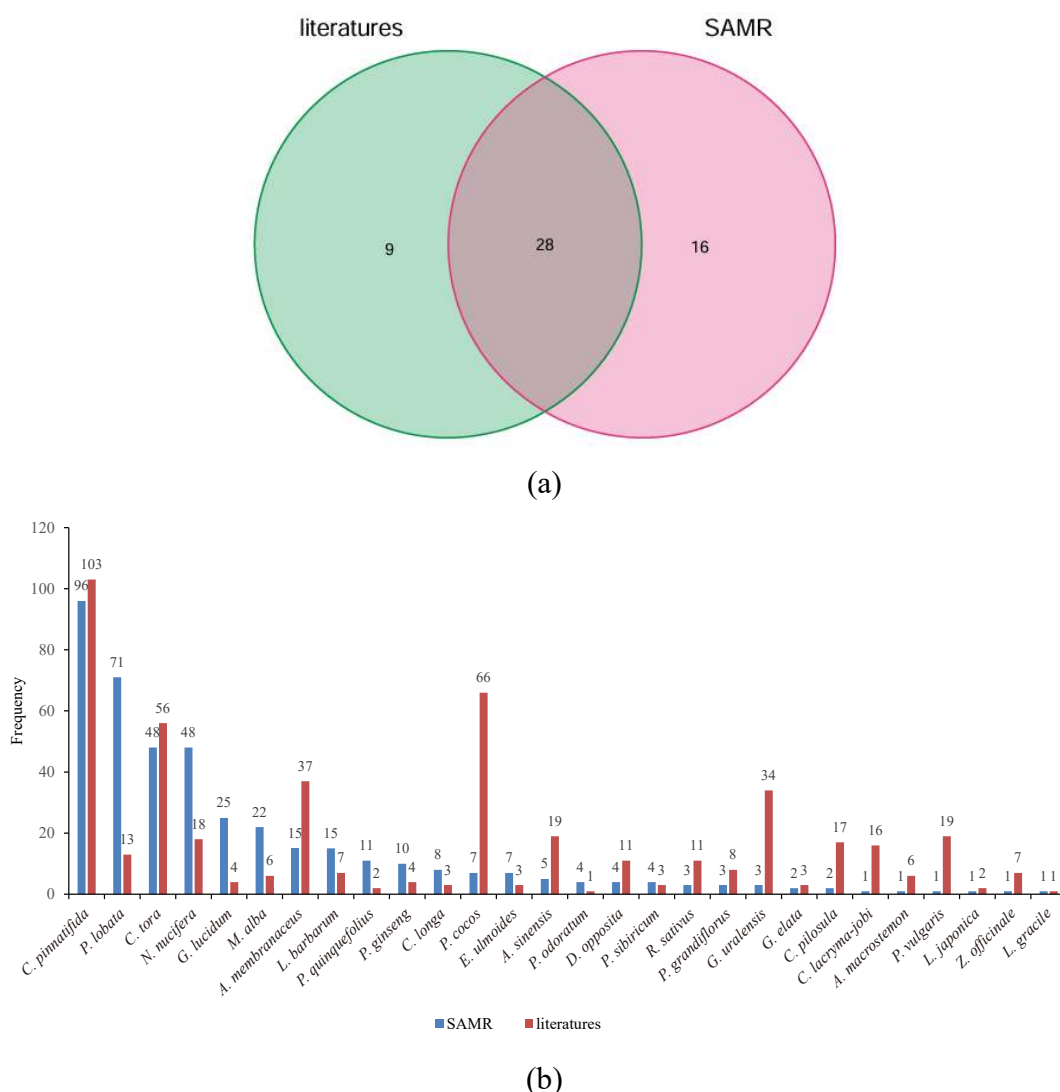
| Medical materials                           | Frequencies | Medical materials              | Frequencies |
|---------------------------------------------|-------------|--------------------------------|-------------|
| <i>Crataegus pinnatifida</i> Bge.           | 103         | <i>A. vulgaris</i>             | 5           |
| <i>Poria cocos</i> (Schw.) Wolf (Poria).    | 66          | <i>Hordeum vulgare</i>         | 5           |
| <i>Cassia obtusifolia</i> L.                | 56          | <i>Ganoderma Lucidum</i> Karst | 4           |
| <i>Astragalus membranaceus</i>              | 37          | <i>Agastache rugosa</i>        | 4           |
| <i>Glycyrrhiza uralensis</i>                | 34          | <i>Panax ginseng</i>           | 4           |
| <i>Angelica sinensis</i> (Oliv.) Diels      | 21          | <i>Eucommia ulmoides</i>       | 4           |
| <i>Persica vulgaris</i>                     | 20          | <i>Zizyphus vulgaris</i>       | 3           |
| <i>Nelumbo nucifera</i> Gaertn.             | 20          | <i>Curcuma longa</i> Linn.     | 3           |
| <i>Codonopsis pilosula</i> (Franch.) Nannf. | 17          | <i>Eucommia ulmoides</i>       | 3           |
| <i>Coix lacryma-jobi</i>                    | 16          | <i>Polygonatum sibiricum</i>   | 3           |
| <i>Pueraria lobata</i> (Willd.) Ohwi        | 14          | <i>L. japonica</i>             | 3           |
| <i>Dioscorea opposita</i>                   | 13          | <i>Galli Gigeriae</i>          | 2           |
| <i>Raphanus sativus</i>                     | 12          | <i>Panax quinquefolius</i>     | 2           |
| <i>Platycodon grandiflorus</i>              | 9           | <i>Dolichos lablab</i>         | 2           |
| <i>Lycium barbarum</i>                      | 7           | <i>Prunus mugus</i>            | 2           |
| <i>Zingiber officinale</i>                  | 7           | <i>Lophatherum gracile</i>     | 1           |
| <i>Amomum villosum</i>                      | 7           | <i>Microcos paniculata</i>     | 1           |
| <i>Allium macrostemon</i>                   | 6           | <i>Polygonatum odoratum</i>    | 1           |
| <i>Morus alba</i> L.                        | 6           |                                |             |

### 2.3 Analysis of the categories and frequencies of food and medicine homology resources between SAMR and literatures

Using Venn diagram, the FMH resources retrieved by the two searches were pooled and analyzed. As shown in Fig. 1, two methods identified 28 common raw materials. The frequencies of occurrence more than 5 times included *C. pinnatifida*, *Poria cocos*, *P. lobata*, *C. tora*, *A. membranaceus*, *N. nucifera*, *L. barbarum*, *M. alba* and *A. sinensis*.

## 3 Functional components for lowering blood lipids in food and medicine homology resources

FMH resources contained a variety of bioactive components



**Figure 1** Intersection plot and histogram of frequencies of FMH resources from SAMR and literature searches. (a) intersection plot of lipid regulating herbs from literature and SAMR searches, (b) Commonly shared FMH resources and their frequencies of use.

with the effects on regulating blood lipids, including triterpenes and their glycosides, flavonoids, alkaloids, polysaccharides, and other components. A total of 53 compounds with bioactivities were obtained from 53 species (Table 3), including 16 triterpenes and their glycosides (30.2%), 11 flavonoids (20.8%), 5 alkaloids (9.4%), 9 coumarins, anthraquinones and other compounds accounted for 17%, and 12 kinds of polysaccharides, accounting for 22.6% (Fig. 2). Moreover, the network diagram among FMH resources and active ingredients showed that one medicinal and edible material generally contains several active ingredients, among which, *P. ginseng*, *C. pinnatifida*, *G. uralensis*, *A. sinensis*, *C. tora*, *M. alba*, etc. contain 3 or more active ingredients with the ability to regulate blood lipids, and the number of active ingredients in *P. ginseng* was the most (Fig. 3).

### 3.1 Triterpenoids and their glycosides

Recently, studies have shown that the hypolipidemic effects of *P. ginseng* and other FMH resources were associated with the triterpenoid saponins. A total of 16 terpenes have been isolated from *P. ginseng*, *P. cocos*, *C. pinnatifida*, *A. membranaceus*, *G. uralensis*, *D. opposita*, *P. grandifloras* and *G. lucidum*, and shown to regulate blood lipids and improve lipid metabolism

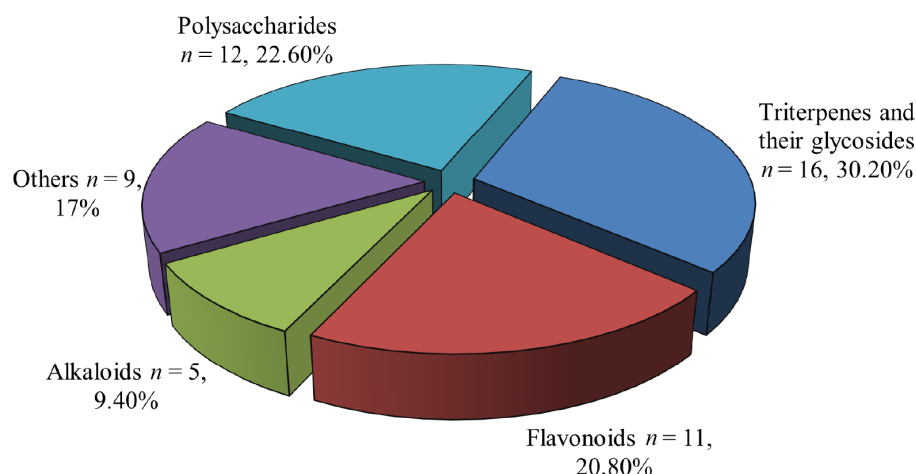
(Fig. 4).

Relevant studies showed that ginsenosides can regulate blood lipids by inhibiting lipogenesis and lipid accumulation, alleviating oxidative stress and inflammation, reducing cholesterol accumulation, increasing energy expenditure, regulating glucose metabolism, and insulin resistance, and modulating the gut microbiota<sup>[12]</sup>. According to their structures, compounds 1-8 could be divided into protopanaxadiol (compounds 1-3) and protopanaxatriol (compounds 4-8). The protopanaxadiols (compounds 1-3) regulated blood lipid levels mainly by inhibiting liver fat formation, reducing liver fat accumulation, and modulating the gut microbiota, while the protopanaxatriols (compounds 4-8) improved blood lipid levels mainly by activating the AMPK pathway, inhibiting adipocyte differentiation, and regulating liver glucose and lipid metabolism<sup>[13]</sup>. Except for *P. ginseng*, *P. quinquefolius* also contains a lot of ginsenoside, such as ginsenoside Rb1, Rg1, Re (compounds 1, 4-5) and so on, and the content of compound 1 was even higher than that of *P. ginseng*, the reason that it was used as a substitute for *P. ginseng*<sup>[14,15]</sup>.

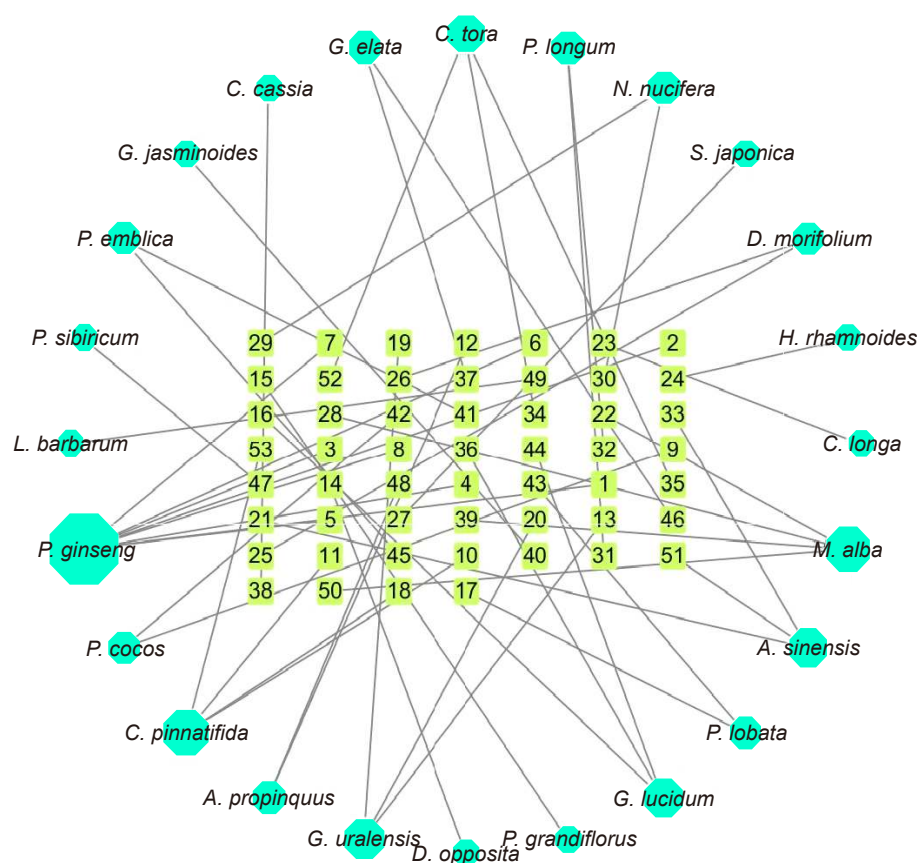
Modern studies have confirmed that the extract species from the fruits, leaves, and flowers of *C. pinnatifida* had a variety of

**Table 3** Name, type and sources of active components in FMH with ability to regulate blood lipids

| Compound No | Names                                       | Types              | Sources                |
|-------------|---------------------------------------------|--------------------|------------------------|
| 1           | Ginsenoside Rb1                             | Triterpenes        | <i>P. ginseng</i>      |
| 2           | Ginsenoside Rg3                             | Triterpenes        | <i>P. ginseng</i>      |
| 3           | Ginsenoside Rc                              | Triterpenes        | <i>P. ginseng</i>      |
| 4           | Ginsenoside Rg1                             | Triterpenes        | <i>P. ginseng</i>      |
| 5           | Ginsenoside Re                              | Triterpenes        | <i>P. ginseng</i>      |
| 6           | Ginsenoside Rh1                             | Triterpenes        | <i>P. ginseng</i>      |
| 7           | Ginsenoside Rg2                             | Triterpenes        | <i>P. ginseng</i>      |
| 8           | 25-OH-PPT                                   | Triterpenes        | <i>P. ginseng</i>      |
| 9           | Pachymic Acid                               | Triterpenes        | <i>P. cocos</i>        |
| 10          | Hawthorn Fruit Acid                         | Triterpenes        | <i>C. pinnatifida</i>  |
| 11          | Ursolic Acid                                | Triterpenes        | <i>C. pinnatifida</i>  |
| 12          | Astragaloside IV                            | Triterpenes        | <i>A. membranaceus</i> |
| 13          | Glycyrrhizic Acid                           | Triterpenes        | <i>G. uralensis</i>    |
| 14          | Protodioscin                                | Triterpenes        | <i>D. opposita</i>     |
| 15          | Platycodin D                                | Triterpenes        | <i>P. grandiflorus</i> |
| 16          | Ganoderic acid A                            | Triterpenes        | <i>G. lucidum</i>      |
| 17          | Puerarin                                    | Flavonoids         | <i>P. lobata</i>       |
| 18          | Vitexin                                     | Flavonoids         | <i>C. pinnatifida</i>  |
| 19          | Isoliquiritigenin                           | Flavonoids         | <i>G. uralensis</i>    |
| 20          | Licochalcone A                              | Flavonoids         | <i>G. uralensis</i>    |
| 21          | 4- hydroxyderricin                          | Flavonoids         | <i>A. sinensis</i>     |
| 22          | Quercetin 3-(6-malonylglucoside)            | Flavonoids         | <i>M. alba</i>         |
| 23          | Curcumin                                    | Flavonoids         | <i>C. longa</i>        |
| 24          | Isorhamnetin                                | Flavonoids         | <i>H. rhamnoides</i>   |
| 25          | luteolin                                    | Flavonoids         | <i>C. morifolium</i>   |
| 26          | Naringenin-7-O-glucoside                    | Flavonoids         | <i>C. morifolium</i>   |
| 27          | Rutin                                       | Flavonoids         | <i>S. japonica</i>     |
| 28          | 1-deoxynojirimycin                          | Alkaloids          | <i>M. alba</i>         |
| 29          | Nuciferine                                  | Alkaloids          | <i>N. nucifera</i>     |
| 30          | Pronuciferine                               | Alkaloids          | <i>N. nucifera</i>     |
| 31          | piperlonguminine                            | Alkaloids          | <i>P. longum</i>       |
| 32          | piperine                                    | Alkaloids          | <i>P. longum</i>       |
| 33          | Decursin                                    | Phenylpropanins    | <i>A. sinensis</i>     |
| 34          | Aurantio-obtusin                            | anthraquinones     | <i>C. obtusifolia</i>  |
| 35          | Chrysophanol                                | anthraquinones     | <i>C. obtusifolia</i>  |
| 36          | Ergosterol Peroxide                         | sterols            | <i>G. lucidum</i>      |
| 37          | Gastrodin                                   | phenolics          | <i>G. elata</i>        |
| 38          | Cinnamaldehyde                              | volatile oil       | <i>C. cassia</i>       |
| 39          | Neochlorogenic Acid                         | Phenylpropanins    | <i>M. alba</i>         |
| 40          | Preventive                                  | Iridoid glycosides | <i>G. jasminoides</i>  |
| 41          | Gallic Acid                                 | polyphenols        | <i>P. emblica</i>      |
| 42          | <i>Poria cocos</i> polysaccharide           | Polysaccharides    | <i>P. cocos</i>        |
| 43          | <i>Pueraria lobata</i> polysaccharide       | Polysaccharides    | <i>P. lobata</i>       |
| 44          | <i>Ganoderma lucidum</i> polysaccharide     | Polysaccharides    | <i>G. lucidum</i>      |
| 45          | <i>Jujube</i> polysaccharides               | Polysaccharides    | <i>Z. jujuba</i>       |
| 46          | <i>Gastrodia elata</i> polysaccharide       | Polysaccharides    | <i>G. elata</i>        |
| 47          | <i>Polygonatum sibiricum</i> polysaccharide | Polysaccharides    | <i>P. sibiricum</i>    |
| 48          | <i>Astragalus</i> polysaccharide            | Polysaccharides    | <i>A. membranaceus</i> |
| 49          | <i>Lycium barbarum</i> polysaccharide       | Polysaccharides    | <i>L. barbarum</i>     |
| 50          | <i>Mulberry leaf</i> polysaccharides        | Polysaccharides    | <i>M. alba</i>         |
| 51          | <i>Angelica sinensis</i> polysaccharide     | Polysaccharides    | <i>A. sinensis</i>     |
| 52          | <i>Cassia seed</i> polysaccharides          | Polysaccharides    | <i>C. obtusifolia</i>  |
| 53          | Hawthorn pectin                             | Polysaccharides    | <i>C. pinnatifida</i>  |



**Figure 2** Structural types of medicinal and FMH resources for lowering blood lipids.



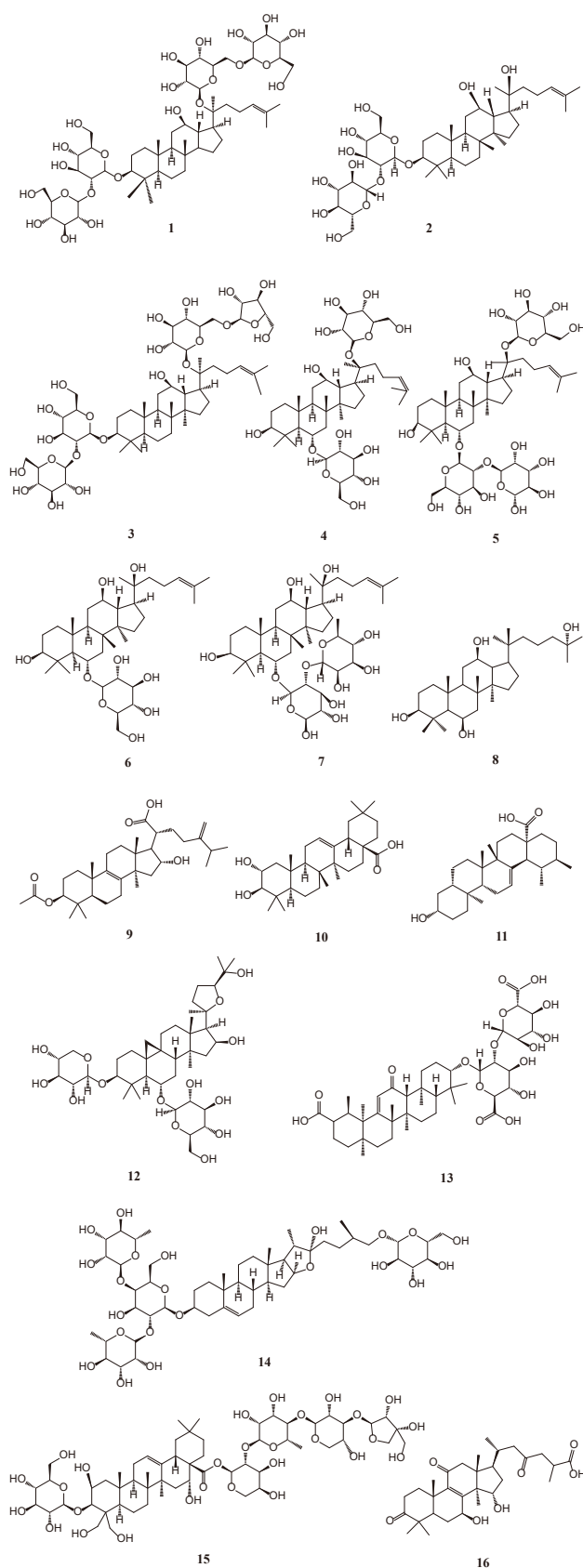
**Figure 3** Network diagram of the effective ingredients of FMH resources for regulating blood lipids. (the octagons for TCM, the squares for the effective ingredients, and the connecting lines for the corresponding effective ingredients of each TCM).

biological and pharmacological activities, including protection against cardiovascular disease, lipid-lowering and antioxidant activities. Compounds **10** and **11** were obtained from *C. pinnatifida* and regulated lipid metabolism by regulating the absorption, synthesis, and metabolism of triglycerides and cholesterol<sup>[16,17]</sup>. Compound **14** from *D. opposita* could ameliorate hypercholesterolemia by improving lipid composition, and reducing oxidative stress<sup>[18]</sup>. Compounds **12**, **13**, **15** and **16** could reduce serum levels of total cholesterol (TC), triglycerides (TG), and LDL cholesterol (LDL-C) to HDL cholesterol (HDL-C) ratio induced by a high-fat diet.

### 3.2 Flavonoids

Flavonoids have various activities, such as anti-inflammatory, analgesic, liver protective, antitumor, antibacterial and antiviral, etc.<sup>[19-21]</sup>. Eleven flavonoids were able to regulate blood lipids have been identified from *P. lobata*, *C. pinnatifida*, *L. barbarum*, *G. uralensis*, *M. alba* and *L. japonica* (Fig. 5).

Compound **17** was isolated and identified from *P. lobata*, which has the effects of promoting blood circulation and removing blood stasis, improving microcirculation, dilating coronary artery and cerebral vessels, and reducing oxygen



**Figure 4** Chemical structural formula of triterpenoids.

consumption of cardiac muscle<sup>[22]</sup>. Studies have shown that compound 17 could enhance the expression of leptin mRNA in white adipose tissue by regulating genes related to lipid and energy

metabolism. It also had antioxidant capacity, and affects the expressions of genes involved in hepatic lipid synthesis and metabolism which helps to maintain lipid homeostasis in mice<sup>[23]</sup>. Studies have also shown that compound 17 protected gut barrier function by regulating the gut microbiota and increasing the number of beneficial bacteria to protect the host from nutritional metabolic disorders and other diseases<sup>[24]</sup>.

Compounds 19 and 20 were identified from *Glycyrrhiza uralensis*. Compound 19 was able to regulate the gut microbiota and gut barrier function-related genes, and then regulate lipid metabolism and energy metabolism disorders. Compound 20 regulated hepatic lipid metabolism by activating the AMPK pathway, reducing hepatic adipogenesis and increasing lipolysis<sup>[25,26]</sup>.

In addition, Compounds 18, 21–27 were respectively from *C. pinnatifida*, *A. sinensis*, *M. alba*, *C. longa*, *H. rhamnoides*, *C. morifolium*, *S. japonica*. Their chemical structures and specific lipid control activities are shown in Table 3 and Fig. 5, respectively.

### 3.3 Alkaloids

Alkaloids were important bioactive constituents of FMH resources (*N. nucifera*, *M. alba*, and *P. longum*), and they had various biological activities, including anti-inflammatory, antibacterial, vasodilator, hypolipidemic, and anticancer<sup>[27]</sup>. Studies have shown that alkaloids can regulate blood lipids by preventing the absorption of cholic acid or cholesterol from the intestinal tract, promoting the excretion of bile acid or cholesterol from feces, and preventing the synthesis of cholesterol and other lipids *in vivo*, or promoting the metabolism of cholesterol and other lipids<sup>[28]</sup>.

*N. nucifera* recorded in *Compendium of Materia Medica* reduces blood lipids and body weight. Alkaloids in *N. nucifera* such as Compounds 29 and 30 were the main effective components that lower blood lipids and body weight in rats with hyperlipidemia<sup>[29]</sup>. Compound 29 could inhibit the proliferation and differentiation of 3T3-L1 preadipocytes and downregulate the mRNA levels of peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), CCAAT enhancer binding protein  $\alpha$  (C/EBP $\alpha$ ) and CCAAT enhancer binding protein  $\beta$  (C/EBP $\beta$ ), fatty acid synthase (FAS), Acetyl-CoA Carboxylase (ACC), hormone-sensitive triglyceride lipase (HSL) and adipose triglyceride lipase (ATGL), resulting in a reduction of lipid accumulation in 3T3-L1 cells. It promoted the expression of adipokines in fully differentiated adipocytes, thereby playing a role in reducing lipid content and lowering blood lipids<sup>[30]</sup>. Other studies have shown that it could prevent obesity in mice fed a high-fat diet by modulating the AMPK-mediated FAS/HSL pathway, attenuating hepatic steatosis, and reducing lipid accumulation in hepatocytes and adipose tissue. It can also modulate the gut microbiota and improve the integrity of the gut barrier, which in turn regulates LPS biosynthesis and lipid metabolism<sup>[31,32]</sup>.

Compound 28 from *M. alba* could increase the differentiation and glucose uptake of HepG2 cells and increase the expression of PPAR $\gamma$ , C/EBP $\alpha$ , and sterol regulatory element-binding protein 1c (SREBP-1c) in 3T3-L1 cells, thereby regulating lipid metabolism<sup>[33]</sup>. In addition to promoting adiponectin production, activating the beta-oxidation system, inhibiting lipid accumulation in the liver, and lowering plasma triglycerides in obese mice, it also restored the structure of the gut microbiota by disrupted by high-fat diets<sup>[34]</sup>. Compounds 31 and 32 isolated from *P. longum* all have lipid-regulating activities (Fig. 6).

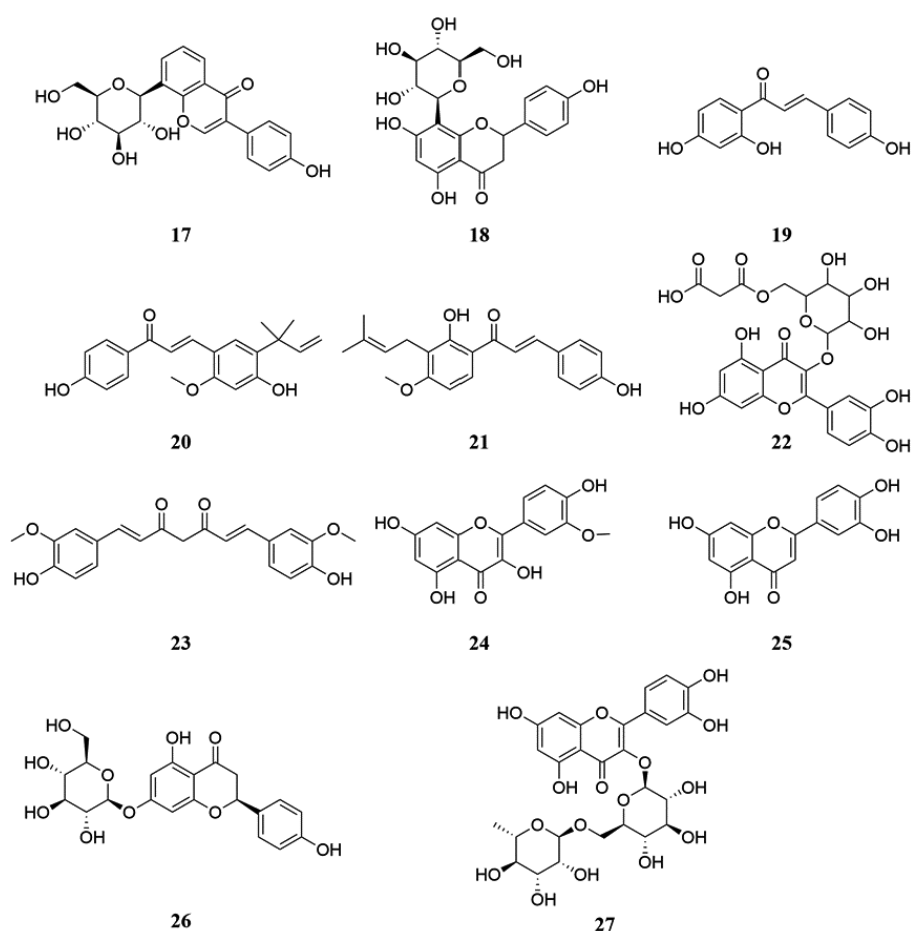


Figure 5 Structures of Compounds 17 to 27 (flavonoids).

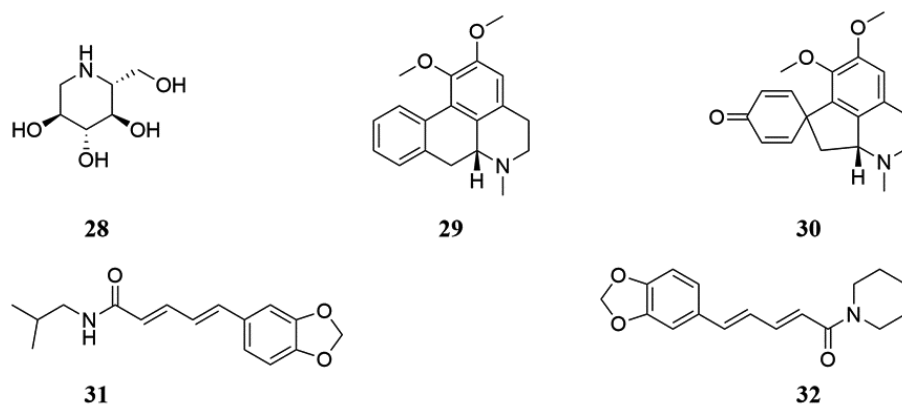


Figure 6 Structures of compounds 28 to 32 (alkaloids).

### 3.4 Others

Other components with blood lipid regulating effects included quinones and phenylpropanoids (Fig. 7). Compound 33 isolated from *A. sinensis* can inhibit adipocyte differentiation and fatty acid synthase expression. It significantly reduced the weight, blood lipid content, and adipocyte size of mice. It also decreased the secretion of adipokines such as leptin, induced by a high-fat diet, and thus played a role in regulating glucose and lipid metabolism<sup>[35]</sup>.

In addition, the seed of *C. tora* contained a significant amount of anthraquinones, among of which compounds 34 and 35 played an important role in the regulation of blood lipids. Compound 34

decreased the expressions of lipogenic genes such as *SREBP-1c*, *FAS*, and stearoyl-Coenzyme A desaturase 1 (*SCD-1*), which leads to inhibition of lipogenesis. It also increased the expressions of *PPAR $\gamma$* , peroxisome proliferators-activated receptor  $\alpha$  (*PPAR $\alpha$* ), carnitine palmitoyl transferase 1 (*CPT-1*), and adiponectin in white adipose tissue, and promotes lipolysis, glucose uptake and insulin sensitivity via the insulin signaling pathway<sup>[36]</sup>. Compound 35 could inhibit the upregulation of *PPAR $\gamma$*  and *FAS*, which in turn inhibits adipocyte differentiation while playing an important role in inhibiting lipid synthesis<sup>[37]</sup>.

Compound 36 from *G. lucidum*, 37 from *G. elata*, 38 from *C. cassia*, 39 from *M. alba* 40 from *G. jasminoides* and 41 from *P. emblica* all could improve blood lipids.

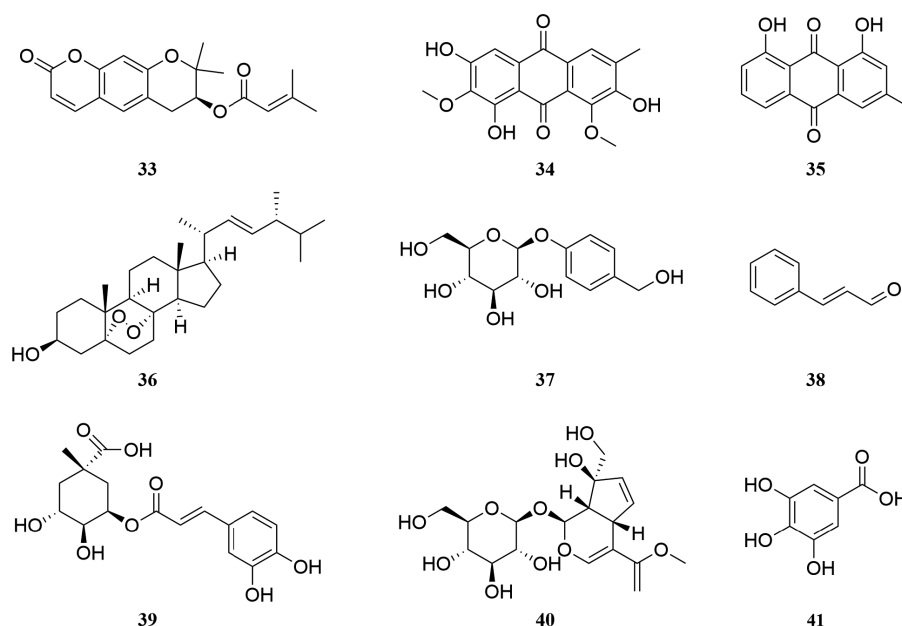


Figure 7 Structures of compounds 33 to 41 in other classes.

### 3.5 Polysaccharides

Polysaccharide is a natural biological macromolecule with a wide range of biological activities such as immunomodulatory, antitumor, antiviral, antioxidant, hypoglycemic, and hypolipidemic. Polysaccharides could regulate glucose and lipid metabolism by protecting islet cells, improving insulin sensitivity, regulating intestinal flora, increasing antioxidant capacity, and regulating the activity of key enzymes for glucose and lipid metabolism<sup>[38, 39]</sup>.

Polysaccharides, as the main active ingredients of *P. cocos*, have been studied extensively. *Poria cocos* polysaccharides reduced inflammation and lipids in mice fed a high-fat diet<sup>[33, 40]</sup>. In addition, *Poria cocos* polysaccharides reversed the gut microbiota and its metabolites, including bile acids, short-chain fatty acids

and tryptophan metabolites in those mice fed a high-fat diet, revealing the potential applications in treating lipid abnormalities.

*In vitro* studies have shown that *Ganoderma lucidum* polysaccharide can downregulate genes encoding transcription factors of adipocyte differentiation (PPAR $\gamma$ , C/EBP $\alpha$ , and SREBP-1c) and lipogenesis (ACC1, PLIN1, and FASN), upregulate the lipolysis gene *HSL*, stimulate AMPK phosphorylation, and thus lower blood lipids. Experimental *in vivo* studies have shown that *Ganoderma lucidum* polysaccharides could inhibit weight gain of mice fed a high-fat diet, improve lesions of liver, heart and white adipose tissue, and reduce the accumulation of blood lipids<sup>[41]</sup>. In addition, polysaccharide from *P. lobata*, *A. membranaceus*, *M. alba*, *A. sinensis*, and *P. sibiricum* also improved blood lipids as shown in Table 4.

Table 4 Mechanism of action of lipid-lowering active ingredients of FMH resources

| Compound No | Experimental model                     | Dosage                     | Efficacy                                        | Potential mechanism                                                                                                                 | Ref.  |
|-------------|----------------------------------------|----------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-------|
| 1           | db/db obese mice                       | 20 mg/kg                   | Reduced ectopic TG accumulation                 | Reduced hepatic fat accumulation and inhibits lipolysis of adipocytes                                                               | [49]  |
|             | Obesity mice                           | 200 mg/kg                  | Reduced TG, LDL-c and free fatty acid           | Improved intestinal flora and amino acid metabolism                                                                                 | [106] |
| 2           | Obesity mice                           | 10 mg/kg                   | Decreased HDL-c and increased TC, TG, and LDL-c | Enhanced lipid oxidation and glycolysis by modulating PPAR $\gamma$ , PGC-1 $\alpha$ , PRDM16 and UCP-1 mRNA and protein expression | [92]  |
| 3           | Apolipoprotein E-deficient (ApoE) mice | 40 mg/kg                   | Reduced TC, TG, LDL-C and increased HDL-C       | Regulation of gut microbiota and faecal metabolites                                                                                 | [109] |
|             | 3T3-L1 cell line                       | 25, 50 and 100 $\mu$ mol/L | Reduced TG                                      | Inhibited fat formation reduces lipid accumulation                                                                                  | [88]  |
| 4           | Type 2 diabetes                        | 25, 100 mg/kg              | Increased HDL-c and reduced TC, TG, and LDL-c   | Improved intestinal flora and regulated glucose and lipid metabolism                                                                | [108] |
| 5           | HepG2 Cells、 High-fat diet fed mice    | 5, 10, 20 mg/kg            | Reduced TG                                      | Activated AMPK to improve hyperlipidaemia                                                                                           | [47]  |
|             | 3T3-L1 Cells and High-fat diet rats    | 40 mg/kg                   | Reduction of fat storage of both visceral       | Inhibition of JNK and NF- $\kappa$ B activation                                                                                     | [80]  |
| 6           | Obesity mice                           | 20 $\mu$ g/ kg             | Reduced TG                                      | Inhibited adipocyte differentiation and inflammation                                                                                | [85]  |
| 7           | High-fat diet rats                     | 10 mg/kg                   | Reduced TG and FFA                              | Induction of AMPK activation and reduction of lipogenic transcription factor expression                                             | [50]  |
| 8           | db/db mice                             | 40 mg/kg                   | Reduced TG and TC                               | Upregulation of GLUT4 and AMPK activates the insulin signalling pathway.                                                            | [116] |
| 9           | 3T3-L1 Cells                           | 1 $\mu$ mol/L              | Increased TG                                    | Stimulation of glucose uptake, GLUT4 gene expression and translocation and promotion of TG accumulation in adipocytes               | [117] |

(Continued)

| Compound No | Experimental model                          | Dosage                 | Efficacy                                        | Potential mechanism                                                                                                               | Ref.  |
|-------------|---------------------------------------------|------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|-------|
|             | Oocytes                                     | 5, 25, and 75 mmol/L   | Reduced TG and TC                               | Inhibition of transport proteins in the enterohepatic circulation of bile acids                                                   | [118] |
| 10          | Hyperlipidemia rats                         | 30, 100 mg/kg          | Reduced TG and TC                               | Activation of the Nrf2/HO-1 signalling pathway                                                                                    | [68]  |
| 11          | Hyperlipidemia rats                         | 50 mg/kg               | Increased HDL-c and Reduced TC, TG, and LDL-c   | Activation of AMPK signalling pathway to reduce lipid accumulation                                                                | [120] |
| 12          | Hyperlipidemia mice                         | 50, 100 mg/kg          | Reduced FFA                                     | Inhibition of lipolysis by reducing the regulation of cAMP accumulation by Akt/PDE3B                                              | [48]  |
| 13          | T2DM diabetic mouse                         | 60, 120, 180 mg/kg     | Increased HDL-c and Reduced TC, TG, and LDL-c   | Regulated blood lipids                                                                                                            | [119] |
|             | THP-1 macrophages                           | 100 µmol/L             | Increased HDL-c and reduced TG, and LDL-c       | Regulated blood lipids                                                                                                            | [121] |
| 14          | Hyperlipidemia rats                         | 0.5% (w/w)             | Increased HDL-c and reduced TC, TG, and LDL-c   | Activation of cellular catabolic pathways via AMPK                                                                                | [122] |
|             | Hyperlipidemia rats and HepG2 cells         | 0.5, 1, 2 mg/kg        | Reduced TC, TG                                  | Regulation of hepatic lipogenesis via AMPK-dependent signaling pathways                                                           | [51]  |
| 15          | Apolipoprotein E-deficient (apoE(-/-)) mice | 1% (w/w)               | Reduced TC, TG                                  | Anti-cholesterol effect by improving LDLR expression and LDL-C uptake                                                             | [69]  |
|             | Hyperlipidemia mice                         | 15, 75mg/kg            | Increased HDL-c and Reduced TC, TG, and LDL-c   | Regulated hepatic fatty acid metabolism and bile acid homeostasis, improving intestinal flora imbalance                           | [123] |
| 16          | Non-alcoholic fatty liver disease in rats   | 20, 40 mg/kg           | Increased HDL-c and reduced TC, TG              | Regulation of free fatty acid production, lipid oxidation and liver inflammation                                                  | [124] |
|             | HepG2 cells                                 | 25, 50, 100 µmol/L     | Reduced TC, TG                                  | Increased expression of p-AMPK and PPARα, decreased lipid synthesis, and increased fatty acid oxidation                           | [58]  |
| 17          | Hyperlipidemia mice                         | 200, 400 mg/kg         | Increased HDL-c and reduced TC, TG, and LDL-c   | Modulated JNK/c-Jun and CYP7A1 pathways                                                                                           | [79]  |
|             | Obesity mice                                | 100 mg/kg              | Reduce weight                                   | Regulating intestinal flora                                                                                                       | [105] |
| 18          | High-fat diet mice                          | 40 mg/kg               | Reduce hepatic fat deposition                   | Reduced hepatic lipid synthesis, increased lipid breakdown inhibit TLR4/NF-κB signaling, and reduce fatty acid synthesis proteins | [125] |
| 19          | Obesity mice                                | 0.02% (w/w)            | Reduced TC, LDL-C                               | Regulated genes involved in gut microbiota and gut barrier function                                                               | [115] |
| 20          | Obesity mice                                | 5, 10 mg/kg            | Increased HDL-c and Reduced TC, TG, and LDL-c   | Activated SIRT-1/AMPK pathway                                                                                                     | [61]  |
| 21          | 3T3-L1                                      | 1, 5, 10, and 30 µM    | Suppressed lipid accumulation                   | Inhibition of preadipocyte differentiation into adipocytes via AMPK and MAPK pathways                                             | [95]  |
|             | LDL receptor-deficient (LDLR-/-) mice       | 0.5 g mg/kg            | Reduced TC                                      | By enhancing LDL resistance to oxidative modifications                                                                            | [126] |
| 22          | Hyperlipidemia mice                         | 0.05 or 0.1% (w/w)     | Increased HDL-c and reduced TC, and LDL-c       | Regulated hepatic and pancreatic secretion of PCSK9 and LDLR                                                                      | [127] |
|             | Apolipoprotein E-deficient (apoE(-/-)) mice | 0.1% (w/w)             | Increased HDL-c and reduced TC, and LDL-c       | Inhibition of cholesterol absorption in the gut                                                                                   | [71]  |
| 23          | High-fat diet hamsters                      | 0.05% (w/w)            | Reduced TC, TG, and LDL-c                       | Inhibition of cholesterol absorption <i>in vivo</i> by inhibition of SREBP-2                                                      | [72]  |
|             | HepG2 cells                                 | 5, 15 or 25 µmol/L     | Increases LDL-R protein expression              | Increased LDL-R expression and decreased cholesterol content via the SREBPs pathway                                               | [73]  |
|             | Apolipoprotein E-deficient (apoE(-/-)) mice | 20 mg/kg               | Reduce the sizes of the atherosclerotic lesions | Activation of PI3K/AKT and induction of HO-1                                                                                      | [128] |
| 24          | C. elegans strains                          | 100 and 200 µmol/L     | Reduced fat accumulation                        | Increased fat oxidation via NHR-49/PPARα-dependent pathway activates AMPK                                                         | [129] |
| 25          | Hyperlipidemia rats                         | 100 mg/kg              | Reduced TC, TG                                  | Regulation of fatty acid, cholesterol and triglyceride metabolism in the liver                                                    | [55]  |
| 26          | 3T3-L1 cells                                | 100 µmol/L             | Down-regulated the diameter of 3T3-L1 cells     | Regulated lipid accumulation and adiponectin secretion by activating phosphorylation of PPARγ as well as the PI3K/Akt pathway     | [93]  |
|             | Hyperglycemic and Hyperlipidemic rats       | 95, 125 and 155 mg/kg  | Increased HDL-c and reduced TC, TG, and LDL-c   | Reduced blood lipids, improved antioxidant activity, and induced repair of damaged islet cells                                    | [130] |
|             | db/db mice                                  | 100 mg/kg              | Reduced TC, TG, and FFA                         | Increased SCFA concentration activates adipose tissue heating                                                                     | [131] |
|             | ApoE mice                                   | 100, 200 and 400 mg/kg | Reduced TC, TG, and LDL-c                       | Regulated lipid metabolism-related genes and insulin signaling                                                                    | [33]  |
| 28          | T2DM mice                                   | 100, 200 mg/kg         | Reduced TC, TG                                  | Increased glucose uptake and promotion of differentiation via AGEs/RAGE and p38 MAPK/NF-κB pathways                               | [94]  |
|             | High-fat diet mice                          | 2 mg/kg                | Increased HDL-c and reduced TC, and LDL-c       | Regulated gut microbiota                                                                                                          | [107] |
|             | Obesity mice                                | 10 and 40 mg/kg        | Increased HDL-c and reduced TC, TG, and LDL-c   | Inhibition of lipid accumulation by modulation of AMPK-mediated FAS/HSL pathway                                                   | [30]  |
| 29          | 3T3-L1 cells                                | 2.5 µmol/L             | Reduced TG                                      | Inhibited lipogenic enzyme expression, inhibits fat synthesis                                                                     | [31]  |
|             | High-fat diet rats                          | 10 mg/kg               | Reduced TC, TG, and LDL-c                       | Regulated intestinal flora                                                                                                        | [110] |

(Continued)

| Compound No | Experimental model                        | Dosage              | Efficacy                                      | Potential mechanism                                                                                            | Ref.  |
|-------------|-------------------------------------------|---------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------|-------|
| 30          | 3T3-L1 cells                              | 1 or 2 mg/L         | reduced TG                                    | Activated AMPK signaling                                                                                       | [45]  |
| 31          | HepG2 cells                               | 2 $\mu$ mol/L       | Increased HDL-c and reduced TC, TG, and LDL-c | Activated AMPK signaling                                                                                       | [46]  |
| 32          | HepG2 Cells                               | 50, 75 $\mu$ mol/L  | Reduced TC, TG, and LDL-c                     | Activated SREBP-1c/PPAR $\gamma$ and AMPK/AKT-mTOR signaling pathways                                          | [96]  |
| 33          | Human Visceral Adipose-Derived Stem Cells | 5, 10 mg/kg         | Reduced TG                                    | Inhibition of adipocytokine production                                                                         | [35]  |
| 34          | Obesity mice                              | 5, 10 mg/kg         | Reduced TC, TG                                | Regulates the activity of genes involved in lipid metabolism and activated the PI3K/Akt/GLUT4 pathway          | [57]  |
| 35          | Human sebocytes                           | 0-100 $\mu$ mol/L   | Reduced fat accumulation                      | Inhibition of JNK/p38 MAPK signaling                                                                           | [81]  |
| 36          | 3T3-L1 cells                              | 20 $\mu$ mol/L      | Reduced the accumulation of lipid droplets    | Regulated AMPK signaling pathway, SREBP-1c expression, and inhibits adipocyte differentiation                  | [54]  |
| 37          | High-fat diet rats                        | 10, 20, 50 mg/kg    | Reduced TG                                    | Activated the pathway of AMPK/Nrf2 and improved oxidative stress/inflammatory response                         | [135] |
| 37          | High-fat diet mice                        | 20 mg/kg            | Reduced TG                                    | Activated AMPK pathway attenuates hepatic inflammation and lipid accumulation                                  | [136] |
| 38          | ApoE mice                                 | 5, 10, 20 mg/kg     | Increased HDL-c and reduced TC, TG, and LDL-c | Reduced energy efficiency and insulin resistance reduces lipid synthesis                                       | [137] |
| 39          | HepG2 cells                               | 120 $\mu$ mol/L     | Regulated the expression of related genes     | Activated SIRT1/AMPK pathway                                                                                   | [63]  |
| 40          | TSOD mice                                 | 50 mg/kg            | Increased HDL-c and reduced TC, TG            | Induced hepatic lipid metabolism-related gene expression                                                       | [52]  |
| 40          | High-fat diet mice                        | 20 mg/kg            | Reduced TC, TG                                | Regulating the miR-142a-5p/SREBP-1c axis to antagonize hyperlipidemia and hepatic lipid metabolism             | [53]  |
| 41          | Hyperlipidemia Rats                       | 25, 50, 100 mg/kg   | Increased HDL-c and reduced TC, TG, and LDL-c | Decreased expression of lipogenic enzymes                                                                      | [56]  |
| 42          | High-fat diet mice                        | 200 mg/kg           | Reduced population of very large adipocytes   | Regulation of gut microbiota and gut metabolites                                                               | [112] |
| 42          | ob/ob mice                                | 0.5, 1 mg/kg        | Reduced TC, TG, and LDL-c                     | Regulated gut microbiota                                                                                       | [113] |
| 42          | Hyperlipidemic rats                       | 50 mg/kg            | Reduced TC, TG, and LDL-c                     | Regulation of bile acid metabolism via the FXR pathway                                                         | [76]  |
| 43          | Diabetic db/db mice                       | 100, 200 mg/kg      | Increased HDL-c and reduced TC, TG, and LDL-c | Activated PI3K/AKT signaling                                                                                   | [99]  |
| 43          | NAFLD mice                                | 400 mg/kg           | Increased HDL-c and reduced TC, TG, and LDL-c | Regulated gut microbiota                                                                                       | [114] |
| 44          | 3T3-L1 cells                              | 50-800 $\mu$ g/mL   | Reduced TG                                    | Regulation of lipid metabolism through modulation of AMPK pathway and expression of adipogenic genes           | [86]  |
| 45          | Dyslipidemia in mice                      | 200 or 400 mg/kg    | Increased HDL-c and reduced TC, TG, and LDL-c | Improved insulin resistance and $\beta$ -cell function                                                         | [132] |
| 46          | High-fat diet rats                        | 90 mg/kg            | Reduced TC, and LDL-c                         | Reduced de novo synthesis of total cholesterol and LDL-R levels                                                | [133] |
| 47          | Hyperlipidemic mice                       | 200, 400, 800 mg/kg | Reduced TC, TG, and LDL-c                     | Regulated expression levels of lipid metabolism-related genes and proteins                                     | [59]  |
| 47          | High-fat diet rats                        | 120, 240 mg/kg      | Increased HDL-c and reduced TG, and LDL-c     | Regulation of gut microbiota and SCFAs                                                                         | [111] |
| 48          | Hypercholesterolemia hamsters             | 250 mg/kg           | Reduced TC, TG, and LDL-c                     | Regulation of cholesterol metabolism and LDLR gene expression                                                  | [74]  |
| 49          | HepG2 cells                               | 600 $\mu$ mol/L     | Increase antioxidant capacity                 | Activated PI3K/AKT/Nrf2 pathway                                                                                | [100] |
| 49          | 3T3-L1 cells                              | 200 $\mu$ mol/L     | Inhibit 3T3-L1 preadipocyte proliferation     | Inhibition of adipocyte differentiation factor PPAR $\gamma$                                                   | [87]  |
| 50          | High-fat diet mice                        | 200, 400, 800 mg/kg | Increased HDL-c and reduced TC, TG, and LDL-c | Inhibition of lipid absorption and expression of pancreatic digestive enzymes in digestive tract               | [134] |
| 51          | High-fat diet-fed mice                    | 80, 160, 320 mg/kg  | Reduced TC, TG                                | Improved glucose and lipid metabolism by regulating relevant metabolic enzymes and activating PI3K/Akt pathway | [60]  |
| 52          | Hyperlipidemic rats                       | 5% (w/w)            | Increased HDL-c and reduced TC, TG            | Facilitated fecal lipid excretion to regulate lipid metabolism                                                 | [78]  |
| 53          | Hypercholesterolemic hamsters             | 300 mg/kg           | Reduced TC                                    | Regulation of fecal bile acid levels improves cholesterol metabolism                                           | [77]  |

#### 4 Mechanisms by which food and medicine homology resources regulate lipids

Abnormal lipid metabolism is the most important factor in the pathogenesis of hyperlipidemia, involving the abnormal metabolism of cholesterol, fatty acids, and triglycerides, as well as abnormal cholesterol transport proteins. Abnormalities in other

physiological and metabolic pathways, such as inflammatory and immune responses, endothelial cell dysfunction, oxidative stress, and disorders in the antioxidant system, can also lead to hyperlipidemia. Therefore, regulating fatty acid and cholesterol synthesis and metabolism, as well as lipid storage and consumption, are key strategies for treating hyperlipidemia.

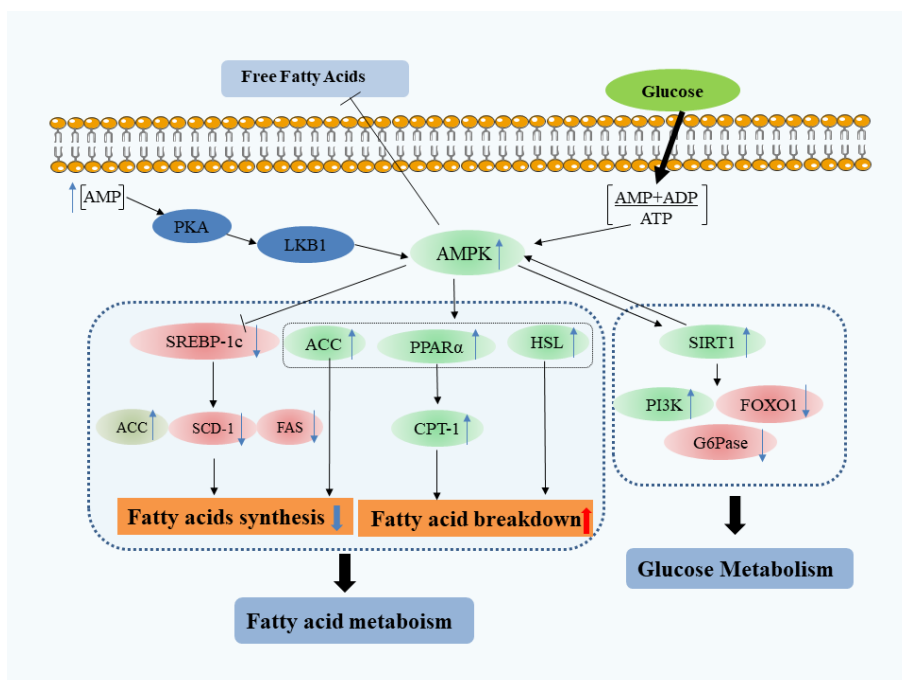
#### 4.1 Activation of AMPK signaling pathway

An important role of AMPK signaling pathway is to control body metabolism by stimulating energy production including glucose and lipid catabolism, or by inhibiting energy-consuming pathways such as protein, fatty acid, and cholesterol synthesis (Fig. 8)<sup>[42,43]</sup>. The key role of AMPK is to promote ATP production needed for physiological activities. In the presence of energy deficiency, AMPK could be activated. This leads to further phosphorylation of downstream signaling molecules, regulating the metabolism of sugar, fat and cholesterol<sup>[44]</sup>. It has been found that the active ingredients of FMH resources such as *P. grandiflorus*, *P. ginseng*, *A. membranaceus*, *G. jasminoides*, *P. emblica*, *D. morifolium*, *P. longum*, *N. nucifera*, *G. lucidum*, *C. obtusifolia*, *A. sinensis*, *G. uralensis*, and *M. alba* have significant therapeutic effects on dyslipidemia through the activation of AMPK. Compound **30** increased Glucose transporter type 4 (GLUT4) expression by promoting AMPK phosphorylation, stimulating glucose uptake, and reducing lipid accumulation, thereby regulating glucose and lipid metabolism<sup>[45]</sup>. Acting as a potent activator of AMPK, Compound **31** could regulate fatty acid biosynthesis and oxidation in the body<sup>[46]</sup>.

AMPK could be activated in several ways. Under the metabolic stresses (e.g., starvation, hypoxia, cold), intracellular ratios of ADP to ATP, and AMP to ATP increase, leading to the activation of AMPK. Firstly, the binding of AMPK with AMP makes AMPK a substrate for its upstream kinases, such as liver kinase B1 (LKB1), which phosphorylates the AMPK- $\alpha$  subunit at Thr172 to activate it. Compound **5** activated AMPK through this way, which inactivates lipogenic enzymes<sup>[47]</sup>. Alternatively, AMP could directly interact with and activate AMPK. Compound **12** has been found to reduce cAMP accumulation in adipose tissue, increase AMP content, inhibit adenylate cyclase activity in adipocytes, and reduce cellular energy charge (increased ratio of AMP and ATP)<sup>[48]</sup>.

Compound **1** accelerated fatty acid oxidation and inhibit adipogenesis-related genes encoding enzymes and proteins by increasing the AMPK-regulated cellular AMP/ATP ratio<sup>[49]</sup>. Pretreatment with compound **7** induced LKB1 phosphorylation, which promotes AMPK and glycogen synthase kinase 3 beta (GSK3 $\beta$ ) phosphorylation, increases small heterodimer partner (SHP) expression, and ultimately inhibits CREB-mediated gluconeogenesis<sup>[50]</sup>.

Activated AMPK is an important regulator of cellular responses to low-energy conditions, and it could orchestrate changes in the activities of enzymes in lipid metabolism, which in turn regulates fatty acid synthesis and metabolism. This is associated with reductions of FAS, SCD1 and SREBP-1c. Many compounds from FMH resources worked like this. Compound **15** activated AMPK and reduced ACC and SREBP-1c, which in turn regulates hepatic lipogenesis<sup>[51]</sup>. Compounds **36** and **40** as well as *Ganoderma lucidum* polysaccharides could regulate hepatic lipogenic gene expression via the AMPK/SREBP-1c pathway and reduce hepatic lipid accumulation, which in turn plays a role in regulating blood lipids and hepatic lipid metabolism<sup>[52-55]</sup>. AMPK is necessary for the phosphorylation of SREBP-1c at Ser372 to inhibit the proteolytic process and transcriptional activity of SREBP-1c, which acts as a master transcription factor for lipogenesis and simultaneously inactivates its transcriptional activity, leading to the repression of adipogenic related genes and thus reduced lipid deposition. In addition, AMPK activation also regulated HSL and adipose triglyceride lipase (ATGL), which are related to the lipolytic process, as well as the fatty acid oxidation-related transcription factor PPAR $\alpha$  and its downstream *CPT1* mRNA level. Compound **29** reduced lipid accumulation in adipocytes by promoting AMPK phosphorylation, inhibiting lipogenesis (SREBP-1c, FAS, ACC), promoting lipolysis (HSL, ATGL), and reducing steatosis<sup>[30]</sup>. Compounds **17**, **34**, **41** and **47** acted similarly



**Figure 8** Mechanism of AMPK signaling pathway regulation by active ingredients of FMH resources. Colors indicate the regulatory effects on downstream signaling molecules when AMPK is activated, with downregulation in red and upregulation in green. Protein Kinase A (PKA), Liver kinase B1 (LKB1), Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), sterol regulatory element-binding protein 1c (SREBP-1c), Acetyl-CoA Carboxylase (ACC), stearoyl-Coenzyme A desaturase 1 (SCD-1), fatty acid synthase (FAS), peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), hormone-sensitive triglyceride lipase (HSL), carnitine palmitoyl transferase 1 (CPT-1), silent Information Regulator 1 (SIRT1), forkhead box O1 (FOXO1), glucose-6-phosphatase G-6-pase (G6Pase).

and regulated blood lipids<sup>[56-59]</sup>.

The AMPK/SIRT1 pathway also regulate glucose and lipid metabolism. Silent Information Regulator 1 (SIRT1) mediate the expression levels of mitochondrial metabolic genes and lipid metabolism and O<sub>2</sub> consumption. SIRT1 and AMPK regulate each other and share many common target molecules. Disruptions in AMPK/SIRT1 signaling pathway could lead to decreased antioxidant activity, accelerated oxidative stress imbalance, and subsequent apoptosis of pancreatic  $\beta$ -cells, which in turn causes disorders of lipid metabolism. The *Angelica sinensis* polysaccharide, compounds **20**, **28** and **32** could alleviate disorders of blood and hepatic lipid metabolism via the AMPK/SIRT1 pathway. Specifically, *Angelica sinensis* polysaccharide activates lipocalin-SIRT1-AMPK pathway and regulates glucokinase (GK), glucose-6-phosphatase G-6-pase (G6Pase), protein kinases (PK), and hexokinase (HK), key liver enzymes for glycolysis and gluconeogenesis, which resulted in an improvement of glucose metabolism in mice fed a high-fat diet<sup>[60]</sup>. Compound **28** activated the lipocalin-SIRT1-AMPK pathway and regulates the expressions of Foxo1 and SIRT1, two important regulators of lipocalin secretion in adipose tissues. The expressions of peroxisome proliferator-activated receptor  $\gamma$  coactivator 1- $\alpha$  (PGC-1 $\alpha$ ), PEPCK and G6Pase, are significantly reduced<sup>[33]</sup>. Compound **20** could promote ATGL expression in lipolysis by inhibiting forkhead box O1 (FOXO1) phosphorylation through activation of the AMPK/SIRT1 pathway, and it could attenuate oxidative stress injury by promoting the SIRT1/Nrf2 pathway in rat primary cortical neurons<sup>[61]</sup>. Compounds **7** and **39** could also regulate lipid accumulation *in vivo* and enhance antioxidant capacity by activating the AMPK/SIRT1 pathway<sup>[62,63]</sup>.

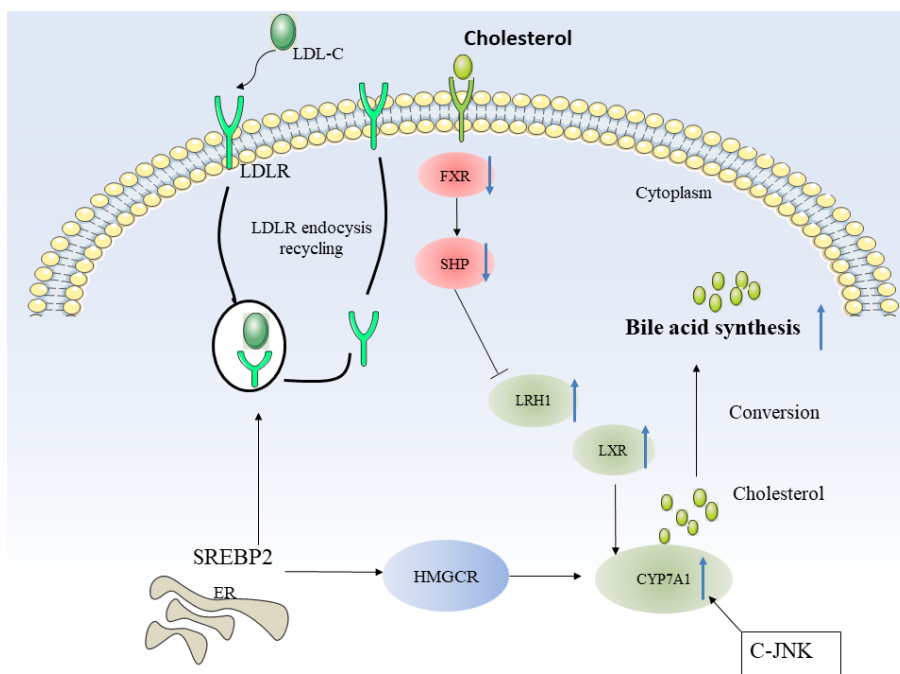
In addition, the AMPK pathway frequently interacts with multiple signaling pathways such as autophagy, apoptosis, and inflammation-related signaling pathways. In lipid metabolism, the roles of apoptosis and autophagy in atherosclerosis has been

largely elucidated by activating the SIRT1-AMPK pathway, which restores autophagy and thereby inhibits hepatic lipid accumulation<sup>[64]</sup>. Compound **1** could restore autophagy and thus inhibit hepatic lipid accumulation by activating the AMPK/SIRT1 pathway.

## 4.2 Regulation of cholesterol metabolism signaling pathways

SREBPs regulate intracellular lipid synthesis and have three main members: SREBP-1a, SREBP-1c, and SREBP-2, of which SREBP-1a and SREBP-1c mainly regulate the expression of FAS, and glucose metabolism-related enzyme genes, and SREBP-2 mainly regulates cholesterol metabolism<sup>[65,66]</sup> (Fig. 9). SREBP-2 can regulate low-density lipoprotein (LDL) receptor (LDL-R), HMG-CoA synthase, HMG-CoA reductase and other genes, thus controlling cholesterol uptake and cholesterol synthesis<sup>[67]</sup>. The FMH resources *M. alba*, *C. longa*, *D. morifolium*, *P. ginseng*, *G. jasminoides*, *A. membranaceus*, *P. lobata*, *C. tora*, *P. grandiflorus* and *P. longum* could regulate cholesterol levels in the body by expressing this pathway and its associated enzymes.

Many compounds identified from FMH resources have been shown to regulate LDLR. Compound **10** was found to regulate cholesterol metabolism by upregulating LDLR expression and downregulating HMGCR expression<sup>[68]</sup>. Compound **15** induced LDLR expression and LDL-C particle uptake by inhibiting LXR-dependent IDOL gene expression, whose effects have a synergistic effect with statins<sup>[69]</sup>. Gene expression and activity of cholesterol 7  $\alpha$ -hydroxylase (CYP7A1), the rate-limiting enzyme of the classical pathway of bile acid synthesis, influence the metabolism of cholesterol. SREBP-2 controls the transcription of a variety of proteins involved in the cholesterol metabolism, including the rate-limiting enzyme for cholesterol synthesis HMGCR, which in turn can inhibit the expression of CYP7A1, resulting in abnormal



**Figure 9** Cholesterol metabolism pathway regulation by active ingredients of FMH resources. FMH resources inhibit the activation of SREBP-2, which induces HMGCR expression to synthesize cholesterol in the liver. FMH resources also induce CYP7A1 expression to increase the conversion of cholesterol to bile acid. low-density lipoprotein (LDL) receptor (LDL-R), Farnesoid X receptor (FXR), liver X receptors (LXR), Sterol regulatory element binding protein-2 (SREBP2), HMG-CoA reductase (HMGCR), Small Heterodimer Partner (SHP), cholesterol 7  $\alpha$ -hydroxylase (CYP7A1), c-Jun N-terminal kinase (c-JNK).

cholesterol degradation<sup>[70]</sup>. Compound **23** regulated hepatic LDLR, HMG-CoA reductase, and CYP7A1, and several studies have shown that compound **23** upregulated LDLR expression and increased LDLR uptake, resulting in increased excretion of cholesterol from the body. In addition, compound **23** inhibited HMG-CoA reductase and hepatic cholesterol biosynthesis. Its hypocholesterolemic function may also be attributed to an increase in CYP7A1 activity in the liver, leading to increased cholesterol excretion and consequently lower cholesterol levels<sup>[71-73]</sup>. Astragalus polysaccharides inhibit cholesterol absorption by upregulating hepatic LDL-R and CYP7A1 gene expression, and increases faecal bile acid excretion, thereby lowering plasma cholesterol levels<sup>[74]</sup>.

Farnesoid X receptor (FXR) and liver X receptors (LXR) are upstream transcriptional repressors and transcriptional activators of CYP7A1, respectively. FXR induces the expression of SHP, which in turn inhibits the expression of liver receptor homolog-1 (LRH-1), prevents LXR from inducing CYP7A1, and reduces the conversion of cholesterol to bile acids. Compound **40** inactivated FXR-mediated negative feedback regulation of bile acids via this pathway, accelerated bile acid synthesis in the liver, enhanced reverse cholesterol transport and cholesterol catabolism, and reduced FXR-mediated reabsorption of bile acids in the ileum, resulting in increased bile acid excretion<sup>[75]</sup>. Pueraria lobata polysaccharides, hawthorn polysaccharides, and cassia polysaccharides could regulate faecal bile acid levels via this pathway<sup>[76-78]</sup>. In addition to the FXR/SHP approach, bile acids could also inhibit CYP7A1 gene expression through their effects on the c-Jun N-terminal kinase (c-JNK) pathway. Compounds **5**, **17** and **35** were responsible for enhancing bile acid metabolism similarly<sup>[79-81]</sup>.

### 4.3 Modulation of PPAR $\gamma$ signaling pathway

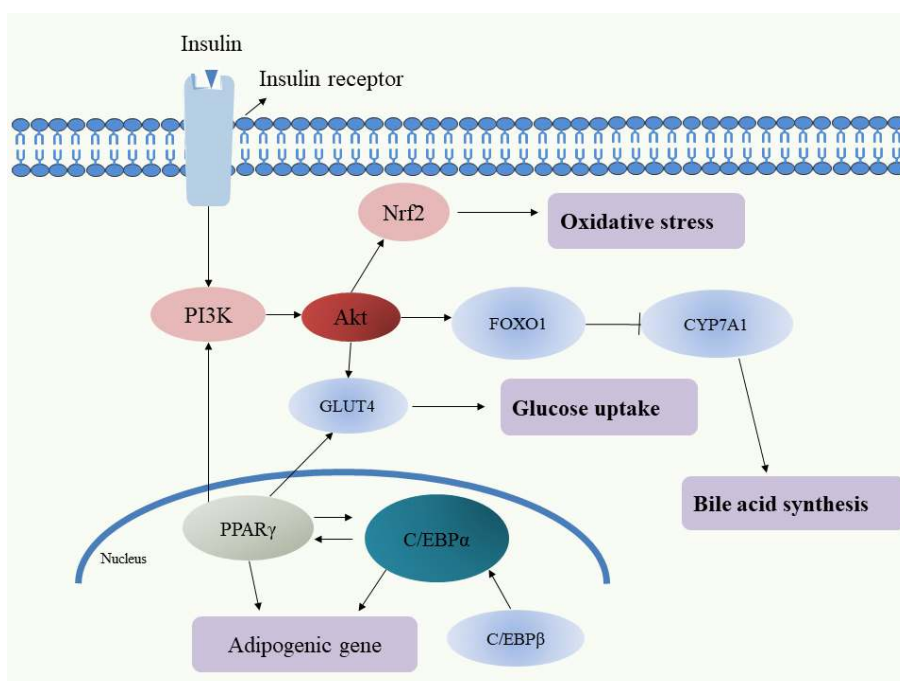
PPARs are important regulators of glucose and lipid homeostasis and targets for the treatment of metabolic diseases such as diabetes. PPARs can be divided into three categories: PPAR $\alpha$ , PPAR $\delta$ , and PPAR $\gamma$  (Fig. 10). PPAR $\alpha$  is mainly found in the liver, heart and kidney and acts on fatty acid and lipid metabolic processes, PPAR $\delta$  is widely expressed and regulates fat oxidation and energy expenditure. PPAR $\gamma$  is expressed in adipose, muscle and macrophage cells and is involved in adipogenesis and lipid storage, as well as insulin sensitivity and glucose metabolism<sup>[82,83]</sup>.

PPAR $\gamma$  is closely associated with adipocyte differentiation, and there are 13 major transcriptional regulators of PPAR $\gamma$ , C/EBPs, and SREBP-1c/ACC during their differentiation. Inhibition of PPAR $\gamma$  is mainly existed in adipose tissue and macrophages. The interaction between PPAR $\gamma$  and C/EBP $\alpha$  positively regulates adipocyte differentiation<sup>[84]</sup>. Compound **6** was found to inhibit cellular differentiation by reducing protein expression and mRNA transcription of PPAR $\gamma$  and C/EBP $\alpha$ , thereby decreasing cellular lipid accumulation<sup>[85]</sup>. *Ganoderma lucidum* polysaccharides could also inhibit adipocyte differentiation, which in turn inhibits lipid accumulation in 3T3-L1 adipocytes, promotes lipolysis, and regulates body lipolysis<sup>[86]</sup>. Compound **29** inhibited differentiation of 3T3-L1 cells by suppressing the expression of PPAR $\gamma$  and C/EBP $\alpha$  and reduced lipid accumulation 3T3-L1 cells and human primary adipocytes by strongly inhibiting the expression of key adipogenic enzymes, especially FAS, and directly inhibiting the promoter activity of FAS<sup>[31]</sup>. *Lycium barbarum* polysaccharides inhibited adipocyte differentiation by reducing the expression of PPAR $\gamma$ , C/EBP $\alpha$ , fatty acid-binding protein 4 (AP2), FAS and

lipoprotein lipase (LPL) mRNA, which in turn inhibited lipid accumulation in adipocytes and differentiation from preadipocytes to mature adipocytes, and increased glucose uptake and utilization<sup>[87]</sup>. Compound **36** inhibited cell differentiation and reduces lipid accumulation in 3T3-L1 cells by decreasing protein expression and mRNA transcription of PPAR $\gamma$  and C/EBP $\alpha$  in 3T3-L1 cell differentiation<sup>[54]</sup>. Compound **3** downregulated the expression of PPAR $\gamma$  and C/EBP $\alpha$ , the major transcription factors of the lipogenic pathway, and directly induces lipolysis in adipocytes. Compound **21** reduced adipocyte development and decreased the expression of transcription factors specific to fat cells, suggesting that they could be employed as PPAR $\gamma$  inhibitors<sup>[88]</sup>.

In addition to its key role in adipocyte differentiation, PPAR $\gamma$  also plays an important role in mediating fatty acid oxidation and lipid metabolism. PPAR $\gamma$  is highly expressed in adipocytes, and a variety of genes involved in fatty acid transport and metabolism are regulated by PPAR $\gamma$  at the transcriptional level. It can also regulate lipid metabolism by reducing leptin and tumor necrosis factor- $\alpha$  expression in adipocytes and improving pancreatic  $\beta$ -cell function<sup>[89]</sup>. Compound **41** could regulate adipocytokines by decreasing TNF $\alpha$  levels and increasing PPAR $\gamma$ -mRNA and lipocalin levels, thereby regulating hyperglycemia and dyslipidemia. In addition, compound **41** could also increase PPAR $\gamma$  expression through the activation of C/EBP, increasing GLUT4 translocation in 3T3-L1 adipocytes and improving insulin resistance<sup>[90]</sup>. PPAR $\gamma$  agonists promote adipocyte differentiation and modulate the expression of the insulin-acting cytokine lipocalin to increase insulin sensitivity. At the same time PPAR $\gamma$  activation enhances the expression of the metabolic process GLUT4 and promotes glucose uptake by liver and skeletal muscle<sup>[91]</sup>. Compound **2** could play an important role in weight loss and lipid reduction by enhancing PPAR $\gamma$ , PGC-1 $\alpha$ , PR domain-containing 16 (PRDM16), and uncoupling protein 1 (UCP-1) mRNA and protein expression in white adipose tissue (WAT) and brown adipose tissue (BAT) in mice and promoting fat oxidation and glycolysis<sup>[92]</sup>. Compound **26** could act as a PPAR $\gamma$  agonist to activate cellular PPAR $\gamma$ , upregulate intracellular lipid accumulation and lipocalin secretion, and improve insulin resistance<sup>[93]</sup>. Moreover, activation of PPAR $\gamma$  can inhibit inflammation through various response mechanisms, such as interaction between PPAR $\gamma$  and proinflammatory NF- $\kappa$ B and inhibition of mitogen-activated protein kinase (MAPK) phosphorylation. Compound **28** inhibited the production of inflammatory cytokines by activating PPAR $\gamma$ , inhibiting cell injury and apoptosis, and reducing the expression of proteins related to the p38 MAPK/NF- $\kappa$ B pathway<sup>[94]</sup>. Additionally, compounds **21** and **32** both had the effect of activating PPAR $\gamma$ , which in turn inhibits inflammation and insulin resistance<sup>[95,96]</sup>.

PPAR activation can also promote phosphoinositide 3-kinase (PI3K) gene expression in the PI3K pathway and improve insulin sensitivity. Activated PI3K genes can participate in body lipid metabolism and glucose transport via PI3K/AKT. Compound **12** increased AKT phosphorylation, promoted binding of AKT to phosphodiesterase 3B (PDE3B), and maintained PDE3B content thereby reducing lipid cAMP accumulation. It also decreased translocation lipid deposition in liver, and inhibited Foxo1 activation regulation of AKT, thereby suppressing excessive hepatic gluconeogenesis<sup>[48]</sup>. FOXO1, a typical regulatory protein of the PI3K/AKT pathway, can be activated by the PI3K/AKT pathway, which phosphorylates FOXO1 protein to drive the gluconeogenesis process involved in insulin regulation of glucose



**Figure 10** Diagram of PPAR $\gamma$  signaling pathway regulated by active ingredients of FMH resources. PPAR $\gamma$  regulates adipocyte differentiation, glucose uptake and lipid peroxidation. Peroxisome proliferator-activated receptors (PPARs), CCAAT enhancer binding protein  $\alpha$  (C/EBP $\alpha$ ) and CCAAT enhancer binding protein  $\beta$  (C/EBP $\beta$ ), Glucose transporter type 4 (GLUT4), Forkhead box O1 (FOXO1), Nuclearfactor erythroidderived 2-like 2 (Nrf2).

metabolism and lipid metabolism<sup>[97,98]</sup>. In insulin resistance, the binding ability of FOXO1 is enhanced, which promotes the formation and development of hyperlipidemia. It has been found that *Pueraria lobata* polysaccharides could inhibit hepatic gluconeogenesis by downregulating the expression levels of PEPCK, G6PC, and FOXO1, and improving body lipid metabolism by regulating the lipid profile<sup>[99]</sup>.

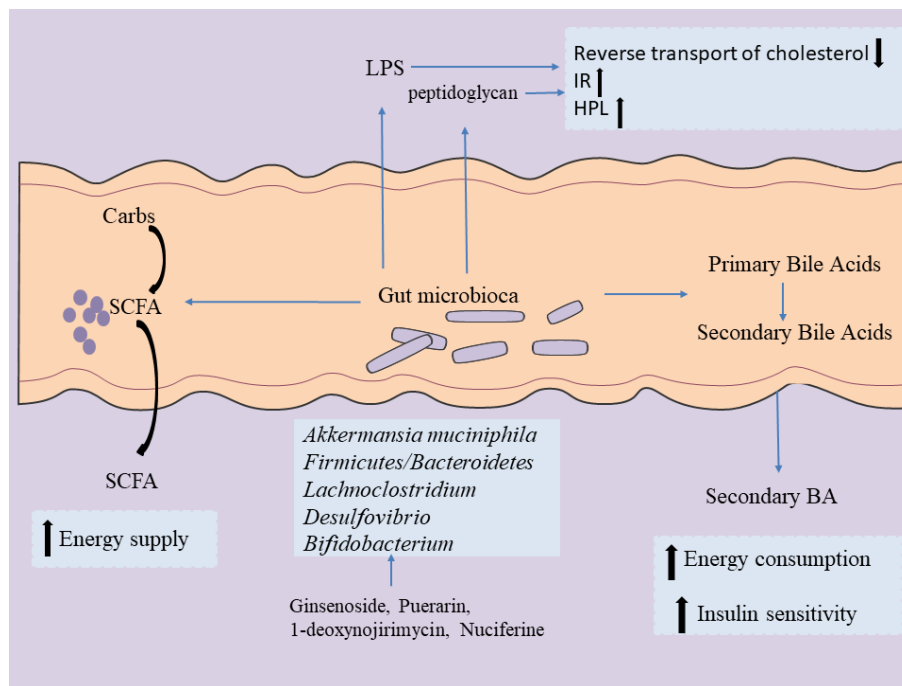
Activation of the transcription factor Nrf2 is one of the main lines of cellular defense against oxidative stress and also affects genes involved in glucose metabolism. Studies have shown that *Lycium barbarum* polysaccharides induced Nrf2 phosphorylation levels and activated the Nrf2/ARE pathway through PI3K/AKT signalling<sup>[100]</sup>. Compound **10** increased the antioxidant capacity of HepG2 cells through activation of the Nrf2/HO-1 pathway<sup>[68]</sup>. Hyperlipidemia is associated with increased oxidative stress and lipid peroxidation. It was reported that fat accumulation leads to an imbalance in the production of adipocytokines in response to oxidative stress, whereas a selective increase in reactive oxygen species (ROS) produced during fat accumulation led to increased systemic oxidative stress<sup>[8]</sup>. Numerous studies have shown that reducing the production of ROS could improve insulin sensitivity, hyperlipidemia, and hepatic steatosis. Intracellular production of ROS is followed by the activation of antioxidant response pathways via nuclear translocation of Nrf2<sup>[101]</sup>.

#### 4.4 Regulating Gut microbiota homeostasis

Gut microbiota plays a critical role in diet-related obesity, diabetes and lipid metabolism disorders. As one of the susceptibility factors for metabolic disorders, gut microbiota influences the expression of host genes that regulate energy consumption and storage, and alteration of gut microbiota may be the key to the etiology of metabolic diseases (Fig. 11). Recent studies have shown that when the intestinal environment is altered, the growth of normal flora such as *Bifidobacterium*, *Lactobacillus*, *Akkermansia muciniphila*, and *Escherichia coli* is

enhanced and dysregulated, leading to dyslipidemia<sup>[102]</sup>. Gut microbiota and its metabolites (such as short-chain fatty acids (SCFAs) and Bile acids (BAs)) can affect the efficiency of energy harvesting and the activity of the immune system, and regulate chronic inflammation by changing the permeability of the intestinal barrier, interfere with the reverse transport of cholesterol, and lead to metabolic disorders such as dyslipidemia<sup>[103,104]</sup>.

Compound **17** might ameliorate dyslipidemia by modulating the abundance of *Akkermansia muciniphila* and acting directly on the integrity of the intestinal epithelium<sup>[105]</sup>. Compounds **1** and **28** increased the abundance of *Akkermansia*, attenuate the dysbiosis of gut microbiota caused by dyslipidemia<sup>[106,107]</sup>. Both *Firmicutes* and *Bacteroidetes* have been found to contribute to host metabolism and regulate lipid metabolism, and an elevated *Firmicutes/Bacteroidetes* ratio (F/B) increases the energy extraction potential of undigested carbohydrates and lipids. Compounds **3** and **4** all increased the body's ability to digest carbohydrates by decreasing the F/B ratio, and compound **4** also increased the growth of SCFAs-producing bacteria such as *Lachnoclostridium* and improves SCFAs content in the body, thereby regulating fatty acid synthesis and oxidation<sup>[108,109]</sup>. Compound **29** could decrease the relative abundance of *Desulfovibrio* and bacteria involved in lipid metabolism and increase the relative abundance of SCFAs-producing bacteria, modulated LPS biosynthesis and lipid metabolism, and improved intestinal barrier integrity through the change of ratio of F/B in rats<sup>[110]</sup>. Furthermore, *Poria cocos* and *Gastrodiae Rhizoma* polysaccharides influenced the activity of bacteria that produce SCFAs and raise the amount of SCFAs in the colon<sup>[111-113]</sup>. In addition to serving as intestinal barrier protectors, SCFAs also affect the permeability of intestinal epithelial cells and aid in the body's defense against intestinal antigens. They also have a significant impact on lipid metabolism and control how cholesterol is distributed in the circulation and liver. By boosting the abundance of *Lactobacillus*, *Bifidobacterium*,



**Figure 11** Mechanisms by which active ingredients of FMH resources regulate gut microbiota. Lipopolysaccharide (LPS), Insulin resistance (IR), Hormone-sensitive triglyceride lipase (HPL).

*Turicibacter* and lowering the abundance of *Desulfovibrio*, *Pueraria lobata* starch improved intestinal dysbiosis<sup>[114]</sup>.

In conclusion, active ingredients in FMH resources could regulate protein, fatty acid and cholesterol synthesis and metabolism through AMPK pathway, further regulate lipogenesis and catabolism, and reduce steatosis. Through the cholesterol metabolic pathway, they regulated the uptake of exogenous cholesterol and the synthesis of endogenous cholesterol, and increased the excretion of cholesterol and bile acid. Through PPAR $\gamma$  pathway, they regulated adipogenesis and lipid storage, enhanced insulin sensitivity and glucose metabolism. They could alter intestinal barrier permeability by regulating intestinal microbiota, interfere with cholesterol transport, and affect the levels of intestinal metabolites SCFAs and bile acids.

## 5 Concluding remarks and prospects

Here, we analyzed the lipid-regulating FMH resources identified from SAMR and literature search, and summarized their active ingredients and mechanisms. There are 102 FMH resources in China, 37 of which are commonly used as lipid-regulating herbs in functional foods. Their main effective lipid-regulating components are triterpenoids and their glycosides, flavonoids, alkaloids, polysaccharides, and others. Through the regulation of the production and activity of important proteins and enzymes in AMPK pathways, cholesterol metabolism, PPAR $\gamma$  activation, and other related pathways, as well as the homeostasis of gut microbiota, these substances influence lipid metabolism.

The effects of hyperlipidemia on the body are insidious, progressive and systemic, and it is a risk factor for various cardiovascular and cerebrovascular diseases, such as atherosclerosis, coronary heart disease, myocardial infarction, cerebral thrombosis, fatty liver, diabetes mellitus, hyperlipidemic pancreatitis, etc. The FMH resources from human diets appear in the forms of medicine, health food, tea drink, etc. Their action mechanisms involve multiple pathways and targets, which have

attracted broad attention. In-depth research on the active ingredients in FMH and their mechanisms of actions for lowering blood lipid is certainly on the way for the prevention and treatment of dyslipidemia and cardiovascular diseases associated with it.

## Conflicts of interest

All authors declare that there are no conflicts of interest regarding this study. Xuqiang Liu is the associate managing editor of this journal, but he is not involved in handling, peer-review or decision of this article.

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