Traditional Chinese Medicine in Treatment of Metabolic Syndrome

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Abstract

In management of metabolic syndrome, the traditional Chinese medicine (TCM) is an excellent representative in alternative and complementary medicines with a complete theory system and substantial herb remedies. In this article, basic principle of TCM is introduced and 22 traditional Chinese herbs are reviewed for their potential activities in the treatment of metabolic syndrome. Three herbs, ginseng, rhizoma coptidis (berberine, the major active compound) and bitter melon, were discussed in detail on their therapeutic potentials. Ginseng extracts made from root, rootlet, berry and leaf of *Panax quinquefolium* (American ginseng) and *Panax ginseng* (Asian ginseng), are proved for anti-hyperglycemia, insulin sensitization, islet protection, anti-obesity and anti-oxidation in many model systems. Energy expenditure is enhanced by ginseng through thermogenesis. Ginseng-specific saponins (ginsenosides) are considered as the major bioactive compounds for the metabolic activities of ginseng. Berberine from rhizoma coptidis is an oral hypoglycemic agent. It also has anti-obesity and anti-dyslipidemia activities. The action mechanism is related to inhibition of mitochondrial function, stimulation of glycolysis, activation of AMPK pathway, suppression of adipogenesis and induction of low-density lipoprotein (LDL) receptor expression. Bitter melon or bitter gourd (*Momordica charantia*) is able to reduce blood glucose and lipids in both normal and diabetic animals. It may also protect β cells, enhance insulin sensitivity and reduce oxidative stress. Although evidence from animals and humans consistently supports the therapeutic activities of ginseng, berberine and bitter melon, multi-center large-scale clinical trials have not been conducted to evaluate the efficacy and safety of these herbal medicines.

Metabolic syndrome characterized by insulin resistance has become a health thread worldwide in the past 20 years (1). In survey of 8,814 people in USA, prevalence of metabolic syndrome was over 40% in people of 60–69 year old (2). In the other geographic areas in the world including Europe and Asia, the prevalence of metabolic syndrome has been increasing dramatically (1). Metabolic syndrome and associated diseases have been one of major burdens in health care system in many industrialized countries.

The concept of metabolic syndrome was generated by Kylin in 1923, who described a cluster of medical conditions, such as hypertension, hyperglycemia and gout (3). The concept did not attract much attention until Dr. Gerald Reaven introduced the syndrome X in 1988 (4), which is similar to the metabolic syndrome. In 1999, WHO (World Health Organization) and EGIR (European Group for the Study of Insulin Resistance) released their diagnostic criteria for the metabolic syndrome, respectively (5;6). Now, there are at least 6 sets of diagnostic criteria for the syndrome from different organizations over the world (1;7). The primary contents of diagnostic criteria are similar among these organizations. They are hyperglycemia, insulin resistance, central obesity, hypertension, elevated triglycerides and decreased high-density lipoprotein-cholesterol (HDL-C). In the treatment of metabolic syndrome, the traditional

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Chinese medicine (TCM) is an excellent example in alternative and complementary medicine with a long history, unique theory system and variety of herb remedies.

TCM ON METABOLIC SYNDROME

TCM is a medical system developed on the basis of Taoist philosophy. The theory of TCM was first documented in an ancient Chinese book, *Huangdi Neijing* (*Yellow Thearch's Inner classic*), which was composed two thousand years ago in China (8). The book provides the foundation for diagnostic methods and therapeutic strategies including acupuncture in TCM. It proposes that the human body contains *Yin*, *Yang* and Five Elements (agents). The Five Elements are metal, wood, water, fire and earth. A perfect balance among these contents is required for the maintenance of health in the body. A disease is a consequence of disbalance of *Yin* and *Yang* or the Five Elements from cold, heat, emotions or other influences. *Qi* (air) and blood serve as mediators in communication between *Yin* and *Yang*, and among the Five Elements. The primary aim in the treatment of illness is to restore the balance, and replenish *Qi* or blood. Herbal medicines, acupuncture, and massage are often used to restore the balance in the clinical practice in TCM (9).

Obesity and type 2 diabetes are two major diseases in the metabolic syndrome. According to the book *Huangdi Neijing,* obesity is a result of over eating, and diabetes is referred as *Xiaoke* disease which is a consequence of obesity. The complications of *Xiaoke* disease include stroke, carbuncle and foot gangrene (10;11). In Chinese, *Xiao* means losing body weight and *Ke* means thirsty, which are similar to the symptoms of diabetes, losing body weight in the presence of increased drinking, eating and urination. In the TCM theory, *Xiaoke* is considered a result of *Yin* deficiency with dryness-heat. The treatment of diabetes should be focused on replenishing *Yin* (fluid) and evacuating fire (heat) from the body (12).

TCM prefers herbology, a Chinese art of combining different medical herbs into one therapy through prescription (13). According to TCM, a disease may have a set of identical symptoms among different patients, but the background (*Qi*, blood, *Yin*, *Yang*, and Five Elements) for development of the same disease is quite different in patients. Each patient should receive personalized herbology because of the difference in the background. In the personalized treatment, multiple herbs are often prescribed to form a special formula and single herb is not often used individually.

The bioactivities of many Chinese herbs have been identified with modern technologies in chemistry and pharmacology. With pharmacological concepts in medicine, many scientists made an effort in isolation and purification of bioactive components in herbs with a hope to enrich the therapeutic activities. This strategy is used widely to study Chinese herbs in China and many other countries. Up to now, hundreds of traditional Chinese herbs and active components have been tested for treatment of diabetes, dyslipidemia and obesity. In this review, twenty two of the herbs were selected from the literature to represent the current understanding of Chinese herbs in the treatment of metabolic syndrome (Table 1). Among these, the well-recognized herbs are ginseng, coptis, bitter melon and tea. Since the effect of tea on metabolic syndrome is reviewed in a separate article in this special issue, we focus on ginseng, berberine from coptis, and bitter melon in this article.

In TCM, the major function of Asian ginseng is to replenish *Qi*, and American ginseng is used to restore *Yin*. Coptis and bitter melon are both bitter herbs and may serve to evacuate fire from the human body. In the theory of TCM, these herbs are beneficial to patients with obesity and diabetes.

GINSENG

Ginseng is one of the most popular Chinese herbal medicines. In TCM, ginseng is only referred as the root of *Panax ginseng* C. A. Mey.. However, the root of *Panax quinquefolium* L. (American ginseng) is also called ginseng sometimes. Since the major effects of ginseng include adaptogen, aphrodisiac and nourishing stimulant, which are required for treatment of aging, ginseng has been historically used in the treatment of most ageing-associated diseases (14). Metabolic syndrome has a high prevalence in aging population. Ginseng has been widely studied for treatment of diabetes, dyslipidemia and obesity. Interestingly, in addition to ginseng root, ginseng berry and leaf were also shown to reduce blood glucose in diabetic models (15; 16).

1. Ginsenosides

Ginseng contains many bioactive compounds. The representative compounds are ginseng-specific saponins (ginsenosides, Fig. 1), which have clear bioactivities in the regulation of blood glucose and blood pressure. The total contents of ginsenosides are 2.6% – 6.6% of dry weight of ginseng roots in Asian ginseng, red ginseng (heated and marinated Asian ginseng) and American ginseng (17). The ginsenosides are divided into several different compounds, such as Rb_1, Rb_2, Rc, Rd, Re and Rg_1. In addition to ginsenosides, some glycans and peptides isolated from ginseng root may also have hypoglycemic effect in mouse models of diabetes (18). In terms of stability, ginsenosides are better than the glycans and peptides. Ginsenosides can be administrated orally or through injection. However, the bioactivities in glycans and peptides are inactivated in the stomach or intestine if taken orally. When ginseng is taken orally, ginsenosides should be the major active compounds in the blood. Ginsenosides are expensive since the price of ginseng root is much higher than many other herbs. As a result, the crude extract of ginseng root is often used instead of ginsenosides in many laboratory studies.

2. Berry and leaf of American ginseng

A recent study reported that ginseng leaf and berry have a higher level of ginsenosides than the ginseng root, and they are also effective in the treatment of diabetes (16). In ob/ob mice, ginseng berry extract was tested in the regulation of blood glucose. After 12-day injection of the berry extract, hyperglycemia was reduced significantly and glucose tolerance was improved markedly. Fasting and postprandial insulin levels were decreased significantly. In the hyperinsulinemic-euglycemic clamp assay, insulin-stimulated glucose disposal was increased by more than twofold in the treated mice. The ginseng berry extract was found to reduce food intake, decrease body weight, and enhance energy expenditure as indicated by increased body temperature. Analysis of compounds in the berry extract indicated that ginsenoside Re was the major component in the ginseng berry extract. Injection of ginsenoside Re for 12 days produced a similar efficacy on glucose metabolism in ob/ob mice. However, the body weight and energy expenditure were not changed by ginsenoside Re, suggesting that the effect on energy metabolism might be induced by other components in the berry extract (19). The berry extract was also tested in db/db mice, and similar results were obtained for glucose and energy metabolism (20). The berry extract was also able to reduce body weight in the lean littermates (20), suggesting that the ginseng bioactivities are observed in both lean and genetic obese mice.

The effects of ginseng root and ginseng berry on metabolic syndrome were compared in a study in ob/ob mice (21). The results showed that the extract of ginseng berry had much stronger effects than ginseng root extract in reduction of blood glucose, improving glucose tolerance and lowering body weight. The root extract had modest effects on glucose metabolism and exhibited no activity in the regulation of body weight (21). The difference might be due to the higher content of ginsenosides in the ginseng berry (19).

In addition to ginseng berry, ginseng leaf also has a high content of ginsenosides, and therapeutic effects of leaf extract were observed in diabetic (ob/ob) mice (22). In the leaf extract, all of the major ginsenosides were detected by high performance liquid chromatography (HPLC), and their contents were even higher than those in the ginseng berry and root. In this study, the leaf extract was shown to reduce blood glucose, increase body temperature and decrease body weight after 12-day injection in ob/ob mice (22).

3. Ginseng on glucose metabolism

In dietary obese mice, an ethanol extract of wild ginseng significantly inhibited body weight gain, decreased blood glucose, triglycerides and free fatty acids (FFA) levels, and improved insulin sensitivity (23). The sizes of white and brown adipocytes were decreased by 50% in the high dose group. Extracts generated using different methods were compared for the metabolic activities of ginseng (24). Vinegar-processed ginseng radix has a better action in the correction of metabolic disorders (24).

Efficacy and safety of ginseng on glucose metabolism have been confirmed in patients with type 2 diabetes in double-blinded placebo-controlled studies (25;26). One report showed that administration of ginseng elevated mood, improved psychophysical and physical performance, reduced fasting blood glucose (FBG), hemoglobin A1c (HbA1c) and body weight in patients (25). Another report indicated that 12 weeks of supplementation with Korean red ginseng decreased plasma glucose and insulin levels, and improved insulin sensitivity significantly in patients (26). The efficacy of American ginseng was tested in lowering postprandial blood glucose (PBG) in human subjects (15;27–30). The PBG was generated by 25 g glucose administration in oral glucose tolerance test (OGTT). The results showed that doses of 1 g to 9 g American ginseng had the same effect on reducing PBG. In the diabetic subjects, administrating at 0 to 2 h before the glucose challenge, ginseng generated equal effects. In the healthy subjects, American ginseng was administrated at 40 min prior to the OGTT and was able to reduce the PBG (15;27–30). Korean red ginseng exhibited similar activities on lowering PBG (31).

4. Ginseng on lipid metabolism

In addition to glucose metabolism, ginseng is also shown to regulate lipid metabolism. The lipid metabolism by ginseng was reported 20 years ago. In one study, ginseng was administrated through diet supplement (32). American ginseng and Chinese red ginseng led to reduction of cholesterol and triglycerides levels in liver and serum of avian. The decrease of cholesterol and low-density lipoprotein-cholesterol (LDL-C) was related to the suppression of β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) reductase and cholesterol 7 α-hydroxylase activities (32). In rats and patients fed on high-cholesterol diet to generate hyperlipidemia, administration of red ginseng powder reduced plasma total cholesterol, triglycerides, FFA, platelet adhesiveness, and increased HDL-C significantly (33). In a clinical trial, administration of ginseng extract led to reduction of total cholesterol, triglycerides and LDL-C, and induction of HDL (34). These effects were attributed to the potent antioxidant effect of ginseng (34).

Ginsenosides are considered as the active components in the regulation of lipid metabolism and body weight. In mice with diet-induced hyperlipidemia, ginsenosides had an additive effect to aerobic exercise in the regulation of lipid metabolism, and antioxidant capacity (35). In obese animals fed on a high-fat diet, ginsenosides isolated from ginseng are able to reduce food intake, fat composition and serum leptin level, prevent weight gain and increase in serum triglycerides (36;37). However, opposite results were obtained by another group using mice. Injection of ginsenosides prepared from Korean red ginseng impaired lipid metabolism through inhibition of PPARα function (38). Thus, more experiments are required to evaluate the efficacy of ginseng on lipid metabolism.

5. Ginseng on β cells

Some studies suggest that ginseng is able to increase insulin secretion. In alloxan diabetic mice, the hypoglycemic effect of ginseng radix extracts was associated with elevation of blood insulin (39). The ginseng activity was abolished by injection of antisera against insulin. Impaired insulin response to glucose in the mice was restored, and insulin release, especially glucose-induced insulin release from isolated rat pancreases, was stimulated by the ginseng extracts (39). The active components of ginseng include ginsenosides and DPG-3-2, a polysaccharide fraction, in the stimulation of insulin secretion (40;41). In cultured islets, ginsenosides are able to augment glucose-stimulated insulin secretion directly (42).

Stimulation of insulin secretion by ginseng extracts may be related to biosynthesis of insulin, release of neurotransmitter acetylcholine, and protection of β-cells from apoptosis. Firstly, biosynthesis of insulin was increased significantly in the pancreatic islets by ginseng extract DPG-3-2 in vivo and in vitro (41). Secondly, release of insulin is increased by ginsenoside Rh2. This mechanism is related to release of neurotransmitter acetylcholine from nerve terminals in pancreases and stimulation of muscarinic M (3) receptors in β-cells (40;43). Finally, ginseng may prevent β-cell apoptosis (44). This mechanism is related to inhibition of uncoupling protein 2 (UCP2) expression in mitochondria, and an increase in ATP production. Ginseng was shown to induce expression of anti-apoptotic factor Bcl-2 while suppress expression of pro-apoptotic factor caspase-9 (44). In β-cell line MIN6N8 cells, ginseng extract and ginsenosides were able to inhibit cytokine-induced apoptosis (45). The antioxidant activity of ginsenosides was involved in the anti-apoptosis activity as production of free radicals, such as nitric oxide (NO), and reactive oxygen species (ROS) was reduced by ginsenosides (45).

6. Mechanism of ginsenosides action

Although the metabolic activities of ginseng have been well established, the molecular mechanism underlying the biological activities remains largely unknown for ginseng. There are very limited reports about the molecular mechanism of ginseng activities. In the regulation of insulin sensitivity, ginsenoside Re was found to enhance glucose uptake in 3T3-L1 adipocytes by enhancing insulin-induced glucose transporter 4 (GLUT4) translocation (46). Inhibition of intracellular inflammatory molecules including JNK and NF-κB may be involved in this mechanism (46). Serine phosphorylation of insulin receptor substrate (IRS) is a major mechanism of insulin resistance. The phosphorylation leads to interruption of signal transduction from insulin receptor to downstream molecules such as Phosphoinositide 3-kinase (PI3K). The phosphorylation is catalyzed by many serine kinases, such as JNK, IKK, S6K and PKC, in the inflammatory signaling pathways (47). Inhibition of JNK and IKK will be able to reduce the serine phosphorylation in the IRS proteins and prevent inhibition of IRS function. It is likely that ginseng extracts increase insulin signaling activity by suppressing inflammatory response.

In the regulation of food intake and nutrient absorption, ginsenosides were found to inhibit Neuropeptide Y (NPY) expression in the hypothalamus (37) and inhibit pancreatic lipase (36). NPY is a neurotransmitter with well-known function in the stimulation of food intake in the brain (48). Pancreatic lipase is an enzyme secreted from the pancreatic exocrine cells to break apart fat molecules through hydrolysis. The effect of ginseng on lipid metabolism may be a result of reduced food intake, decreased lipid absorption and enhanced insulin sensitivity.

In summary, ginseng has anti-hyperglycemia, and anti-obesity effects (Fig. 2). The mechanism of action is related to insulin sensitization, insulin secretion, β-cell protection, thermogenesis and antioxidantion. It's a promising herbal remedy in the treatment of metabolic syndrome. However, the cellular and molecular mechanisms of the metabolic activities of ginseng remain largely unknown. More research is required to establish the signaling pathway for ginseng.

BERBERINE

Berberine, a botanical alkaloid in the root and bark of several plants, is the major active component of rhizoma coptidis, a popular traditional Chinese medication in the treatment of diabetes and infections. Rhizoma coptidis is prepared from rhizoma of several herbs including *Coptis chinensis French*, *Coptis deltoidea C. Y. Cheng et Hsiao* and *Coptis teetoides C. Y. Cheng*. Rhizoma Coptidis was recorded as a medication as early as A.D. 200 in *The Herbal Classic of the Divine Plowman* (Shen Nong Ben Cao Jing). In about A.D. 500, the anti-diabetes activity of Rhizoma Coptidis was recorded for the first time in a book "Note of Elite Physicians" by Hongjing Tao. However, in most records or books, the major therapeutic activity of Rhizoma Coptidis is claimed for the treatment of infection and inflammation because infectious diseases were much more popular than diabetes in ancient China (49;50).

Berberine (Fig. 3) is the bioactive compound in Rhizoma Coptidis for anti-diabetes and anti-infection. The content of berberine in Rhizoma Coptidis is 5.2%–7.7%. Since Rhizoma Coptidis is expensive, most berberine used in clinical application is prepared from herbs other than Rhizoma Coptidis, such as *Berberis amurense Rupr.* and *Phellodendron amurense Rupr.*. Berberine has many chemical forms, i.e., berberine hydrochloride, berberine sulfate, berberine citrate or phosphate (50). Among then, berberine hydrochloride is the most common form. Berberine has a well-established antimicrobial activity in the control of infection by bacteria, viruses, fungi, protozoans and helminthes (8,14). In China, berberine is an over-the-counter drug for the treatment of gastrointestinal infections, such as bacteria diarrhea. In 1988, the hypoglycemic effect of berberine was found when berberine was used to treat diarrhea in diabetic patients in China (13). Since then, berberine has been used as an anti-hyperglycemic agent by many physicians in China. There is substantial numbers of clinical reports about the hypoglycemic action of berberine in Chinese literatures.

1. Efficacy of berberine on diabetic patients

Berberine was reported to have a comparable activity to sulphonureas or metformin in reducing blood glucose in diabetic patients in the Chinese literatures. Our study confirmed that administration of berberine (0.5 g t.i.d.) at the beginning of each major meals was able to reduce FBG as well as PBG in adult patients with newly-diagnosed type 2 diabetes (51). HbA1c of the patients was decreased by 2.0% with berberine treatment, which is comparable to that of metformin. In the poorly-controlled diabetic patients, berberine reduced HbA1c by 0.8%. Besides the hypoglycemic action, a beneficial effect of berberine on lipid metabolism was also observed (51;52). However, up to now, there is no multicenter, well controlled, long-term clinical trial to evaluate the efficacy of berberine in the treatment of diabetes.

2. Berberine on glucose metabolism in animals

Berberine was shown to reduce weight gain, enhance insulin sensitivity and decrease blood glucose in both dietary and genetic animal models of type 2 diabetes. In obese rats fed on a high-fat diet, berberine was reported to decreases body weight, FBG, PBG, fasting insulin and HOMA-IR (53–55). In rats with type 2 diabetes induced by high-fat diet and low dose of streptozotocin (STZ), FBG was decreased and insulin tolerance was improved significantly by berberine (55;56). In db/db mice, body weight was reduced and glucose tolerance was improved by berberine (54). Berberine also restored the pancreas damaged by alloxan in Wistar rats (57).

3. Berberine on lipid metabolism

Effects of berberine on lipid metabolism were evaluated in animals and human subjects. In rats fed on high-fat diet, berberine was shown to decrease serum triglycerides (55–57). Triglycerides deposition in liver and muscle was reduced significantly, and liver steatosis was

prevented by berberine administration (55;58). In addition to the activity in obese and diabetic rats, berberine reduces serum FFA in normal lean rats (55;56). Recently, berberine was demonstrated to reduce cholesterol. Two clinical trials demonstrated that berberine was able to decrease triglycerides by 35% and 22%, serum cholesterol by 29% and 16%, and LDL-C by 25% and 20% in subjects with dyslipidemia (52;59). In animal, berberine was shown to decrease triglycerides, serum cholesterol and LDL-C markedly in hamster or diabetic rats fed with high-cholesterol diet (52;57;60). However, berberine seems to have little or no effects on HDL level (52;59).

4. Insulin-independent effects of berberine in vitro

Regarding mechanism of berberine action, the first study was conducted using hepatocytes (HepG2 cell line) and published in 2002 (61). In this study, berberine was shown to have insulin-independent activity in the stimulation of glucose consumption in cultured cells, and this activity is similar to that of metformin. Berberine did not induce insulin secretion in β cells (β-TC3 cell line) (61). In later studies conducted by several labs, the insulin-independent activity of berberine was confirmed in other cell models including muscle cells (L6 and C2C12 cell lines) and adipocytes (3T3-L1 cell line) (53;54;62–66). In the presence of insulin, berberine was able to enhance the insulin-induced glucose consumption and glucose uptake. Since berberine is a strong stimulus for glucose uptake, several groups investigated the effect of berberine on glucose transporters. The conclusions were controversial. Two groups reported that berberine was able to stimulate GLUT4 translocation (54;66), but this activity was not observed by other groups (63;64). One study indicated that berberine was able to enhance GLUT1 expression (63). However, this effect was not observed in other studies (53;64). Our study suggests that berberine may have a weak direct effect on the translocation or expression of glucose transporters, and this is only detectable with high concentration of berberine (≥10 μM). Regulation of GLUTs is not the major mechanism by which berberine stimulate glucose metabolism (53).

5. Berberine activates AMPK

AMPK (AMP-activated protein kinase) is a target for berberine in the regulation of glucose metabolism. AMPK is an important energy-sensing/signaling system in mammalian cells. It is a member of a metabolite-sensing protein kinase family that acts as a fuel gauge by monitoring cellular energy levels, such as AMP/ATP ratio (67). Activation of AMPK is well known to increase insulin sensitivity and mitochondrial function (68). Phosphorylation of Thr-172 within the activation loop of the catalytic domain of the alpha subunit (AMPKα) is necessary for AMPK activity. Five published studies consistently demonstrate that berberine is a strong inducer for Thr-172 phosphorylation in AMPK (53;54;60;62;63). In cells, the phosphorylation was increased at 0.5 h after exposure to berberine and the increase was maintained for at least 16 h (53).

6. Berberine inhibits mitochondrial function

Berberine may activate AMPK through increasing AMP/ATP ratio (53;62). Berberine inhibits ATP biosynthesis in mitochondria. It was reported 20 years ago that berberine inhibited NAD-linked respiration in isolated mitochondria of rat liver in vitro (69;70). This activity was confirmed in a recent study published in 2003 (71). In the mitochondria, berberine was shown to inhibit monoamine oxidase directly (72–74). The mitochondrial inhibition was demonstrated in living cells in our recent study (53). In search for mechanism of increased AMP/ATP ratio, we investigated berberine effect on oxygen consumption by living cells. We observed that berberine inhibited oxygen consumption and enhanced glycolysis as indicated by increased lactate production. As the efficiency of ATP biosynthesis by glycolysis is much lower compared to that in mitochondria, this change is responsible for the increased AMP/ATP ratio.

Based on these observations, we hypothesized that AMPK activation may be a consequence of mitochondrial inhibition by berberine (53). The study also suggests that modest inhibition of mitochondrial function may contribute to improvement of insulin sensitivity. This possibility is supported by a recent report in which inhibition of mitochondrial oxidative phosphorylation through gene knockout provided protection of mice from diet-induced insulin resistance, diabetes and obesity (75). This mechanism may be used by berberine in the up-regulation of glucose and lipid metabolism. However, this possibility remains to be tested in vivo.

7. Berberine as an α-glucosidase inhibitor

Berberine may reduce glucose absorption in intestine. It is interesting that berberine also acts as an α-glucosidase inhibitor. α-Glucosidase is an intestinal enzyme for digestion of carbohydrates, such as starch and table sugar, into monosaccharides. Inhibition of this enzyme will lead to suppression of absorption of dietary carbohydrates. α-Glucosidase inhibitor is a class of oral hypoglycemic agent for type 2 diabetes that works by reducing glucose absorption. α-Glucosidase activity was inhibited by berberine in Caco-2 cells (76). Glucose transportation cross the intestinal epithelium was also decreased after berberine treatment (77). These two events may be involved in control of blood glucose by berberine.

8. Berberine inhibits adipogenesis

Inhibition of adipogenesis may contribute to anti-obesity activity of berberine. Berberine was shown to suppress adipocytes differentiation and reduce lipid accumulation in 3T3-L1 adipocytes (54;65;78–80). In the cells treated by berberine, expression of several lipogenic genes including PPARγ, C/EBPα, SREBP-1c, fatty acid synthase, acetyl-CoA carboxylase, acyl-CoA synthase, lipoprotein lipase, aP2 and CD36 was suppressed. Since PPARγ and C/EBPα are master transcription regulators of adipogenesis and most of these genes (fatty acid synthase, acetyl-CoA carboxylase, acyl-CoA synthase, lipoprotein lipase, aP2 and CD36) are targets of the two transcription factors (81). Inhibition of PPARγ and C/EBPα is likely the key mechanism for inhibition of adipogenesis by berberine.

9. Berberine increases LDLR mRNA level

The mechanism by which berberine reduces cholesterol is related to the increased expression of LDL receptor (LDLR) in both mRNA and protein in liver (52;82). The increase in mRNA of LDLR is a result of extended half-life of mRNA in HepG2 cells (52;82). Activation of extracellular signal-regulated kinases (ERK) by berberine may contribute to the increased mRNA stability, and the ERK activation by berberine is specific to liver as no ERK activation was observed in other type of cells (53;83;84). Activation of JNK by berberine was reported and might be involved in the elevation of LDLR (85). The effect of berberine on LDLR was blocked by a JNK inhibitor.

In summary, berberine, a single compound identified from a Chinese herb, has a promising activity in the control of blood glucose and lipid in patients (Fig. 4). The metabolic activity has been confirmed in various animal models, and the action mechanism has been suggested by recent studies. However, the mitochondrial inhibition and AMPK signaling pathway remain to be understood in detail, and tested in vivo for the metabolic activities of berberine. Additionally, the role of berberine in the regulation of gut flora is not clear, and required to be investigated given the anti-bacteria activity of berberine in the intestine. The gut flora are the microorganisms that normally live in the digestive tract and can regulate energy absorption in their hosts through fermentation of dietary fibers (86).

BITTER MELON

Bitter melon (bitter gourd, karolla or cerasee) is a popular vegetable as well as an herb in China. The species name of bitter melon is *Momordica charantia.* Bitter melon has been used as an herb for at least 600 years in South China (87).

1. "Plant insulin" of bitter melon

Bitter melon is known for its "plant insulin", a polypeptide with 166 residues, which exerts a potent hypoglycemic effect after subcutaneous injection (88). Oral administration of "plant insulin" is not effective in the regulation of glucose metabolism as the peptide is inactivated in the gut. Requirement for injection limited its clinical application. In addition to the "plant insulin", bitter melon may also contain unknown bioactive components since a substantial number of reports indicate that bitter melon is able to exert a hypoglycemic effect in a variety of animal models through oral administration.

2. Hypoglycemic effect of bitter melon on animal models

In normal mice, oral administration of bitter melon extracts decreased blood glucose (89;90). This was observed in the absence of change in intestinal absorption of glucose, insulin secretion or liver and kidney function. In STZ-induced diabetic mice, bitter melon was able to decrease blood glucose. Several possibilities were proposed for the effect of bitter melon. These include suppression of STZ-induced peroxidation and apoptosis in β-cells, and increasing glycogen content in liver and muscle, and activation of hepatic glucokinase, hexokinase, and phosphofructokinase (91). In KK-Ay mice, a genetic type 2 diabetic model, insulin sensitivity was enhanced significantly by a water extract of bitter melon (92). The effect was observed with enhanced GLUT4 translocation (92). Bitter melon was shown to enhance exercise effect on reducing blood glucose and insulin in KK-Ay mice (93).

In alloxan-induced diabetic rats, blood glucose was decreased and cataract formation, a side effect of hyperglycemia, was delayed with oral administration of bitter melon (94). Acetone extract of bitter melon was reported to reduce blood glucose and cholesterol to normal range after 15–30 days administration. The blood glucose kept in the low level even after 15 days of discontinuation of the treatment (95). Ethanol extract of bitter melon decreased FBG in normal and STZ diabetic rats. Gluconeogenesis was inhibited through down-regulation of hepatic glucose-6-phosphatase and fructose-1,6-bisphosphatase activities, and glucose oxidation was enhanced by up-regulation of glucose-6-phosphate dehydrogenase (G6PDH) activity in red cells and hepatocytes (96).

Efficacy of bitter melon was compared with other drugs in the animals. One study suggested that bitter melon had comparable hypoglycemic effect to glibenclamide in alloxan diabetic rats (97). However, another study indicated that the hypoglycemic effects of bitter melon were weaker than tolbutamide in the normal rats or metformin in STZ diabetic rats (98). The difference may be due to bitter melon had stronger effect in alloxan diabetic rats than in STZ diabetic rats. Some reports indicated that bitter melon had no hypoglycemic effects on healthy or type 1 diabetic animals (99–101). The discrepancy may be a result of difference in origin or preparation of bitter melon.

3. Hypolipidemic effect of bitter melon

Hypolipidemic effect of bitter melon was reported with the hypoglycemic effect in diabetic rats. Administration of bitter melon extracts decreased serum cholesterol, triglycerides, LDL-C, urea, creatinine, alanine transaminase (ALT), aspartate transaminase (AST), and increased serum HDL-C, suggesting that bitter melon may correct hyperlipidemia and protect hepatic-renal functions (90;102;103). Ten weeks administration of bitter melon fruit extract nearly

restored the increased triglycerides, TC, phospholipids, LPO and malonedialdehyde (MDA), together with decreased HDL-C (104). The disturbed activities of lipogenic enzymes in liver and in kidney were also restored by bitter melon (105). Once the bitter melon extract was withdrawn, the hyperglycemia and dyslipidemia appeared again (106).

4. Mechanism of bitter melon

Antioxidant and protection of β-cells are considered the major mechanisms of bitter melon in the treatment of diabetes. In the STZ-induced diabetic rats, expression of glutathione S-transferase (GST) isoenzymes was altered in the liver, kidney and testis. This disturbance was reverted by administration of bitter melon extract (107). In addition to meat, seeds of bitter melon also exerted rapid protective effects against lipid peroxidation by scavenging of free radicals (108). In vitro and in vivo, bitter melon markedly reduced the STZ-induced lipid peroxidation and apoptosis in islets of mice and RIN cells (109). The number of β-cells was significantly increased after bitter melon treatment in STZ rats (110).

Additionally, bitter melon may also act through inhibition of glucose absorption, enhancement of glucose disposal and recover of impaired peripheral nerves. Firstly, Na^+- and K^+-dependent glucose absorption was reduced in the brush border membrane vesicles of the jejunum by administration of bitter melon juice (111;112). Another study indicated that bitter melon supplementation was able to inhibit digestion of carbohydrate by reducing maltase activity in intestine (113). Secondly, the lyophilized juice of bitter melon was able to stimulate the glucose uptake in L6 myotubes, which may be via the insulin pathway since it can be completely blocked by wortmannin, an inhibitor of PI3 kinase. Finally, the structural abnormalities of peripheral nerves were normalized with bitter melon in STZ rats (111;112).

5. Clinical trials on bitter melon

Hypoglycemic effect of bitter melon extract was also tested in more than one hundred patients with type 2 diabetes. Administration of the fruit juice or homogenized suspension of bitter melon led to significant reduction of both FBG and PBG (114;115). Nearly 75% of the patients had good response to bitter melon. Bitter melon administrated together with 50% dose of metformin or glibenclamide led to a greater reduction in blood glucose than that by full doses of the drugs, which indicated that bitter melon had synergistic effect with other oral hypoglycemic agents (116). However, these results are not supported by a recent clinical trial with forty patients that is randomized, double-blind, placebo-controlled (117). In that study, HbA1c was decreased by 0.22% in favor of bitter melon, and the difference is not significant. No significant effects were observed in FBG, total cholesterol and body weight under treatment with bitter melon. Thus, the clinical application of bitter melon needs more evidence from clinical trials.

In summary, bitter melon has some activities in the regulation of glucose and lipid metabolism (Fig. 5), which were tested in animals and patients. The results are controversial. The action mechanism remains to be established. The therapeutic efficacy of bitter melon needs to be evaluated in the clinical trials with large sample size.

CONCLUSION

TCM is an excellent system in complementary and alternative medicine. It holds great and unique potential in the management of metabolic syndrome, especially in the control of glucose and lipid metabolism. Its potential in the treatment of diabetic complications is not reviewed, but is promising to provide new effective therapies. The metabolic activities of many Chinese herbal medicines have been proved in well-designed animal experiments. The mechanism of

action remains to be investigated, and large-scale clinical trials have not been conducted for these Chinese herbal medicines.

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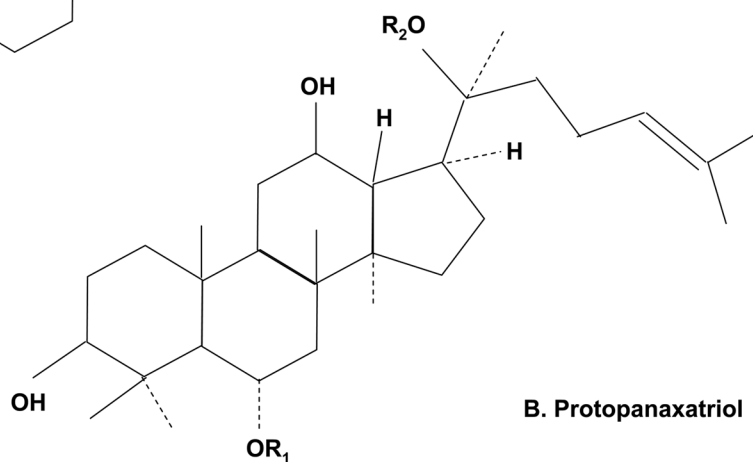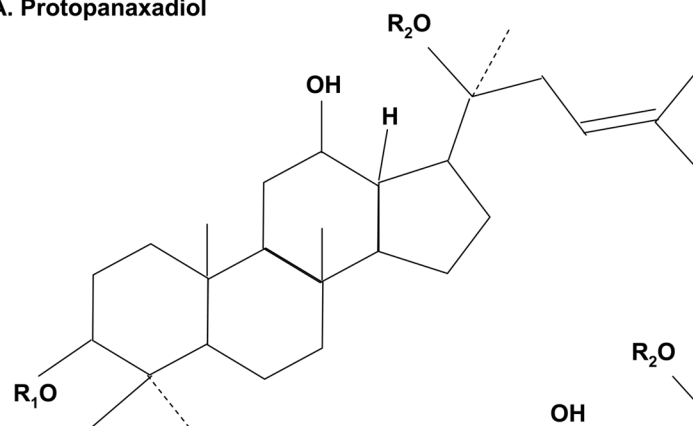
Fig. 1.
Structure of ginsenosides (ginseng-specific saponins). **A.** The ginseng saponins of protopanaxadiol include Ra1, Ra_2, Ra_3, Rb_1, Rb_2, Rb_3, Rc, Rd, Rg_2, Rg_3, Rs_1, Rs_2, et al. **B.** The ginseng saponins of protopanaxatriol include Re, Rf, Rg_1, Rg_2, Rh_1, et al.
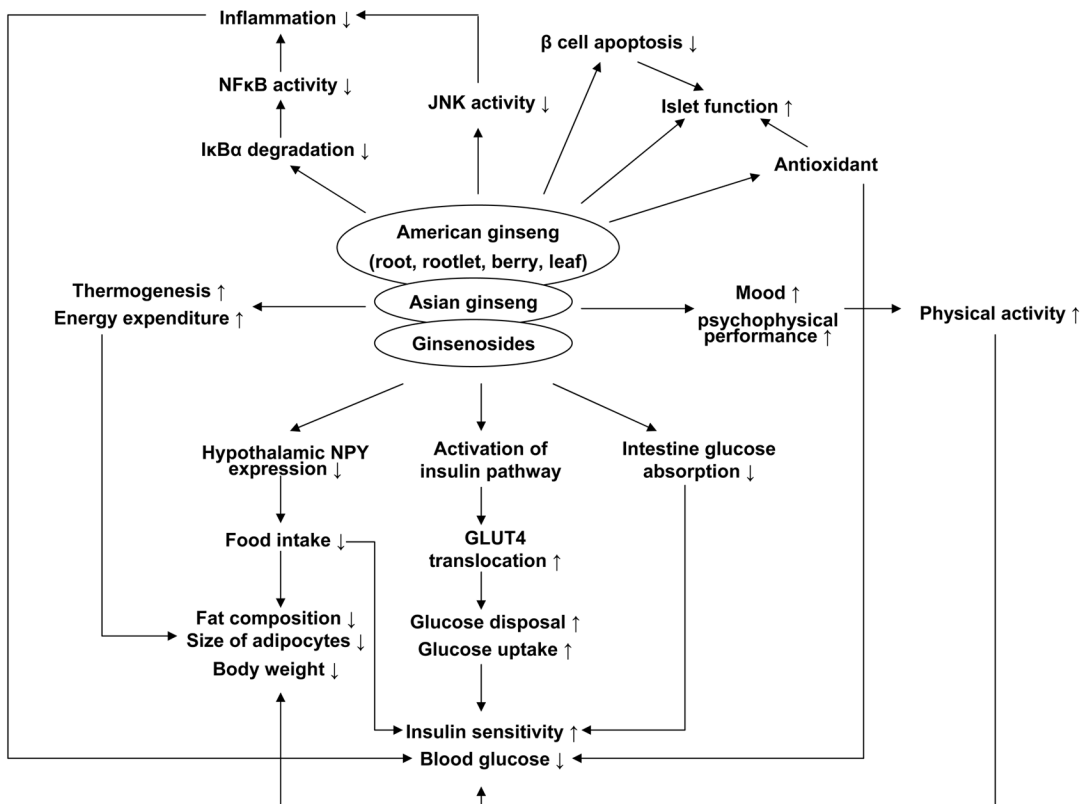
Fig. 2.
Ginseng is able to improve glucose metabolism through multiple pathways: 1) Glucose disposal is increased partially due to activation of insulin signaling pathway and GLUT4 translocation by ginseng; 2) Ginseng is able to suppress food intake through inhibition of NPY expression in hypothalamus; 3) Physical activity is increased with ginseng through improvement of mood and psychophysical performance; 4) Fat composition and body weight are reduced partially related to up-regulation of thermogenesis and energy expenditure; 5) Antioxidant and anti-inflammation of ginseng may be involved in the mechanisms of insulin sensitization; 6) Ginseng protects islet function through antioxidant and inhibition of β cell apoptosis.
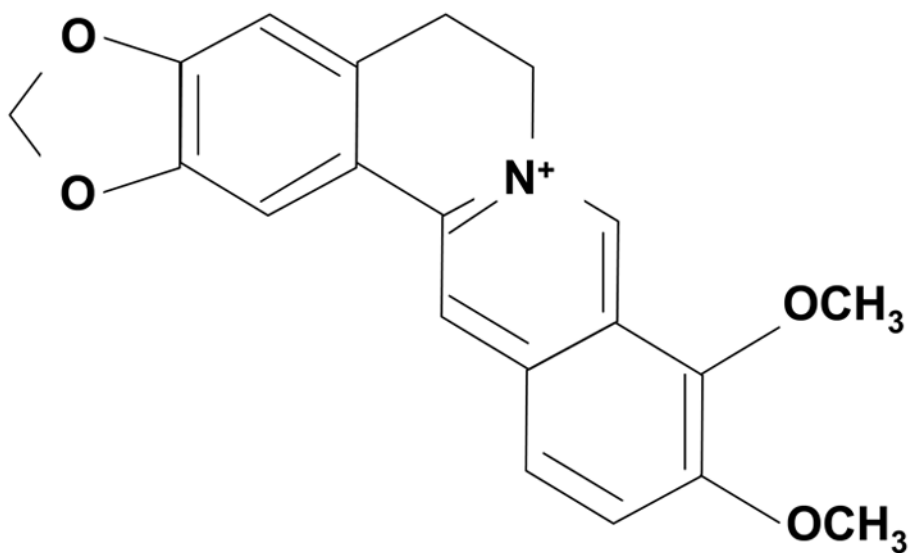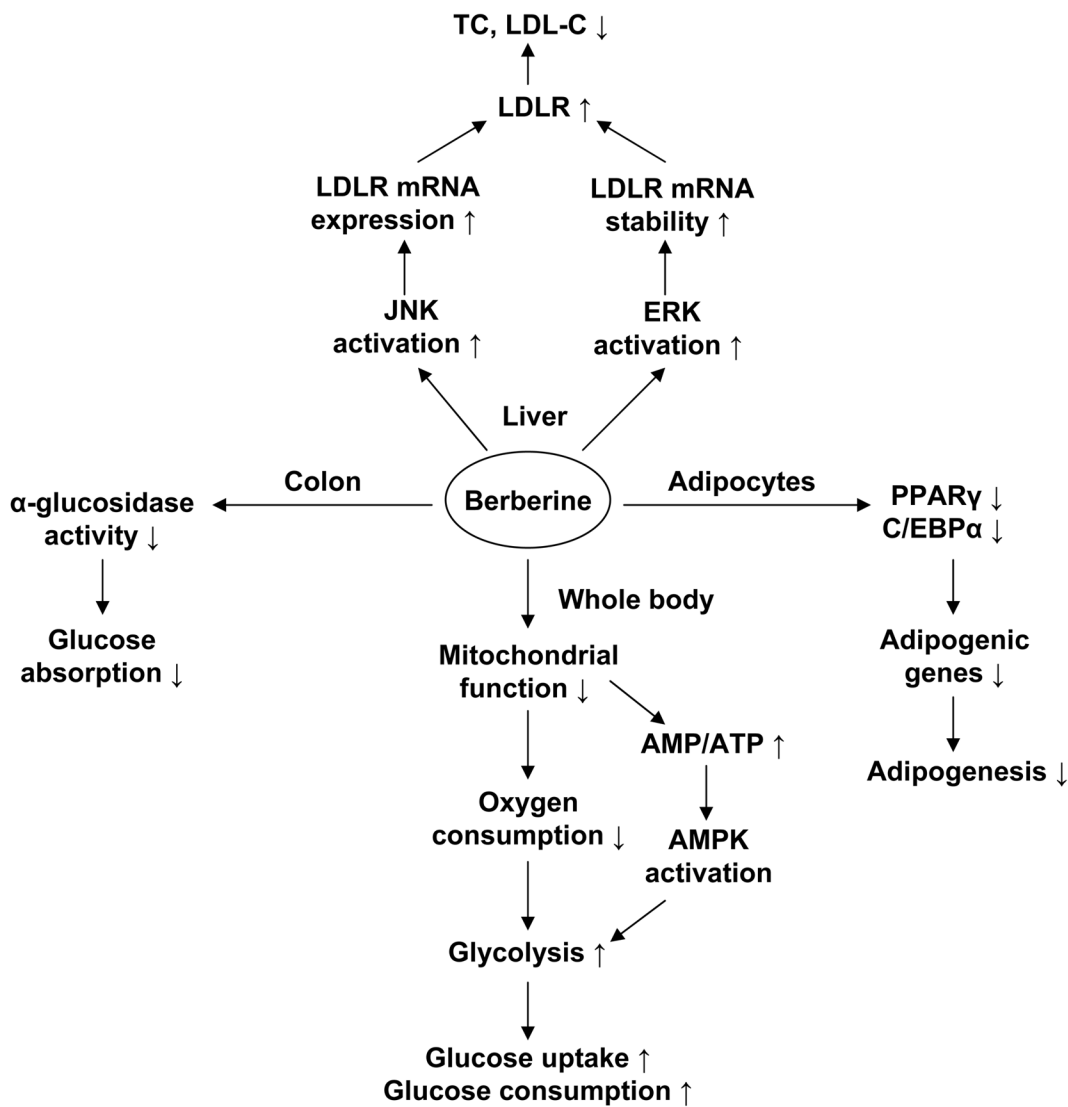
Fig. 3.
Structure of berberine

Fig. 4.
Mechanism of berberine in regulation of metabolism: 1) Berberine enhances glucose uptake through induction of glycolysis, which is due to inhibition of aerobic respiratory; 2) AMPK activation stimulated by berberine is a consequence of inhibition of mitochondrial function; 3) Berberine suppresses adipogenesis through inhibition of PPARγ and C/EBPα function; 4) Berberine is able to decrease intestinal glucose absorption by inhibition of α-glucosidase; 5) Berberine up-regulates LDL receptor (LDLR) expression through increasing LDLR mRNA, which is related to inactivation of ERK and activation of JNK pathway.
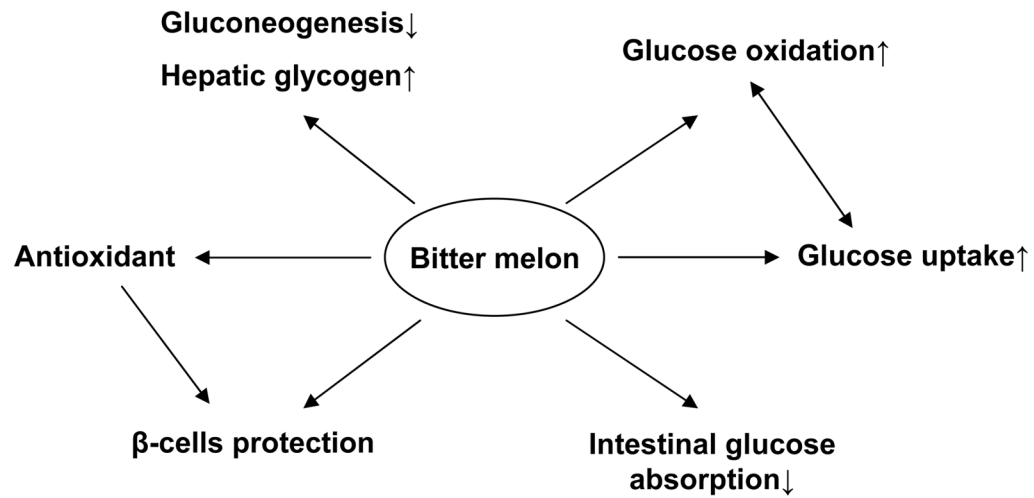
Fig. 5.
Mechanism of bitter melon in reduction of blood glucose. Antioxidant and β-cells protection are considered the major mechanisms of bitter melon action in the treatment of diabetes. Additionally, bitter melon is able to inhibit glucose absorption in intestine, reduce hepatic gluconeogenesis, and increase glucose uptake, glucose oxidation and hepatic glycogen content.

Tab 1

Effects of traditional Chinese herbs on metabolic syndrome

Name	Plant	Extract	Effect	Mechanism	Model	Ref.
Aloe vera leaves	AloeveraL. Var.Chinens is (Haw.) Berger	Pulp extracts, ethanolic extract	FBG, TC, TG, FFA, hepatic transaminases, phospholipids ↓ Insulin ↑	Hydroperoxides, GSH ↓	T1DM (STZ) rats, T2DM rats	(118)(119)(120)
Cortex Cinnamoni	Cinnamomum zeylanicum	Bark extract, aqueous extract	FBG, insulin, protein-bound sugars, TC, TG ↓ HDL ↑	α-glycosidase ↓ Glucose uptake, insulin-signaling pathway in skeletal muscle ↑	Fructose-fed rats, T2DM patients, db/db mice	(121)(122)(123)(124)(125)
Crataegus	Crataegus cuneats Sieb. Et Zucc.	Alcoholic extract of fruit, aqueous extract of leaf	TC, TG, LDL, VLDL, lipid deposits in liver and aorta, FBG ↓		HFD rats, T1DM (STZ) rats	(126)(127)
Fructus Corni	Cornus officinalis Sieb. et Zucc.	Anthocyanin and ursolic acid, alcohol extract, oleanolic acid	Lipid accumulation in liver, TG, body weight, FBG ↓ Insulin, C-peptide ↑	Proliferation of islet and postprandial insulin, GLUT4 ↑	HFD mice, T2DM rats	(128)(129)(130)
Fructus Ligustri Lucidi	Ligustrum lucidum Ait.	Decoction	FBG ↓		T1DM (alloxan) mice	(131)
Fructus Lycii	Lycium barbarum L.	Decoction, polysaccharide fractions	Anti-oxidative, FBG, TC, TG, MDA ↓ HDL, SOD activity ↑		T1DM (STZ or alloxan) rats, T1DM (alloxan) rabbits	(132)(133)(134)
Ganoder ma Lucidum	Ganoderma lucidum (Leyss.ex Fr.) Karst.	Polysaccharides, ganoderan B	TC, TG, LDL, LPO, fecal cholate, FBG ↓ Insulin, HDL, fecal TC, coprostanol ↑	Ca^{2+} inflow to the pancreaticβ cells, insulin-releasing, hepatic glucokinase, phosphofructokinase and glucose-6-phosphate dehydrogenase ↑ HMG-CoA reductase, hepatic glucose-6-phosphate, glycogen synthetase ↓ Antioxidation	HFD rats, hamsters and minipigs, T1DM (STZ or alloxan) mice	(135)(136)(137)(138)(139)(140)
Rhizoma Zingiberis	Zingiber officinale Roscoe	Aqueous extract, juice, ethanol extract, methanolic extract	FBG, TC, TG, blood pressure, body weight, LDL oxidation, atherosclerosis, LPO, lipoproteins, phospholipids ↓ Insulin, HDL, GSH-Px ↑		T1DM (STZ) rats, fructose fed rats, APOE-deficient mice, hyperlipidemic rats, cholesterol fed rabbits	(141)(142)(143)(144)(145)(146)(147)(148)
Radix Glycyrrhizae	Glycyrriza Uralensis Fisch.G.Glabra L.	Ethanolic extract, flavonoid oil	FBG, visceral adipose tissues, body weight ↓	Genes for β-oxidation, genes for fatty acid synthesis ↓ PPARγ ↑	KK-Ay mice, HFD mice	(149)(150)(151)
Radix Notoginseng	Panax notoginseng(Burk.) F.H. Chen	n-Butanol extract, pulverized root, ginsenoside Rg1	TC, TG, LDL, FBG ↓	Accumulation of abnormal lipid ↓ FXR/LXR α agonist	HFD or high-cholesterol fed rats, T1DM (alloxan) mice, APOE-deficient mice	(152)(153)(154)(155)
Radix Platycodi	Platycodon grandiflorum	Crude saponins, aqueous extract, platycodin saponin	TG, LDL, TG, liver surface fat pads, calorie intake, body weight ↓	Intestinal absorption of dietary fat ↓	Lipid emulsion fed rats, HFD mice, HFD rats	(156)(157)(158)
Pumpkin	Cucurbita moschata(Duch. ex Lam.) Duch. ex Poiret	Water extract, protein-bound polysaccharide	Fatty liver, TC, TG, FBG ↓	Lipid synthesis ↓	HFD mice, T1DM (alloxan) rats	(159)(160)

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Name	Plant	Extract	Effect	Mechanism	Model	Ref.
Radix Astragaliseu Hedysari	Astragalus membranaceus (Fisch.) Bunge var. mongholicus (Bunge) Hsiao and Astragalus membranaceus (Fisch.) Bunge	Astragalus polysaccharide	Glucose tolerance, insulin↑ FBG↓, Insulin sensitivity, glucose-insulin tolerance, ACTH, glucagon, insulin↑	Fatty acid breakdown, hepatic β-oxidation↑ PTP1B↓, insulin antagonistic hormones, Th1/Th2 cytokine ratio, apoptotic β cell percentage↓ Glycogen synthesis, PPARγ, islet mass↑	T1DM (STZ) mice and rats, TNF-α injected rats	(161)(162)(163)
Radix et Rhizom Rhei	Rheum palmatum L.	Aqueous extract and alcohol extract, wine steamed Radix et Rhizoma Rhei	FBG, LPO↓ Oral glucose tolerance↑	Insulin-stimulated glucose uptake↑ α-glucoamylase↓	APOE-deficient mice, T1DM (STZ) mice	(164)(155)(165)
Radix Puerariae	Pueraria lobata (Willd.) Ohwi.	Ethanol extract, puerarin	FBG, glycation products, insulin, abdominal fat, TC, TG, body mass↓	Antioxidant enzymes, GLUT4 and intracellular insulin signaling, α-adrenoceptors on the adrenal gland, the secretion of β-endorphin, glucose utilization, β-endorphin-like imunoreactivity↑ Aldose reductase↓	D-galactose fed rats, T1DM (STZ) rats, rats with islet damage induced by hydrogen peroxide, HFD rats, ovariectomized rats	(166)(167)(168)(169)(170)(171)(172)
Radix Rehmanniae	Rehmannia glutinosa Libosch.		FBG, urea nitrogen, 5-hydroxymethylfurfural, thiobarbituric acid reactive substance↓		T1DM (STZ) rats after nephrectomy	(173)
Radix Salviae Miltiorrhizae	Salvia miltiorrhiza Bge.		TG↓	Bcl-2 protein, cerebral SOD↑ Cerebral MDA, LPO, Bax↓	Four-vessel occlusion and reperfusion rats, APOE-deficient mice, high cholesterol diet fed rabbits	(174)(155)(175)
Rhizoma Polygonati	Polygonatum sibiricum Red.	Methanol extract	FBG↓	Hepatic glucose output, GLUT2↓	KK-Ay mice, Wistar obese rats, T1DM (STZ) mice	(176)(177)(178)(179)
Rhizoma Polygonati Odorati	Polygonatum odoratum (Mill.) Druce	Water extract, asteroidal glycoside	FBG, TG, glycosylated hemoglobin↓	α-glucosidase in digestive canal↓ Whole body glucose disposal rates, glycogen, glycogen synthase↑	Diabetic mice and rats, 90% pancreatectomized rats	(180)(181)
Salix matsudana leaves	Salix matsudana Koidz.	Polyphenol fractions, apigenin-7-O-d-glucoside, luteolin-7-O-d-glucoside and chrysoeriol-7-O-d-glucoside	Body weight, parametrial adipose tissue weights, TC↓	α-amylase and palmitic acid uptake into small intestinal↓ Norepinephrine-induced lipolysis↑	HFD mice	(182)(183)
Semen Cassiae	Cassia obtusifolia L.	Water extract	TC, TG, LDL, apoB, body weight, Lee's index, insulin, MDA↓		Hyperlipidemic mice, HFD rat	(184)(185)
Tea	Camellia sinensis	Black tea, green tea, water extracts, crude tea polysaccharides, tea polysaccharide fraction, oolong tea	FBG, phosphate, body weight, GSP, TC, TG, FFA, LDL, systolic blood pressure, LPO↓ GSH, vitamin, glucose tolerance, adiponectin, LDL particle size, insulin, HDL↑	Insulin response, enzyme activities of carbohydrate metabolism and antioxidant defenses, PPARα and PPARγ↑ Weight of the intestine↓	Healthy humans, HFD rats, T1DM (alloxan) mice, T1DM (STZ) rats, KK-A(y)/TaJcl mice, fructose-fed hamster, patients with coronary artery disease	(186)(187)(188)(189)(190)(191)(192)(193)(194)

ACTH, Adrenocorticotropic hormone; APOE, apolipoprotein E; FBG, fasting blood glucose; FFA, free fatty acids; HDL, high-density lipoprotein; HFD, high-fat diet; HMG-CoA reductase, 3-hydroxy-3-methyl-glutaryl-CoA reductase; GSH, Glutathione; GSP, glucosylated serum protein; LDL, low-density lipoprotein; LPO, lipid peroxidation; MDA, malondialdehyde; PPARγ, peroxisome proliferator-activated receptor γ; Ref., reference; SOD, superoxidase dismutase; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein.