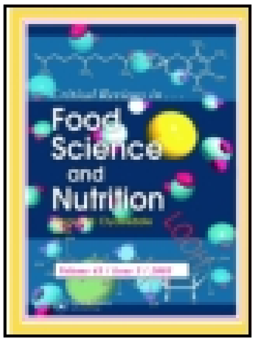

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REVIEW

# Hypoglycemic effects of bioactive ingredients from medicine food homology and medicinal health food species used in China

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**ABSTRACT**

Diabetes mellitus (DM) is a chronic progressive systemic disease caused by a metabolic disorder. In recent years, a large number of studies have shown that certain traditional Chinese medicines and their bioactive ingredients have obvious hypoglycemic effects. This literature review focuses on medicine food homology (MFH) and medicinal health food (MHF) species used in China with a hypoglycemic function and emphasizes the bioactive ingredients and their pharmacological effects. The bioactive ingredients of MFH and MHF have been divided into six categories: saponins, flavonoids, terpenoids, alkaloids, polysaccharides, and others; and their sources, models, efficacy, and mechanisms of action have been described. It is noteworthy that the mechanisms of the bioactive ingredients of MFH and MHF with hypoglycemic effects have been summarized as follows: a) insulin-mimetic effects and restoration of the damaged pancreas; b) effect on glucose metabolism; c) increased insulin sensitivity and improved insulin resistance; and d) regulation of intestinal flora. We conclude that this review provides useful data and information to support the further investigation and application of MFH and MHF to treat DM.

**KEYWORDS**

Hypoglycemic; bioactive ingredients; medicine food homology; medicinal health food; diabetes mellitus

## Introduction

Diabetes mellitus (DM) is a metabolic endocrine disease characterized by hyperglycemia. Type 2 DM accounts for more than 90% of all patients with DM. The condition is characterized by a relative lack of insulin secretion, insulin resistance (IR), or both (Defronzo and Banting 2009). It is often accompanied by a variety of chronic complications, resulting in considerable damage to multi-organ systems with high morbidity (Zhang and Jiang 2012) (Figure 1). It is a common and frequently encountered disease that is detrimental to human health. Presently, the incidence of diabetes is increasing gradually worldwide. According to the World Health Organization (WHO), the number of patients with DM globally has reached 415 million (Zhao et al. 2017). Oral hypoglycemic therapy with drugs such as biguanides, thiazolidinediones (TZDs), and glucosidase inhibitors, is the primary therapeutic modality for type II DM. Despite their efficacy in maintaining glycemic control, oral hypoglycemic agents may not prevent the long-term complications of DM such as nephropathy and cardiovascular disorders. Further, long-term use of these drugs is often associated with serious side effects such as gastrointestinal disorders with acarbose, granulocytopenia and hypoglycemia with glibenclamide, and lactic acidosis with metformin therapy (Sun and Luo 2017).

Traditional Chinese medicine (TCM) has been practiced for thousands of years in China and plays a major role in health care. Since ancient times, several Chinese herbal formulations and medicinal herbs have been commonly used in patients with 'Xiao Ke', a diabetic condition characterized by persistent thirst and hunger, copious urination, and weight loss. Recently, research on TCM has become popular, and numerous investigations have been carried out to search for effective components to reduce blood sugar levels. Compared to modern chemical drugs, TCM formulations are known to modulate physiological regulation to effectively prevent or delay the multi-systemic long-term complications of DM in addition to lowering blood sugar levels (Ni and Li 2012; Zhao, Chen, and Liu 2017; Chen and Liu 2012; Zhao and Wang 2010; Liang, Bian, and Wang 2010; Zhang 2016). In addition, TCM formulations typically have a lower propensity for severe toxicity and adverse reactions.

Historically, many of the formulations have been used as food for long-term consumption, which is safety and effectively. The concept of 'medicine and food homology' was mentioned in the *Huang Di Nei Jing Su Wen*: 'eating on an empty stomach as food and administering to the patient as medication' reflects the theory of medicine food homology (MFH), that is, there are food classes that can also be used as drugs. Health foods, also called functional foods, are specific types of foods that are not intended to cure diseases but can regulate human body functions. In 2012, the Notice on Further Regulating the Management of Raw Materials for Health Foods was issued by the Ministry of Health, which pertains to both foods and drugs (Shan et al. 2015; Wang

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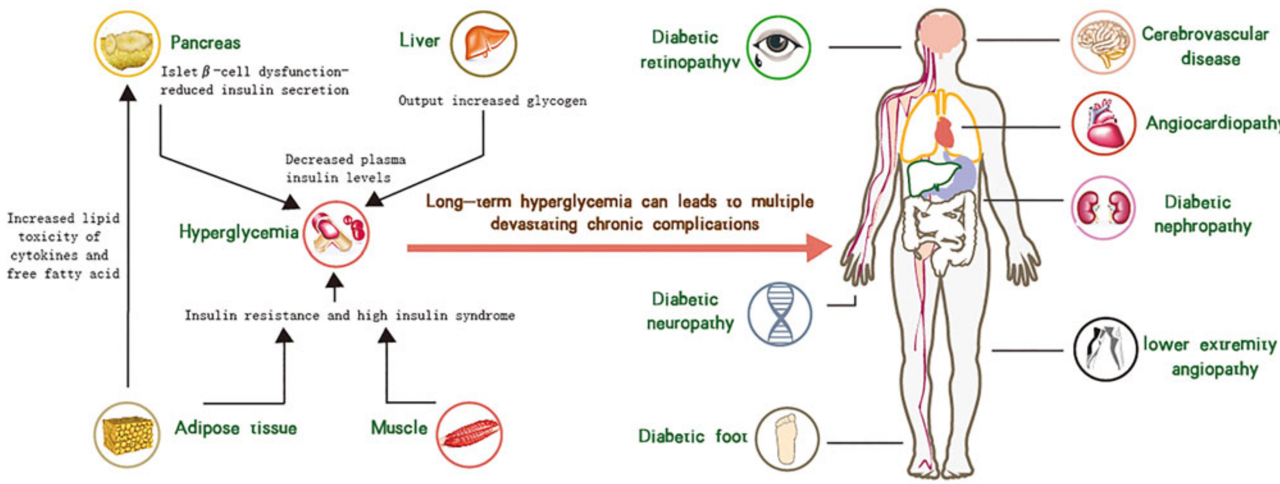


**Figure 1.** The pathogenesis and chronic complications of T2DM.

et al. 2016; Zhang 2009). Furthermore, 110 and 114 species of MFH and medicinal health food (MHF) are currently included in this promulgated management method. Table 1 shows common MFH species and MHF in China and their main applications.

MFH and MHF have been widely sought recently and research into their use for DM has evoked considerable interest. The bioactive ingredients of MFH and MHF can be divided into six categories: saponins, flavonoids, alkaloids, terpenoids polysaccharides, and others (Figure 2). More extensive development and use of food and medicinal foods should be encouraged as a novel approach to the treatment and prevention of DM and its complications. The authors reviewed and evaluated recent progress in the research into the effective components of MFH and MHF.

## Hypoglycemic drugs and bioactive ingredients of MFH and MHF

We investigated the hypoglycemic effects of the bioactive ingredients of MFH and MHF, including saponins, flavonoids, terpenoids, alkaloids, and polysaccharides. Saponins and flavonoids are the main bioactive components present in the MFH and MHF species.

### *Saponins*

Saponins are a class of glycosides composed of triterpene or spiral sterane, which are widely found in nature and distributed in both monocots and dicots (Liu and Henkel 2002). Studies have shown that saponins have a wide range of targets and pathways for hypoglycemic effects. In addition to directly repairing damaged islet cells and increasing insulin levels to maintain normal blood glucose, saponins regulate blood lipids and improve glucose tolerance. These compounds show good biological effects such as increasing liver glycogen content and antioxidant activity, which indicates they are good prospects for broad research and development as antidiabetics.

It has been reported that several saponins, such as the diosgenin in *Dioscorea opposita* Thunb., ginsenoside Rg1 in *Panax ginseng* C.A. Mey and *Panax notoginseng* (Burk.) F. H. Chen., mogroside V in *Siraitia grosvenorii* (Swingle.) C., and astragaloside IV in *Astragalus membranaceus* (Fisch.) Bge., exhibit very good antidiabetic effects. Furthermore, we summarized the structures of hypoglycemic steroidal saponins from MFH and MHF in Figure 3.

The antidiabetic effect and mechanism of action of mogroside extracts have been reported in alloxan-induced hyperglycemic mice. The results showed that feeding mice with mogroside extracts at a dose of 100 mg·kg$^{-1}$ body weight (bw) for 30 d significantly lowered the fasting blood glucose ($p < 0.01$). Mogroside extracts decreased the total cholesterol (TC) and triglyceride (TG) content and increased that of high-density lipoprotein-cholesterol (HDL-C) in alloxan-induced diabetic mice. The hypoglycemic effect of mogroside extracts is equivalent to that of *Xiaokewan*, a positive control drug ($p > 0.01$). Mogroside extracts have obvious glucose-lowering effects on hyperglycemic mice, and their mechanism of action may be related to improving antioxidation level and restoring the blood lipid levels of hyperglycemic mice (Zhang et al. 2006).

Research has been carried out on streptozotocin (STZ)-induced diabetic rats to evaluate the hypoglycemic and hypolipidemic effects of *Gynostenma pentaphyllum* saponins (GPs), and determine the involvement of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway in their hypoglycemic mechanisms. Fasting blood glucose levels were measured on day 0, 10, 20, 30, and 40, and they remained consistently at similar levels over the time course from day 0 to 40 in the normal and DM control groups. However, in the DM + GPs-treated groups significantly lower blood glucose levels were observed than those in the DM control group at the same time points ($p < 0.05$ and 0.01). The decreasing rates of the plasma glucose levels on day 40 were 47.95% and 60.84% in the DM + GPs low-dose (LD) and DM + GPs high-dose (HD) groups, respectively. This finding indicated that DM + GPs HD group showed a more favorable hypoglycemic status than that of the DM + GPs LD group, although there was no statistical difference. This data

**Table 1.** Common MFH and MHF species in China and their main applications.

| Classification | Source (Latin name/English name/Pinyin) | Pharmacological effects | Food applications | Medicine applications | Ref. |
|---|---|---|---|---|---|
| Medicine food homology | *Coix lacryma-jobi* L. var. *mayuen*. (Roman.) Stapf/Coicis Semen/Yiyiren | Anti-tumor effect, enhance immunity effect, hypoglycemic effect and anti-inflammatory effect | Semen coicis porridge and Semen coicis tea | *Yiyiren San*,*Yiyiren Tang*, and *Yiyiren Pills* | Liu et al. 2010 |
| | *Mentha haplocalyx* Briq./Menthae Haplocalycis Herba/Bohe | Anti-tumor effect, Curative effects on the nervous system and digestive system | Make dishes, cakes, drinks and sweets | *Fangfengtongsheng Pills*, and *Ganmao Qingre Granules* | Zhou and Zhong 2010 |
| | *Chrysanthemum morifolium* Ramat./Chrysanthemi Flos/Juhua | Anti-inflammation, anti-virus, anti-bacteria, and anti-oxidation | Chrysanthemum cakes, chrysanthemum tea and chrysanthemum wine | *Fufang chrysanthemum granules* | Wang et al. 2018 |
| | *Platycodon grandiflorum* (Jacq.) A. DC./Platycodonis Radix/Jiegeng | Expectorant, antitussive, anti-inflammatory, anti-tumor, and enhance immunity effect | Pickled pickles and make dishes | *Fufang platycodon grandiflorum antitussive tablet*, and *Juhong tablet* | Xie et al. 2018 |
| | *Lycium barbarum* L./Lycii Fructus/Gouqizi | Anti-oxidation, anti-tumor, and protective effects on the liver | Bubble water, boil soup, and porridge | *Qiju Dihuang soft capsules*, and *Zhikang Granule* | Wei et al. 2018 |
| | *Siraitia grosvenorii* (Swingle.) C. Jeffrey ex A. M. Lu et Z. Y. Zhang/Siraitiae Fructus/Luohanguo | Anti-oxidant activity, hypoglycemic effect, immunologic effects, and hepatoprotective effect | *Luohanguo*-fermented wine, *luohanguo* cake, *luohanguo* preserved fruit, and *luohanfruit* compound beverage | *Luohanguo xueligao*, *Luohanguo yanhoupian*, and *Fufang luohanguo zhikechongji* | Zhang et al. 2017 |
| | *Hippophae rhamnoides* L./Hippophae Fructus/Shaji | Anti-tumor effect, crative effects on the cardiocerebral vascular system and digestive system | seabuckthorn probiotic jams, seabuckthorn beverage or directly edible | *Shaji Huangtong oft capsule*, and *Shaji seed oil soft capsule* | Wang et al. 2018 |
| | *Crataegus pinnatifida* Bge./Crataegi Fructus/Shanzha | Crative effects on the cardiocerebral vascular system, hypolipidemic effects, hypotensive effect, and hypoglycemic effect | Ued in cakes, beverages, and sweets or directly edible | *Shanzha Neixiao Pills*, and Shanzha Jiangzhi pill | Yu, Yan, and Sun 2015 |
| | *Prunus mume* (Sieb.) Sieb. et Zucc./Mume Fructus/Wumei | Anti-bacterial, anti-tussive, anti-virus, and hypoglycemic effect | Preserved fruits or directly edible | *Wumei Pill* | Zhang, Li, and Fu 2017 |
| | *Dioscorea opposita* Thunb./Dioscoreae Rhizoma/Shanyao | Improve immunity, improve digestive function, hypolipidemic effects, hypoglycemic effect, and anti – tumor effects | Make dishes, and yam rhizome porridge | *Jianwei Xiaoshi tablet* | Jing et al. 2016 |
| | *Illicium verum Hook. f.*/Anisi Stellati Fructus/Bajiaohuixiang | Anti-bacterial, analgesic, and anti-oxidant | Used in spices, and spice | *Star anise pill*, and *star anise oil* | Han 2018 |
| | *Codonopsis pilosula* (Franch.) Nannf/Codonopsis Radix/Dangshen | Regulate blood sugar, enhance immunity and hypotensive effect | Used in Soup, porridge, steamed rice, cooking, hot pot materials, wine, and dried fruit | *Bazhen pills*, and *Sijunzi pills* | Sun, Shao, and Guo 2015 |
| | *Cistanche deserticola* Y.C. Ma/Cistanches Herba/Roucongrong | Enhance immunity, anti-oxidant, hepatoprotective effect, neuroprotective effect | Used in dishes, wine, and tea | *Congrong bushen pill*, and *Fufang cistanche capsule* | Li, Song, and Zhang 2010 |
| | *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao/Astragali Radix/Huangqi | Enhance immunity, Curative effects on the respiratory system, digestive system, and cardiovascular system | Used in dishes, porridge and wine | *Milkvetch root oral liquids*, and *Fufang huangqi danggui tablet* | Yang 2018 |
| | *Glycyrrhiza uralensis* Fisch./Glycyrrhizae Radix Et Rhizoma/Gancao | Adrenal cortical hormone - like effect, anti-peptic ulcer, immunosuppressive effect, anti-virus effect | Used in tea, and spiced spice | *Compound Licorice Tablets*, and *Acute Bronchitis Sirup* | Jiang et al. 2017 |

(*continued*)

**Table 1.** Continued.

| Classification | Source (Latin name/English name/Pinyin) | Pharmacological effects | Food applications | Medicine applications | Ref. |
|---|---|---|---|---|---|
| Medicinal health food | *Plantago asiatica* L./Plantaginis Herba/Cheqiancao | Anti-bacterial effect, diuretic effect, and anti-oxidant effect | Make dishes | *Yinhua miyan ling tablet* | Xia et al. 2013 |
| | *Rehmannia glutinosa* Libosch./Rehmanniae Radix/Dihuang | Regulate immune function, enhance hematopoietic function, and protect cardiovascular system | Boil porridge and stew soup | *Liuwei Dihuang Pills* | Li and Meng 2015 |
| | *Gynostemma pentaphyllum* (Thunb.) Makino/fiveleaf gynostemma herb/Jiaogulan | Neuroprotective effect, anti-tumor, hypoglycemic, and regulating immunity effect | Tea | *Gypenoside tablets* | Bao, Tao, and Zhang 2018 |
| | *Ophiopogon japonicus* (L.f) Ker-Gawl./Ophiopogonis Radix/Maidong | Anti-myocardial ischemia, anti-thrombosis, and hypoglycemia | Tea | *Pulse-activating injection*, and *pulse-activating powder* | Peng et al. 2018 |
| | *Aloe barbadensis* Miller/Aloe/Luhui | Anti-tumor, and anti-diabetes | Aloe drink, and aloe yogurt | *Angelica root aloe pill* | Wang, Lv, and Zhang 2009 |

also indicated that GPs treatment promoted further translocation of Nrf2 into the nucleus and activated its expression in the hepatic nuclei of STZ-induced diabetic rats, as evidenced by the significant elevation of Nrf2 in the nuclear fractions ($p < 0.05$) (Gao et al. 2016).

Modern studies have shown that saponins have significant physiological and pharmacological activities, especially in the prevention and treatment of DM. Recently, domestic and foreign scholars have been actively searching for new hypoglycemic drugs from natural medicinal sources. Saponins have an important role in many formulations. Recent studies showed that the hypoglycemic effects of numerous MFH and MHF were mediated by their saponin ingredients (Table 2).

## *Flavonoids*

Flavonoids are an important class of natural organic compounds with a basic 2-phenyl-chromone structure, and they are widely distributed in the plant kingdom (Patra and Chua 2011). Flavonoids have a wide range of pharmacological effects including anti-inflammatory, antibacterial, and cardiovascular and central nervous system protective effects. Currently, flavonoids with antioxidant and free radical-scavenging activity are of high interest to the pharmaceutical industry (Jin and Chen 2015). Flavonoids can prevent and treat DM mainly by affecting the function of islet β cells and resistance to lipid peroxidation (Chen and Liu 2012).

Figure 4 shows a summary of the structures of the hypoglycemic flavonoids in MFH and MHF. It has been reported that flavonoids, such as hyperoside and quercetin in hawthorn leaf, liquiritigenin in *Glycyrrhiza uralensis* Fisch, puerarin in *Pueraria lobata* (Willd.) Ohwi, and rutin in the buds of *Sophora japonica* L. (Li et al. 2009; Ren 2016; Yang et al. 2014; Pan, Liu, and Jian 2016).

Rat models of STZ-induced DM have been used to study the antihyperglycemic effect of flavonoids from sea buckthorn (FSH) in rats orally administered FSH seed residue for 4 weeks. The results showed significantly reduced serum glucose, fructosamine, and triglyceride levels; obviously increased serum total protein and albumin concentrations; and enhanced antioxidant capacity in STZ-induced diabetic rats compared with those in the control group. However, in the positive control group, metformin had no effect on serum total protein and albumin concentrations. Dietary supplementation with FSH at different levels evidently and effectively controlled blood glucose levels and improved metabolic derangements in STZ-induced diabetic rats (Cao et al. 2005).

Research has shown the hypoglycemic effect of the total flavonoids of epimedium (TFE) on alloxan-induced diabetic mice. The hypoglycemic effects were investigated in alloxan-induced diabetic mice after oral administration of $50\,mg\cdot kg^{-1}$ and $100\,mg\cdot kg^{-1}$ TFE for 14 days. The results indicated that TFE significantly reduced the fasting blood glucose of diabetic mice and improved their impaired glucose tolerance. Furthermore, TFE increased liver and muscle glycogen concentrations, decreased methane

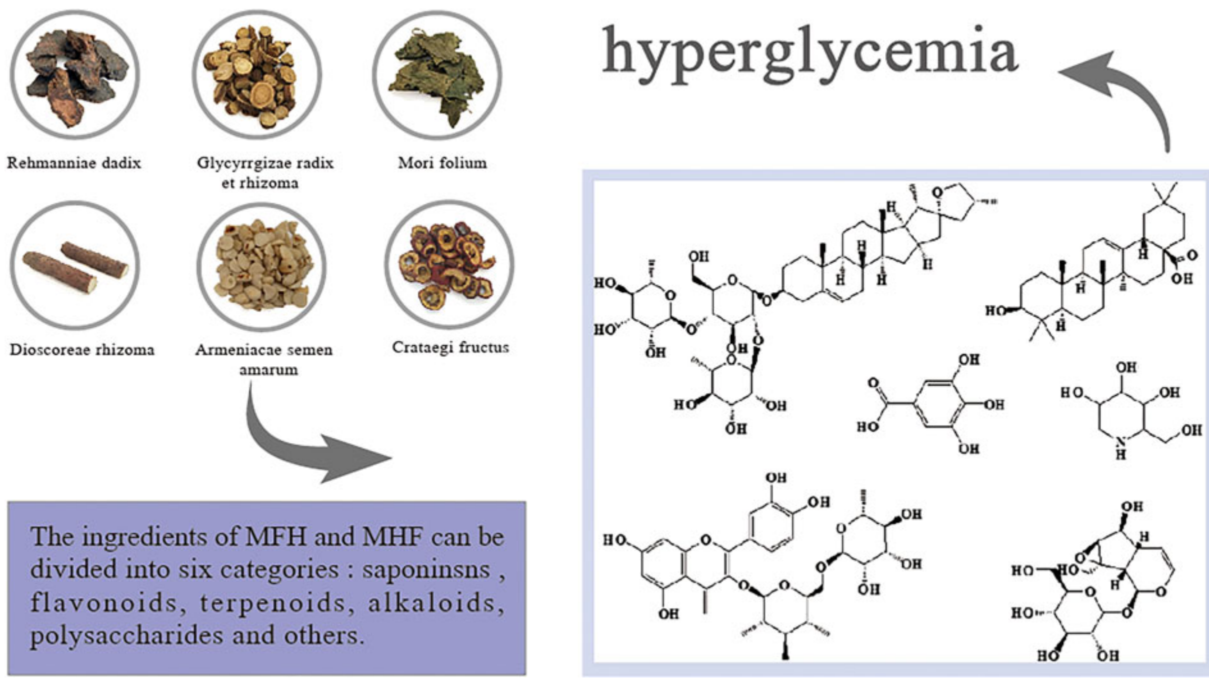


Figure 2. The ingredients of MFH and MHF.

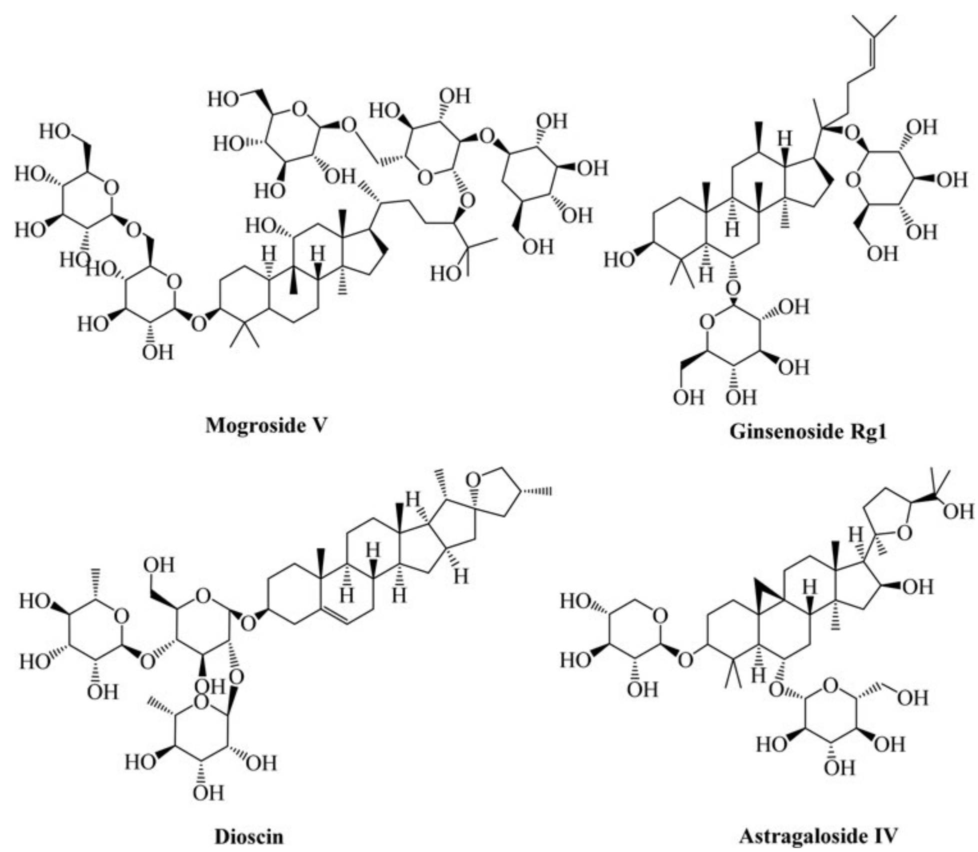


Figure 3. The structure of hypoglycemic compounds of saponins from MFH and MHF.

dicarboxylic aldehyde (MDA) levels, and enhanced superoxide dismutase (SOD) activity. TFE has a hypoglycemic effect that may be partly mediated through an increase in glycogen concentration and antioxidant activity (Zhang, Hai, and Ding 2011).

Some flavonoids have a natural hormone-like activity and compared with other hypoglycemic ingredients of Chinese medicinal formulations, flavonoids have no harmful effect on the human body. They do not cause adverse reactions even when used for a prolonged time (Liu 2016). Table 3

**Table 2.** The role and mechanism of saponins bioactive ingredients in MFH and MHF on diabetes.

| Classification | Source | Bioactive ingredient | Experimental model | Efficacy | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| Medicine food homology | *Dioscorea opposita* Thunb. | Dioscin | A | Significantly reduce drinking amount and blood glucose levels, restore the weight of the mice. The hypoglycemic effect of dioscin is equivalent to that of acarbose, a positive control drug | Have inhibitory effect on intestinal alpha-glucosidase accelerating the degradation of sugar | (He et al. 2011; Gao 2004; He and Tan 2010) |
| | *Polygonatum odoratum* (Mill.) Druce | Polygonatum odoratum total saponins | B, D | Significantly increase glucose tolerance and reduce fasting blood glucose. The hypoglycemic effect of 600 $mg \cdot kg^{-1}$ is equivalent to that of metformin | Repair corrupted islet cells directly to enhance insulin levels, improve glucose tolerance, protect and restore pancreatic islet β cells | (Li et al. 2015; Guo et al. 2011) |
| | *Panax ginseng* C.A.Mey. | Ginsenoside Rg1 | B | Significantly reduce blood glucose levels, promote muscle glycogen synthesis, increase the active of superoxide dismutase (SOD) | Increase glycogen synthesis. And it has a certain effect on maintaining homeostasis of glucose metabolism in vivo | (Feng 2010) |
| | *Siraitia grosvenorii* (Swingle.) C. Jeffrey ex A. M. Lu et Z. Y. Zhang | Mogroside V | B | Significantly reduce blood glucose levels | Repair corrupted pancreatic to promote insulin secretion, scavenge-free radicals and prevent lipid peroxidation. Have inhibitory effect on intestinal alpha-glucosidase | (Wan, Wu, and Wu 2016; Chen 2012) |
| | *Panax quinquefolium* L. | Panax quinquefolium total saponins | B | Reduce blood glucose levels and increase the serum insulin levels. The hypoglycemic effect is not as good as the positive control drug Gliclazide | Repair corrupted pancreatic β cells | (Yin et al. 2004; Zhang et al. 2005; Zhen and Zhu 2014) |
| | *Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao | Astragaloside IV | D | Increased the activity of glutathione peroxidase in nerves, depressed the activation of aldose reductase in erythrocytes, and decreased the accumulation of advanced glycation end products in both nerves and erythrocytes | Inhibit lipid oxidation | (Yu et al. 2006; Xie 2010;) |
| Medicinal health food | *Panax notoginseng* (Burk.) F. H. Chen | Ginsenoside Rg1 | C | Significantly reduce fasting blood glucose and increase glucose tolerance | Improve insulin sensitivity | (Zhong et al. 2008; Zhong et al. 2014; Huang, Liang, and Tang 2016; Gong and Jiang 1991) |
| | *Paeonia lactiflora* Pall. | Paeony total glucosides | B, D | Reduce blood glucose levels | Improve insulin sensitivity and lipid metabolism | (Yin 2009; Sun et al. 2014; Liu and Ma 2013; Yuan et al. 2007; Chang et al. 2014) |
| | *Acanthopanax senticosus* (Rupr.et Maxim.) Harms | Acanthopanax senticosus saponins | E | Enhance the ability of insulin secretion, and reduce blood glucose levels | Improve insulin resistance, protect and restore pancreatic islet B cells | (Hu et al. 2003; Zhai et al. 2016) |
| | *Anemarrhena asphodeloides* Bge. | Timosaponins | B | Significantly increase glucose tolerance, and reduce fasting blood glucose | Repair islet cells and promote the regeneration of islet cells, Secretory function of enhanced islets | (Chen and Zhang 2014; Li et al. 2005; Cai et al. 2011) |

(*continued*)

**Table 2.** Continued.

| Classification | Source | Bioactive ingredient | Experimental model | Efficacy | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| | *Gynostemma pentaphyllum* (Thunb.) Makino | Gynostemma total saponins | B | Significantly reduce blood glucose levels, enhance liver glycogen synthesis and protect renal function. The hypoglycemic effect of gynostemma total saponins is equivalent to that of metformin, a positive control drug | Promoting liver glycogen synthesis to regulate blood glucose metabolism | (Lin and Chen 2011) |
| | *Trigonella foenum-graecum* L. | Trigonella foenum-graecum saponins | D | Significantly reduce blood glucose levels | Repair corrupted islet cells, increase insulin secretion and the content of liver glycogen, protecting kidney tissue and improving insulin resistance | (Wang 2017) |
| | *Tribulus terrestris* L. | Thistle saponins | B | Significantly reduce blood glucose levels, the content of TG, low-density lipoprotein-cholesterol and improve the activity of SOD. The hypoglycemic effect of thistle saponins is equivalent to that of metformin, a positive control drug | Protect and restore pancreatic islet B cells | (Li et al. 2002) |

**A** Diabetic mice; **B** Alloxan-induced diabetic mice (rats); **C** KK-Ay DM Mice; **D** STZ-induced diabetic mice (rats); **E** High fat diet induced diabetic mice; **F** Normal mice; **G** Type II diabetes patients; **H** High fat diet induced insulin resistance mice; **I** Spontaneous hyperglycemic mice; **J** Zucker diabetic fatty rat. The same as below.

shows the effects and mechanisms of action of flavonoids from MFH and MHF, which have been studied more clearly in DM in recent years.

## Terpenoids

Terpenes are natural hydrocarbons that exist widely in nature and can be linked by isoprene or isopentane in various ways. Monoterpenoids, sesquiterpenes, diterpenoids, and triterpenoids play an extremely important role in organisms. Studies have shown that some terpenoids have a preventive effect on DM (Table 4). The hypoglycemic mechanism of terpenoids may be mediated through their protection of islet β cells or repair of damaged β cells and increasing glucose tolerance and hepatic glycogen synthesis (Jin and Chen 2015).

Studies have been conducted using STZ-induced diabetic mouse models and terpenoids from the seed coat of *Euryale ferox* Salisb. After four weeks of treatment, the body mass, blood glucose, and pancreatic function of the mice were measured, and these substances restored body mass, regulated blood glucose level, improved pancreas condition, and decreased the expression of protein tyrosine phosphatase 1B in the mice. Moreover, the expression of the insulin receptor substrate protein was also increased (Yang 2014).

The total terpenoids of *Cornus officinalis* Sieb. et Zucc. showed good hypoglycemic effects on animal models of DM [there was no significant difference in hypoglycemic effect compared with the positive control group ($p > 0.05$)], which may have been mediated by a protective effect on pancreatic islet cells or promotion of repair of damaged β cells, thereby improving glucose tolerance and increasing liver glycogen synthesis (Han et al. 2006).

In general, many natural terpenoids used in TCM have strong biological activity (Figure 5), especially in preventing and treating DM and its complications. Terpenoids have been the focus of considerable attention in recent years, and studies of its hypoglycemic effect have been carried out over the past decade, indicating that terpenoids could be exploited as precursor drugs.

## Alkaloids

Alkaloids are a class of nitrogen-containing organic compounds derived in nature mainly in the plant kingdom. Most alkaloids have complex ring structures in which the nitrogen atoms are bound to the ring. Most alkaloids are alkaline and have significant biological activity and are one of the important bioactive ingredients in MFH and MHF (Jin and Chen 2015).

The hypoglycemic action of alkaloids is mainly mediated through inhibition of gluconeogenesis, improvement of intestinal flora structure, promotion of glycolysis and anti-glucagon activities to lower blood sugar, promotion of the regeneration and secretion of pancreatic β cells, enhancement of leukocyte phagocytosis, and scavenging of oxygen free radicals (Xiang et al. 2004; Zhang et al. 2012). Table 5 shows recent studies on the mechanism of antidiabetic action of alkaloids in MFH and MHF.

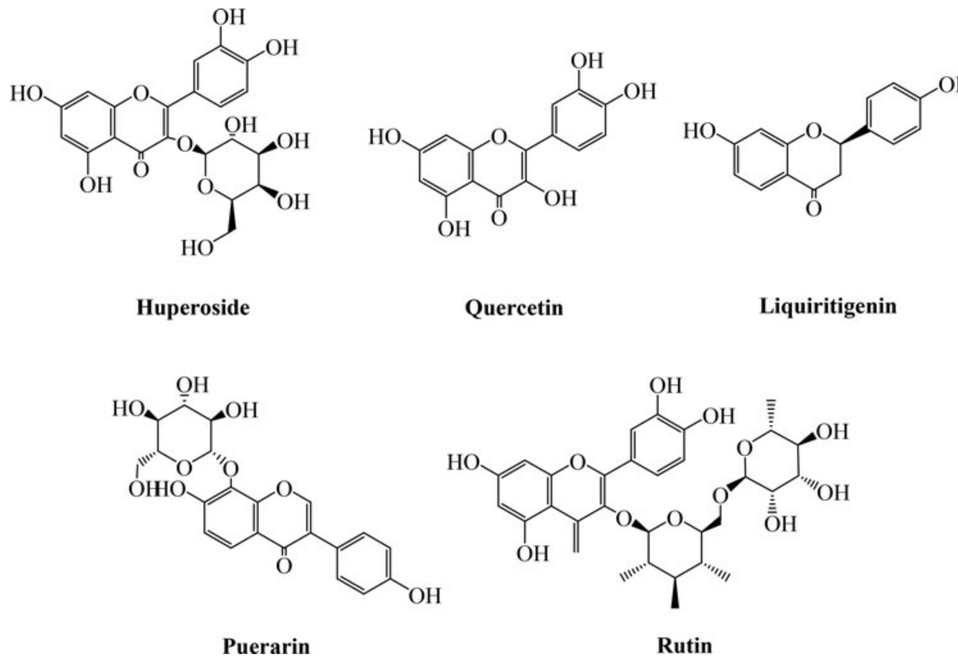

Figure 4. The structure of hypoglycemic compounds of flavonoids from MFH and MHF.

Berberine is the main component of Coptidis Rhizome, which is safe and inexpensive, as well as exerts low toxicity (Li et al. 2017). Studies have found that in STZ-induced diabetic mice, berberine is almost not absorbed by the intestinal tract, but can significantly reduce the activity of intestinal glycosylase and glucuronidase to reduce glucose absorption and reduce postprandial blood glucose (Liu et al. 2008). It was reported that berberine can improve intestinal GLP-1 secretion after sugar load in normal mice, suggesting that the hypoglycemic mechanism of berberine may be related to the intestinal MAPK, PKC, and GnRh-Glp-1 pathways (Yu et al. 2010; Zhang et al. 2014). Therefore, berberine can possibly regulate the growth of intestinal flora, affect the absorption of intestinal glycolipid components and *in vivo* glycolipid metabolism, and play an indirect role in lowering blood glucose (Zhang et al. 2012).

1-DNJ, which is isolated from mulberry leaves, branches, and roots, is an efficient inhibitor of α-glucosidase and it slows down the decomposition of disaccharide into glucose, delays its absorption, and significantly inhibits a sharp increase in postprandial blood glucose level. The underlying mechanism may involve inhibition of gluconeogenesis and promotion of glycolysis (Zou 2004; Liu et al. 2012).

Alkaloid substances have a wide range of physiological and pharmacological activity (Figure 6), although their content is relatively low in MFH and MHF. Alkaloids with complex and diverse antidiabetic mechanism have been attracting increasing attention.

## *Polysaccharides*

Polysaccharides, which are composed of 10 or more single sugar molecules polymerized by a glucoside bond, have relatively high molecular weight and generally consist of hundreds or even tens of thousands of single sugar molecules. Most polysaccharides with pharmacodynamic efficacy in TCM formulations are distributed in organisms such as fungi, algae, and plant roots (Gan et al. 2004). The biological activities of polysaccharides have recently attracted considerable attention in biochemical and medical research because of their immunomodulatory effects (Ooi and Liu 2000).

Research shows that polysaccharides with hypoglycemic effect in MFH and MHF can be used as drugs that can promote glucose utilization, protect β cells, stabilize insulin, increase the number of insulin receptors, improve insulin sensitivity to receptors, regulate the structure of intestinal flora, enhance cellular immune function, and inhibit glucosidase activity. The medicinal properties of polysaccharides are relatively mild, and they often have a synergistic effect with other hypoglycemic ingredients (Chen et al. 2009). The polysaccharides from MFH and MHF with diabetic effects are shown in Table 6.

Research has shown that kelp polysaccharides regulated the blood glucose of alloxan-induced diabetic mice. *In vitro* experiments were performed in diabetic mice induced with a 55 $mg \cdot kg^{-1}$ bw dose of alloxan injected through the tail vein and fed 125, 250, and 500 $mg \cdot kg^{-1}$ bw of kelp polysaccharides. After 3 weeks, fasting blood glucose level, urea nitrogen level, serum calcium level, serum insulin level, pancreatic pathology, and other indicators were determined. The results showed that kelp polysaccharides significantly reduced blood glucose and urea nitrogen in diabetic mice, and the blood glucose level of the groups treated with 125, 250, and 500 $mg \cdot kg^{-1}$ bw kelp decreased by 34.96%, 20.70%, and 26.82%, respectively (Wang et al. 2001; He 2007).

**Table 3.** The role and mechanism of flavonoids bioactive ingredients in MFH and MHF on diabetes.

| Classification | Source | Bioactive ingredient | Experimental model | Efficacy | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| Medicine food homology | *Crataegus pinnatifida* Bge. | Hawthorn leaf flavonoids | B | Significantly reduce serum blood glucose levels, the content of TC, TG, MDA, fructosamine (FA), increased the HDL-C | Regulating glucose metabolism and improve insulin resistance and enhancement of body lipid peroxidation | (Ye et al. 2005; Li and Hu 2011) |
| | *Glycyrrhiza uralensis* Fisch | Isoamyl alkenyl flavonoids | B, D | Reduce blood glucose levels. The hypoglycemic effect of isoamyl alkenyl flavonoids is equivalent to that of metformin, a positive control drug | Improving glucose tolerance | (Huo et al. 2014) |
| | *Hippophae rhamnoides* L. | Flavonoids from sea buckthorn seed | D | Significantly reduce blood glucose levels, FA blood lipid level. Increase the contents of serum albumin and total protein and enhance the antioxidant ability of the body | Protect islet β cells, prevent lipid peroxidation and scavenge free radicals | (Cao et al. 2005) |
| | *Siraitia grosvenorii* (Swingle.) C. Jeffrey ex A. M. Lu et Z. Y. Zhang | Momordica grosvenori total flavonoids | D | Significantly reduce blood glucose levels, enhance the activity of SOD and GSH-Px. Reduce the content of MDA, TC, TG and increase the serum insulin levels. The hypoglycemic effect of *momordica grosvenori* total flavonoids is equivalent to that of metformin, a positive control drug | Repair corrupted β cells, increase insulin secretion | (Wan, Wu, and Wu 2016; Zhen et al. 2011) |
| | *Morus alba* L. | Mulberry leaves total flavonoids | B | Significantly reduce blood glucose levels. The hypoglycemic effect of mulberry leaves total flavonoids is equivalent to that of phenformin, a positive control drug | Improve insulin sensitivity, stimulate insulin release and increasing the use of peripheral sugar | (Hou and Peng 2013; He, Su, and Wu 2014; Zen et al. 2016) |
| | *Morus alba* L. | Mori fructus total flavonoids | D | Significantly reduce blood glucose levels, glycosylated serum protein levels and MDA | Increase insulin secretion, regulating blood lipid metabolism and improving antioxidant capacity | (Wang 2011) |
| | *Nelumbo nucifera* Gaertn. | Lotus leaf total flavonoids | B | Reduce blood glucose levels | Increase insulin secretion, regulating blood lipid metabolism and improving antioxidant capacity | (Zhu 2008; Song et al. 2017) |
| | *Pueraria lobata* (Willd.)Ohwi | Pueraria flavonoids | B | Significantly reduce blood glucose levels. The hypoglycemic effect of pueraria flavonoids is equivalent to that of Tangmaikang, a positive control drug | The formation of sorbitol in polyol pathway was blocked. Protect organs from damage to reduce blood glucose levels | (Zhang et al. 2010) |
| | *Sophora japonica* L. | Rutin | D | Significantly reduce blood glucose levels, improving the trend of weight loss in mice enhance the activity of SOD, reduce the content of MDA in heart, liver and kidney. The hypoglycemic effect of rutin is equivalent to that of Xiaokewan, a positive control drug | Improving antioxidant capacity glucose and lipid metabolism | (Wang et al. 2017) |
| | *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H.F.Chou | Flavonoids Extracted from Semen Ziziphi Spi | D | Renal function index was improved obviously. Reduce the content of MDA, enhance the activity of SOD. The number of apoptotic cells in kidney decreased significantly | Inhibition of oxidative stress in renal tissue and renal cell apoptosis to play a protective role in kidney | (Gao 2013)74 |
| | *Citrus reticulata* Blanco | Citrus peels flavonoids | B | Significantly reduce serum blood glucose levels, the content of TC, TG, MDA, LDL-C, and enhance the HDL-C. The hypoglycemic effect of citrus peels flavonoid is equivalent to that of Youjiangtang, a positive control drug | Enhance body immunity and antioxidant capacity, improve dyslipidemia | (Xiao et al. 2013) |

(*continued*)

**Table 3.** Continued.

| Classification | Source | Bioactive ingredient | Experimental model | Efficacy | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| | *Coriandrum sativum* L | Coriander flavonoids | D | Reduce serum blood glucose | Increase the utilization rate of glucose. Reduce the rate of glycogen degradation and slow down the pathway of glycometabolism | (Eidi et al. 2009; Xu et al. 2017) |
| | *Rosa rugosa* Thunb. | Rosa flavonoids | B | Significantly reduce blood glucose levels, the content of MDA and enhance the activity of SOD and GSH-Px in hepar. The hypoglycemic effect of rosa flavonoids is equivalent to that of metformin, a positive control drug | Scavenging free radicals in vivo, Structural and functional integrity of protective cells, improving antioxidant capacity | (Zhou, Lu, and Luo 2011) |
| Medicinal health food | *Cirsium japonicum* Fisch.ex DC. | Cirsium japonicum flavonoids | D | Significantly reduce blood glucose levels, TC, TG | Our data indicated that the flavones improved adiponectin expression, accompanied by restoring of the dysregulated activities of the glucose metabolism-related enzymes, ultimately resulting in well improved glucose and lipid homeostasis | (Liao, Chen, and Wu 2010) |
| | *Fagopyrum dibotrys* (D.Don) Hara | Fagopyrum dibotrys flavonoids | D | Reduce serum blood glucose, fasting blood glucose, the serum insulin levels, the content of TC, TG, MDA, LDL-C, and enhance the SOD, HDL-C, GSH-Px | Regulating lipid metabolic disorders and enhance the antioxidant capacity of the body | (Ruan et al. 2017) |
| | *Trigonella foenum-graecum* L. | Trigonellae semen flavonoids | D | Reduce fasting blood glucose. Inhibition of weight loss and increase glucose tolerance | Repair corrupted islet, promote insulin secretion, increase liver glycogen content, increase liver glycogen content | (Jiang 2015) |
| | *Cyperus rotundus* L. | Cyperi rhizoma total flavonoids | D, E | Reduce blood glucose, the content of TC, TG, LDL-C, and enhance the SOD, HDL-C, CAT, GSH-Px | Protection of damaged cells, regulate oxidative stress disorder effectively | (Luo and Huang 2017) |
| | *Morus alba* L. | Mori cortex total flavonoids | D | Significantly reduce blood glucose levels and TC. Increase liver glycogen content. The hypoglycemic effect of mori cortex total flavonoids is equivalent to that of rosiglitazone, a positive control drug | Promoting glucose metabolism in liver, protect and restore pancreatic islet β cells | (Zhou, Dong, and Li 2010) |
| | *Epimedium brevicornu* Maxim. | Epimedii folium total flavonoids | B | Reduce blood glucose and MDA. Increase liver glycogen and muscle glycogen content, the active of SOD | Increase in liver glycogen and muscle glycogen, enhance the antioxidant capacity of the body | (Zhang, Hai, and Ding 2011) |
| | *Ginkgo biloba* L. | Ginkgo folium total flavonoids | D | Reduce blood glucose levels, the content of TC, TG, LDL-C, and enhance the HDL-C. The hypoglycemic effect of ginkgo folium total flavonoids is equivalent to that of metformin, a positive control drug | Regulate blood lipids and scavenging free radical | (Wang et al. 2008) |

**Table 4.** The role and mechanism of terpenoids bioactive ingredients in MFH and MHF on diabetes.

| Classification | Source | Bioactive ingredient | Experimental model | Efficacy | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| Medicine food homology | *Euryale ferox* Salisb. | Ethanol extract | D, G | Significantly reducing blood sugar levels in patients with diabetes. Significantly reducing 24 h urinary protein, blood urea nitrogen and blood serum creatinine levels | — | (Yang 2014; Yang 2015) |
| | *Gardenia jasminoides* Ellis | Geniposide | E | Significantly hypoglycemic effect, together with lowering body weight, increasing the insulin content in plasma, and improving the oral glucose tolerance test | Promote the proliferation of islet β cells and increase plasma insulin level, Activation of downstream Akt pathway of insulin receptor | (Yao et al. 2014) |
| | *Cornus officinalis* Sieb.et Zucc. | Terpenes from Fructus Corni | B, D | Significantly decreased blood sugar levels ($p < 0.05$) and elevated the fasting insulin level ($p < 0.05$, Significantly increased the hepatic glycogen content and evidently alleviate the level of glycosylated serum protein ($p < 0.05$), No significant difference compared with the positive control acarbose ($p > 0.05$) | Increased glucose tolerance and liver glycogen synthesis. Protected islet β cells or repaired damaged β cells | (Han et al. 2006) |
| Medicinal health food | *Ligustrum lucidum* Ait. | Oleanic acid | B | Significantly reduced blood sugar, TC, TG, LDL-C levels, and improved HDL-C | Anti-free radical damage and enhance the body's antioxidant defense system capabilities | (Gao et al. 2009) |
| | *Rehmannia glutinosa* Libosch. | Catalpol | B | Significantly decreased the blood glucose, improved the oral glucose tolerance and blood lipid level in a dose depend, the hypoglycemic effect of 200 $mg{\cdot}kg^{-1}$ catalpol is equivalent to that of 500 $mg{\cdot}kg^{-1}$ metformin, a positive control drug | Promote the release of β-endorphin, increase glucose transport rate and inhibit glycosylation | (Zhao et al. 2009) |

By investigating the effect of MDG-1 from *Ophiopogon japonicus* (Thunb.) KerGawl. on glucose tolerance and regulation of intestinal flora in diabetic KKay mice, the possible hypoglycemic mechanism of MDG-1 was analyzed. The results showed that the number of *Escherichia coli* and *Streptococcus* in the gut of diabetic mice increased significantly, whereas the number of lactic acid bacteria and *Bifidobacterium* decreased significantly, compared to those in the normal control group. MDG-1 at all doses tested had a certain inhibitory effect on the proliferation of *E. coli* and *Streptococcus*, and promoted the proliferation of *Bifidobacterium* and lactic acid bacteria. Taken together, MDG-1 can improve clinical symptoms and glucose tolerance and modulate intestinal microecological imbalance in KKay mice (Wang et al. 2011).

In summary, polysaccharides not only show positive effects, such as enhancing immune function, improving the body's resistance, and reducing side effects, but they also significantly prevent and treat DM and its complications Polysaccharides in MFH and MHF have broad prospects in future research and development of clinical drugs because of their wide range of biological activities and low toxicity.

### Others

In addition to the bioactive ingredients mentioned above (saponins, flavonoids, terpenoids, alkaloids, and polysaccharides), other components extracted from medicinal homology and health food have blood glucose-lowering effects. Although some bioactive ingredients have not been determined, others have been found to show certain preventive and therapeutic effects on blood sugar in ongoing research, such as safflor glycoside in *Crocus sativus* L., volatile oils in *Cinnamomum cassia* Presl, organic acids in *Cornus officinalis* Siet. et Zucc., and magnolol in *Magnolia officinalis* Rehd. et Wils (Jin, Xie, and He 2009; Li et al. 2012; Li and Kang 2012; Sun 2013). We reviewed relevant literature and summarized the hypoglycemic effects and underlying mechanisms of MFH and MHF extracts in Table 7, whereas the basic structure of the hypoglycemic compounds is shown in Figure 7.

## Hypoglycemic mechanisms of MFH and MHF

Recently, the number of studies on MFH and MHF in TCM has been increasing. It is noteworthy that the mechanism of

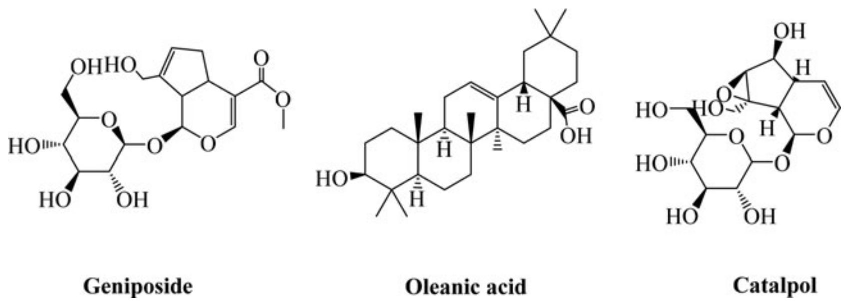


Figure 5. The structure of hypoglycemic compounds of terpenoids from MFH and MHF.

Table 5. The role and mechanism of alkaloids bioactive ingredients in MFH and MHF on diabetes.

| Classification | Source | Bioactive ingredient | Experimental model | Efficacy | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| Medicine food homology | *Morus alba* L. | 1-DNJ | D | Significantly reduce blood glucose levels | Inhibit gluconeogenesis promote glycolysis and the effect of anti-glucagon to have hypoglycemic effect | (Zou 2004; Yuan et al. 2005) |
| | *Nelumbo nucifera* Gaertn. | Nuciferin | H | Significantly reduce the weight, blood glucose levels, Serum insulin levels and insulin resistance index | Improved the glucose metabolism and insulin sensitivity. And related to the regulation of insulin signaling pathway and the activation of glucose transport pathway | (Pu, Zhang, and Lei 2015) |
| Medicinal health food | *Euodia rutaecarpa* (Juss.) Benth. | Evodiamine | C | Reduce glucose level and increase glucose tolerance | Enhancing insulin sensitivity and inhibition of mTOR-S6K signaling and IRS1 serine phosphorylation | (Wang et al. 2013) |

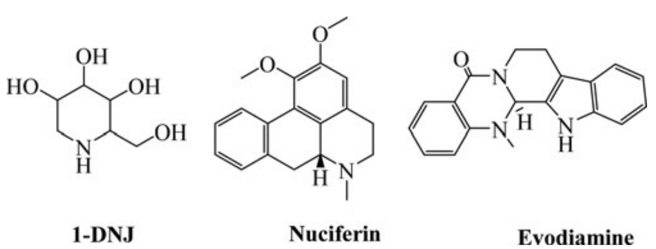


Figure 6. The structure of hypoglycemic compounds of alkaloids from MFH and MHF.

the bioactive ingredients of MFH and MHF with hypoglycemic effects can be summarized as follows:

## Insulin-mimetic effects and restoration of damaged pancreas

### Restoration of islet β cells function

A study found that islet β cell dysfunction is one of the main pathogenesis of DM (Weir and Bonner-Weir 2013). Insulin is the main hormone regulating blood sugar level in the body. β cells in the central region of the pancreas are the primary sites of insulin synthesis (Lovre and Fonseca 2015). Islet β cell damage directly leads to decreased islet function and elevated blood glucose level. Thus, the state and insulin secretion function of pancreatic tissue are particularly important for maintaining normal insulin and blood sugar levels. However, studies have indicated that MFH and MHF can increase insulin secretion by protecting and restoring islet β cells (Li et al. 2017). *Ganoderma* polysaccharides effectively control elevation of blood glucose level by repairing islet cells and increasing insulin secretion and glucose kinase activity. Studies have shown that berberine regulates islet function in two ways. For DM patients with significant IR, berberine can lower blood sugar levels by increasing insulin sensitivity. For advanced DM patients with islet β cell failure, berberine increases insulin secretion by repairing islet cells (Chueh and Lin 2012). Another study showed a protective effect of *Camellia nitidissima* polyphenols (CNP) on blood glucose level and the pancreas of type 2 diabetic rats. The results indicated that CNP repaired pancreatic injury and promoted insulin secretion, effectively reducing fasting blood glucose level and improving glucose tolerance, thereby suggesting that CNP have a dose-dependent protective effect on pancreas (Ma et al. 2017).

## Insulin-mimetic effects and stimulation of insulin secretion

Insulin is a blood sugar-lowering hormone secreted by islet cells. After binding to receptors on target cells, it causes a series of post-receptor signaling that activates glucose transporters to transport glucose to target cells for oxidative metabolism and maintenance of normal blood glucose level (Li and Zhen 2006). Absolute and relative lack of insulin secretion is an important cause of persistent hyperglycemia in DM. Various substances in MFH and MHF have shown direct insulin-mimetic effects and direct stimulating effect on functional β cells to secrete insulin. For example, bitter melon saponin, which is called ‘plant insulin’, has a direct insulin-like effect (Chai et al. 2008). Besides, research studies in STZ-induced diabetic mice administered water-soluble *Ophiopogon japonicus* (OJP1) showed a significant reduction in blood glucose and serum insulin levels, indicating protective effects on islet β cells (Chen et al. 2011).

**Table 6.** The role and mechanism of polysaccharides bioactive ingredients in MFH and MHF on diabetes.

| Classification | Source | Bioactive ingredient | Experimental model | Efficacy | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| Medicine food homology | *Polygonatum sibiricum* Red. | Rhizomapolygonatum polysaccharides | B | Significantly reduce blood glucose and MDA, increase SOD and GSH-Px activity | Inhibition of islet cell apoptosis | (Gong et al. 2008) |
| | *Portulaca oleracea* L. | Portulaca polysaccharides | B | Reduce fasting blood glucose and blood fat | Repair of islet cells, enhancement of insulin secretion and serum insulin level | (Li et al. 2012) |
| | *Polygonatum odoratum* (Mill.) Druce | Polygonatum odoratum polysaccharides | B | Reduce blood glucose, the content of TC, TG, LDL-C, and enhance the HDL-C | Improve lipid metabolism disorder | (Zhu, Xie, and Wang 2008) |
| | *Dioscorea opposita* Thunb. | Yam polysaccharides | B | Significantly reduce blood glucose and elevate C-peptide levels | Increase insulin secretion and improve the function of impaired pancreatic β cells | (Sun and Xie 2011) |
| | *Lilium brownie* F.E.Brown var.*viridulum* Baker | Lily polysaccharides | B | Significantly reduce blood glucose. The hypoglycemic effect of lily polysaccharidesl is equivalent to that of Jiangtanglin, a positive control drug | Repairs beta islet cells, enhances insulin secretion and reduces adrenocortical hormone secretion, and promotes the conversion of blood glucose into glycogen in the liver | (Liu et al. 2002) |
| | *Laminaria japonica* Aresch. | Kelp polysaccharides | B | Significantly reduce blood glucose and blood urea nitrogen, increase serum calcium and serum insulin levels, and promote damaged islet β cells to restore | Promote islet β cells to secret insulin, restore damaged islet and have a protective effect on islet cells | (Zeng and An 2007) |
| | *Lycium barbarum* L. | Medlar polysaccharides | B | Significantly reduce blood sugar | Promote glucose to transport to insulin-sensitive tissues for cells using, improve the insulin sensitivity | (Zhao 2018) |
| | *Poria cocos* (Schw.) Wolf | Pachyman polysaccharides | B | Significantly reduce blood glucose and MDA levels, improved SOD. The hypoglycemic effect of pachyman polysaccharides is equivalent to that of rosiglitazone, a positive control drug | Inhibits the production of reactive oxygen species in the body and reduces the damage of islet β cells | (Zheng 2010) |
| | *Platycodon grandiflorum* (Jacq.) A.DC. | Platycodon grandiflorum polysaccharides | D | Reduce fasting blood glucose and significantly increase glucose tolerance. The hypoglycemic effect of platycodon grandiflorum polysaccharides is equivalent to that of glibenclamide, a positive control drug | Improving insulin resistance and antioxidant capacity | (Qiao and Meng 2015) |
| | *Taraxacum mongolicum* Hand. -Mazz | Herba taraxaci polysaccharides | B | Reduce serum blood glucose and the content of MDA, enhance SOD and GSH-Px activity | Inhibit glycosidase activity | (Song, Liu, and Wang 2009) |
| | *Coix lacryma-jobi* L. var. *mayuen*. (Roman.) Stapf | Coix seed polysaccharides | D | Improve the diabetic rats impaired glucose tolerance increase the amount of glycogen, and show some dose-effect relationship | Inhibit glycosidase activity | (Xu, Zhou, and Huang 2000) |
| | *Angelica sinensis* (Oliv.) Diels. | Angelica polysaccharides | D | Significantly reduce blood glucose and glycosylated hemoglobin. The hypoglycemic effect of angelica polysaccharides is equivalent to that of metformin, a positive control drug | Regulating blood lipids and cholesterol | (Li and Chen 2007) |

(*continued*)

**Table 6.** Continued.

| Classification | Source | Bioactive ingredient | Experimental model | Efficacy | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| | *Dendrobium officinale* Kimura et Migo | Dendrobium officinale polysaccharides | B | Reduce fasting blood glucose and glycosylated serum protein content, and enhance serum insulin levels | — | (Tang et al. 2016) |
| | *Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. | Astragalus polysaccharides | J | Reduce fasting blood glucose, the content of TC, TG LDL-C | Improving liver lipid metabolism disorder | (Ji, Yao, and Xu 2017) |
| Medicinal health food | *Plantago asiatica* L. or *Plantago depressa* willd. | Plantain polysaccharides | D | Reduce blood sugar, improve glucose metabolism disorder, and increase insulin secretion | Repair of damaged islet β cells | (Li, Lian, and Cui 2016) |
| | *Rehmannia glutinosa* Libosch. | Rehmannia glutinosa polysaccharides | D | Have the hypoglycemic effect | Promote pancreatic β cells to secret | (Li and Meng 2015) |
| | *Eucommia ulmoides* Oliv. | Eucommia ulmoides polysaccharides | B | Reduce blood glucose, weight, MDA, enhance the SOD | Improve the immunity and antioxidant capacity of the body | (Liu et al. 2010) |
| | *Paeonia suffruticosa* Andr. | Mudan cortex polysaccharides | D | Significantly reduce fasting blood glucose, improve glucose tolerance and dyslipidemia, increase the low-affinity of liver cell and the maximum binding capacity of insulin receptor to increase insulin sensitivity index | Increase the number of insulin receptors and improve insulin resistance in the receptor chain | (Wang et al. 2001) |
| | *Ophiopogon japonicus* (L.f) Ker-Gawl. | Ophiopogon japonicas polysaccharides | D, I | Inhibit high blood sugar | Protect and restore pancreatic islet B cells and promote insulin secretion, thereby improving insulin sensitivity | (Sha et al. 2014; He 2007) |
| | *Anemarrhena asphodeloides* Bge. | Anemarrhena asphodeloides polysaccharides | D | Significantly reduce blood glucose levels and TC, LDL-C | Improving insulin resistance and repairing damaged islet cells | (Hou et al. 2018) |
| | *Ilex latifolia* Thunb. | Ku ding tea polysaccharides | B | Significantly reduce blood glucose levels, and increase glucose tolerance | Improving the function of damaged β cells and enhancing the antioxidant ability of organism | (Yu et al. 2017) |
| | *Codonopsis pilosula* (Franch.) Nannf. | Codonopsis pilosula polysaccharides | B | Significantly reduce blood glucose levels, improving insulin resistance | Improving the Antioxidant function of the body, and inhibitory effects of oxygen free radicals on islet β cells | (Fu, Hong, and Yang 2008) |
| | *Cuscuta australis* R. Br. or *Cuscuta chinensis* Lam. | Cuscuta chinensis polysaccharides | D | Reduce postprandial blood glucose, and inhibition α-amylase activity | Improve the level of oxidative stress, enhance immune function and antioxidant capacity | (Li et al. 2008) |

**Table 7.** The role and mechanism of other bioactive ingredients in MFH and MHF on diabetes.

| Classification | Source | Bioactive ingredient | Experimental model | Efficacy | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| Medicine food homology | *Lilium lancifolium* Thunb. | Dietary fiber | B | Inhibit postprandial blood sugar, delayed glucose tolerance curve | Inhibiting the rise of blood sugar caused by exogenous glucose, inhibiting the glycogen decomposition promoted by adrenaline, facilitating glycogen synthesis, and weakening the damage of alloxan to islet cells | (Li et al. 2005) |
| | *Cinnamomum cassia* Presl | Volatile oil | D | Significantly reduce the blood glucose levels | — | (Li et al. 2012) |
| | *Phyllanthus emblica* L | Gallic acid | B | Significantly reduce blood glucose levels, the hypoglycemic effect of gallic acid is equivalent to that of metformin, a positive control drug | Increasing the expression of glut-2 and PPAR gamma and inhibiting related inflammatory pathways | (Li et al. 2017; Han et al. 2009) |
| | *Prunus armeniaca* L. var. ansu Maxim. | Polypeptide | D | Significant hypoglycemic effect and dose-effect relationship. Inhibiting the increase of serum total cholesterol and triglyceride in diabetic rats also showed obvious dose-effect relationship. Promote insulin secretion in diabetic rats and resist the decline of beta cells | Significantly promote insulin secretion and resist the decrease in the number of islets β cells | (Liu et al. 2010) |
| | *Pana:c ginseng* C. A. Mey | Glycopeptide | D | Significantly reduce blood glucose levels | Related to improving pancreatic β cell function, improving insulin resistance and glycolipid metabolic disorder, promoting hepatic glycogen synthesis, scavenging free radicals and resisting lipid peroxidation in diabetic rats | (Chen et al. 2014) |
| | *Coriandrum sativum* L. | Phenols | D | Significantly reduce blood glucose levels and increase insulin secretion | Improving the utilization rate of glucose and accelerating glycolytic pathway will also reduce the speed of glycogen degradation and slow down the pathway of gluconeogenesis | (Xu et al. 2017) |
| | *Hibiscus sabdariffa* L. | Polyphenol | A | The levels of dipeptidyl peptidase IV inhibitor (DPP-4), high glucose-induced angiotensin II receptor-1 (AT-1), vimentin and fibronectin were reduced, and the compensation of glucagon-like peptide-1 receptor (GLP-1R) in the body was reversed | Insulin sensitivity can be improved by lowering DPP-4 and downstream signals and reducing AT-1 mediated renal epithelial mesenchymal transition | (Li et al. 2017) |
| | *Curcuma Longa* L | Curcumin | B | Significantly reduce blood glucose, the hypoglycemic effect of curcumin is equivalent to that of metformin, a positive control drug | Related to the enhancement of antioxidant capacity, immunity and hepatic glucokinase activity. It may also be related to increasing hepatic glycogen synthesis and decreasing hepatic glycogen output | (Wang and Zhong 2014; Huang and Li 2016; Tian et al. 2017) |
| | *Prunus mume* (Sieb.) Sieb. Et Zucc | malic acid 、citric acid and Dark plum meat 、Dark plum charcoal | B | Reduce fasting blood glucose content, but has poor drug effect when the dosage is lower than the treatment dosage | Associated with promoting the repair of damaged islet beta cells, increasing the body's insulin level, increasing the content of hepatic glycogen, accelerating glucose synthesis or conversion to fat, and lowering blood glucose | (Lu et al. 2005) |

(*continued*)

**Table 7.** Continued.

| Classification | Source | Bioactive ingredient | Experimental model | Efficacy | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| Medicinal health food | *Gastrodia elata* Bl. | Gastrodin | D | Obviously reduce fasting blood glucose level and improve glucose tolerance | Gastrodin showed certain antioxidant capacity, which could enhance the activity of oxidase in vivo and reduce the concentration of lipid peroxidation products | (Han, Qiao, and Liu 2013) |
| | *Actium lappa* L. | Arctiin | A | Obviously reduce FBG and gsp of db/db mice, improve glucose tolerance, and shows good blood glucose control function and stability. | Directly regulating lipid metabolism, through regulating adiponectin - AMPK signal pathway, reducing blood lipid concentration and improving tissue utilization of glucose, insulin resistance can be improved | (Zhang et al. 2014) |
| | *Amomurn kravanh* Pierre ex Gagnep. | Volatile oil | D | Lowering blood glucose level has protective effect on kidney damage in diabetic rats | The renal protective effect on diabetic nephropathy rats may be related to the expression of MMP-2, TGF-β1, IGF-2 | (Chen et al. 2017) |
| | *Magnolia officinalis* Rehd. et Wils. | Honokiol | D | Obviously reduce the blood glucose of diabetic mice and obviously improve the tyrosine phosphorylation level in the body | The activity of PTP1B enzyme is inhibited and the insulin signal pathway is activated so as to achieve the effect of lowering blood glucose | (Sun 2013) |
| | *Rheum palmatum* L. | Rheum emodin | C | Reduce blood glucose, blood fat and inflammatory factor production and improve insulin resistance | Related to PI3-K and GluT4 genes | (Song and Liu 2011) |
| | *Anemarrhena asphodeloides* Beg. | Total polyphenol | B, D | Obviously reduces fasting blood glucose of diabetic animals caused by alloxan and streptozotocin, and mangiferin isolated from the diabetic animals has a better effect of inhibiting alpha-glucosidase activity in vitro. | — | (Huang et al. 2005) |
| | *Cornus officinalis* Sieb. et Zucc. | Organic acid | B | Effectively controlling the blood glucose of diabetic mice | Promoting the release of acetylcholine from nerve endings, thus activating m3 receptor of islet β cells in rats, increasing insulin secretion and lowering plasma glucose level, indicating that organic acids are active ingredients for increasing plasma insulin level in rats | (Li and Kang 2012; Gao et al. 2008; Song et al. 2008; Hsu et al. 2006) |

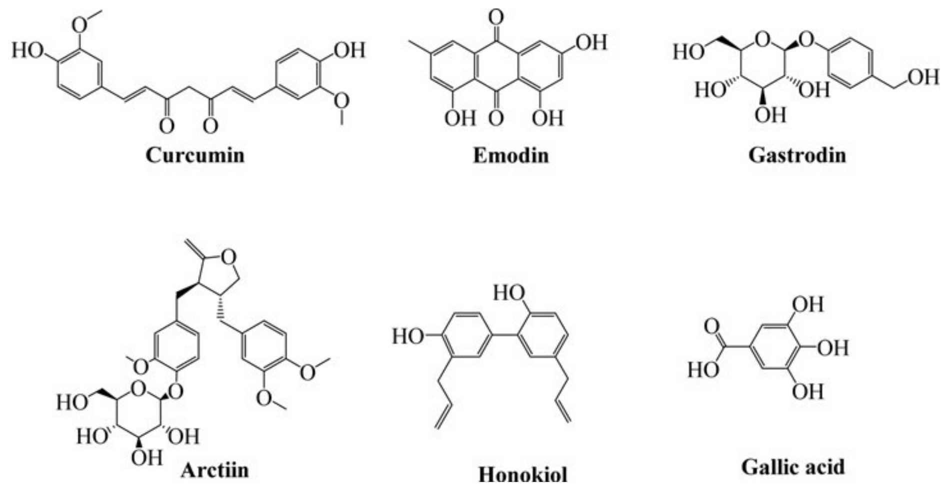


**Figure 7.** The structure of hypoglycemic compounds of other ingredients from MFH and MHF.

Furthermore, an INS-1 model of cell apoptosis was induced by $H_2O_2$, and then the cells were treated with *Lycium barbarum* polysaccharide (LBP) (100 mg/L) to investigate the effects of LBP on apoptosis and insulin secretion in INS-1 cells. The experiment result proved that LBP may improve insulin secretion and inhibit apoptosis in INS-1 cells induced with $H_2O_2$ by promoting Bcl-2 expression and reducing Bax and Caspase-3 expression (Zhang et al. 2014).

## Effects on glucose metabolism

### Glycolysis promotion and increased glucose utilization in peripheral tissues

Glucose metabolism is composed of glycolysis, aerobic oxidation of glucose, gluconeogenesis, the pentose phosphate pathway, glycogen synthesis and glycogenolysis (Guo et al. 2017). Glucose transporter-4 is mainly distributed in the skeletal muscle and fat cells and carries glucose through biological cell membranes under the action of insulin. Dysfunction in glucose utilization also causes of high blood glucose in patients (Kitabchi, Temprosa, and Knowler 2005). MFH and MHF can promote glycolysis and increase glucose utilization in peripheral tissues. Ginseng polypeptides can increase the activity of succinate dehydrogenase (SDH) and cytochrome oxidase (CCO) in the animal liver as well as the content of pyruvic acid in blood. This observation indicated that their hypoglycemic effects may be due to increased mitochondrial oxidative phosphorylation as well as activity of SDH and CCO, which are two important respiratory enzymes, reflecting the activity status of the middle and the last section of the respiratory chain. In addition, the promotion of the aerobic oxidation process in liver and cells and, hence, the acceleration of the aerobic oxidation metabolism of glucose may be involved (Huang et al. 2000).

### Inhibition of glucose absorption

Under the action of glucosidase, carbohydrates in diets release glucose that are then absorbed into blood by the small intestine; this is the main cause of postprandial blood glucose increase. α-Glucosidase and α-amylase inhibitors, which interfere with enzyme activity in the brush-border of the small intestine, could slow the liberation of D-glucose from oligosaccharides and disaccharides, resulting in delayed glucose absorption and decreased postprandial glucose level (Ye et al. 2010). Mulberry leaves exert a hypoglycemic effect by effectively inhibiting or delaying the hydrolysis of starch and maltose to glucose and inhibiting the activity of α-glucosidase (Yuan et al. 2005). The total phenols in *Anemarrhena asphodeloides* significantly reduce the fasting blood glucose level of alloxan- and STZ-induced diabetic animals, and inhibition of α-glucosidase activity by mangiferin may be one of their hypoglycemic mechanisms (Huang et al. 2005). In recent years, an increasing number of studies have been conducted on the hypoglycemic mechanism of TCM targeting the inhibition of dipeptidyl peptidase IV (DPP-4). DPP-4 inhibition, a new approach to treat type 2 DM, exerts a hypoglycemic effect by prolonging the degradation time of glucagon-like peptide-1 *in vivo*. Studies have shown that Raphani Semen and Cuscutae Semen have dpp-4 inhibitory effects (Zhou et al. 2016).

### Increased liver glycogen content

MFH and MHF improve glucose tolerance, increase the content of glycogen, and inhibit the decomposition of glycogen. Glucose disorder and gluconeogenesis are also factors leading to hyperglycemia. Early detection and intervention treatment of impaired glucose tolerance (IGT) can reduce the occurrence of DM. Research shows that syringin promotes the absorption and utilization of sugar and the synthesis of glycogen, to reduce blood glucose levels in rats (Niu et al. 2008). Mulberry total polysaccharides can increase liver glycogen levels and lower liver glucose levels in alloxan-induced hyperglycemic mice, indicating regulatory effects on glucose metabolism (Miyahara et al. 2004).

### Increased insulin sensitivity and improved IR

IR is an important and significant pathogenic feature of type 2 DM. IR refers to the body’s decreased glucose uptake ability and processing, and at certain insulin levels, the muscle and fat cells cannot utilize sugar. Furthermore, under those conditions, the liver cells cannot effectively inhibit glycogen decomposition and glycogenesis, and excessive glucose is released into the blood, resulting in increased blood glucose concentration. MFH and MHF have been shown to increase insulin sensitivity and improve IR as follows. Firstly, they increase the number and affinity of insulin receptors. It has been shown that cinnamon polyphenols improve the sensitivity of target cells to insulin by increasing the level of insulin receptors (Cao, Polansky, and Anderson 2007). Secondly, they act after insulin binds to its receptor, to improve the signal transduction process. Ginsenosides are the most important active component mediating the physiological activity of ginseng. Ginsenosides show significant antidiabetic effect by affecting glycolipid metabolism, increasing energy consumption, and regulating the activity and expression of the peroxidase proliferator-activated receptor (Cho et al. 2007).

### *Regulation of intestinal flora*

In addition to the above mechanisms, structural imbalance of intestinal flora is a possible important mechanism of the occurrence of diabetes (Zhang et al. 2018). Gastrointestinal homeostasis is a dynamic balance under the interaction between the host, GI tract, nutrition and energy metabolism. Glucose is the main energy source in living cells. Thus, glucose metabolic disorders can impair normal cellular function and endanger the health of an organism (Chen et al. 2017). These disorders are reflected by destruction of the diversity and stability of bacterial flora, such as reduction of beneficial bacteria or enhancement of pathogenic bacteria, which can induce low-degree and chronic inflammation in the intestinal tract and promote the release of bacterial endotoxin, thereby leading to insulin resistance (Wang, Zhang, and Jia 2003). The occurrence of diabetic diseases affects sugar and energy absorption in the body while promoting the synthesis and storage of fat. Thus, dietary intervention is an important treatment strategy for these diseases. More importantly, dietary interventions can affect intestinal flora. A study showed that oral administration of *Rehmannia glutinosa* oligosaccharides exerts hypoglycemic effects and regulates intestinal flora in alloxan-induced diabetic rats. The number of bifidobacteria and lactobacilli in the diabetic model group was significantly lower than that in the normal control group. After 14 days of treatment with *R. glutinosa* oligosaccharides, the number of bifidobacteria and lactobacilli was significantly increased compared with that in the diabetic model group ($p < 0.01$) (Xia, Ju, and Tan 2008). In another study, the effects of *Maydis stigma* polysaccharide on the intestinal microflora of STZ-induced type 2 diabetic mice was investigated, and the results indicated that *M. stigma* polysaccharide showed significant hypoglycemic effects ($p < 0.01$). The quality and quantity of *Lactobacillus* and *Bacteroides* colonies were highly increased along with increasing concentration of *M. stigma* polysaccharide (Wang et al. 2016).

## Conclusion

In summary, hypoglycemic drugs from MFH and MHF have a considerable benefit as treatments for DM, a chronic metabolic disease with no radical cure and requiring long-term medication. Dietary intervention is the most basic and important treatment strategy for this disease. In the prevention and treatment of DM, MFH and MHF are considered low-cost, safe strategies with stable efficacy. Most bioactive ingredients of MFH and MHF have bidirectional regulatory effects, and MFH and MHF can also be used to treat various complications of DM (Zhao and Wang 2010).

Recent progresses have laid the foundation for further studies of hypoglycemic MFH and MHF agents. However, the pathogenesis of DM is related to many factors. Therefore, based on the characteristics and benefits of the hypoglycemic effect of the bioactive ingredients of MFH and MHF, several aspects should be considered in developing effective compounds as a hypoglycemic treatment. Firstly, the components and mechanisms responsible for the hypoglycemic activity of MFH and MHF are unclear. Moreover, most studies of the efficacy of MFH and MHF are still at the stage of animal experimentation, whereas clinical trials are scarce. Future clinical research should be performed using modern scientific methods to afford significant discovery and innovations regarding hypoglycemic MFH and MHF agents. Secondly, the relationship between the hypoglycemic activities of MFH and MHF components and their chemical structures should be focused on in future studies, and chemical fingerprinting coupled with systems biology should be used to explore the pharmacokinetics of the multi-ingredients in these TCMs (Lu, Liao, and Li 2016). Thirdly, considering the diverse pathogenesis of diabetes, the mechanism of the hypoglycemic activity of MFH and MHF should be studied from multiple perspectives. Furthermore, in multi-targeted screening of MFH and MHF agents as novel antidiabetics, modern technologies such as *in situ* hybridization, immunohistochemistry, and gene chips should be used to explore the effects of these agents (Bai 2009; Shen et al. 2017). Finally, the prescription of hypoglycemic drugs should be based on the multi-factor, multi-locus, multi-link, and multi-mechanism characteristics of DM.

In conclusion, overcoming chronic diseases is an important task that evidently requires considerable commitment in both basic and clinical studies aimed at identifying and validating novel drug targets and new drugs. MFH and MHF, which are renewable resources, have a broad prospect for the development and production of novel antidiabetics or healthcare products that can prevent hyperglycemia.

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