

Herbal medicine in the treatment of patients with type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM)^[1] is a type of metabolic disease caused by metabolic disorders in the endocrine system and characterized by hyperglycemia. Insufficient insulin secretion and insulin resistance are the basic pathologic characteristics of T2DM. According to the International Diabetes Federation (IDF),^[2] the prevalence of diabetes among adults aged 20–79 in 2017 was 8.8% from a total population of 425 million, which will reach 629 million by 2045. Additionally, it is estimated that approximately half of all adult patients worldwide have not been diagnosed as of 2017. In 2017, approximately 4 million adults died of diabetes, and 46.1% of patients died before reaching the age of 60 years. These data show that the number of patients with diabetes is increasing at an alarming rate and have come to represent a challenge for human health. In addition, T2DM accounts for approximately 95% of the total population of diabetes, which leads to significant losses for human and economic health.^[3] T2DM is a chronic disease that can cause a series of complications that can lead to death.^[4] Therefore, preventing or delaying the occurrence of complications is the main purpose of treating T2DM, and the key link for those suffering from diabetes is to maintain blood glucose levels within the normal range.^[5] At present, the treatment of T2DM mainly depends on lifestyle intervention^[6] (such as nutrition therapy and physical activity), oral medication^[7] (such as biguanides, sulfonylureas, and α -glucosidase inhibitors), injected drugs^[8] (such as insulin and glucagon-like peptide-1 [7-36] amide [GLP-1] agonists), surgical treatment,^[9] and complementary and alternative treatment.^[10]

T2DM is known as a major “Xiao-Ke disease” in ancient Chinese books. And Chinese have used herbal medicines to treat the diseases for more than 1500 years. There is a growing body of research showing that herbal medicine can effectively treat T2DM.^[11–13] In this study, we reviewed the therapeutic action of herbal medicine in T2DM via anti-inflammatory and anti-oxidation characteristics, regulation of blood lipid metabolism, anti-glucose effects, and other mechanisms [Figures 1–5].

Anti-inflammatory effects

The state of low-grade inflammation is a typical manifestation of T2DM that can generate increased production of pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α).^[14,15] These inflammatory cytokines not only damage the beta cells of the pancreas, leading to decreased insulin secretion, but also contribute to insulin resistance through the decrease in glucose extraction and in utilization efficiency of the peripheral tissues.^[14,16,17] Therefore, the inhibition of inflammatory cytokines is seen as an important step for treating T2DM.^[18] Herbal medicine has gradually attracted attention. IL-6 is an important pro-inflammatory cytokine in the pathogenesis of T2DM. Additionally, the levels of IL-6 can directly reflect the level of inflammation in patients with T2DM.^[16,19] *Memecylon umbellatum*^[20] is a type of Melastomataceae, which is often used to treat diabetes. This herb is also known as the iron wood tree, which grows in the Western Peninsula and in most coastal areas. Reports^[20] have shown that the extract of *M. umbellatum* produces a hypoglycemic effect in diabetic models designed by Amalraj and Ignacimuthu in 1998.

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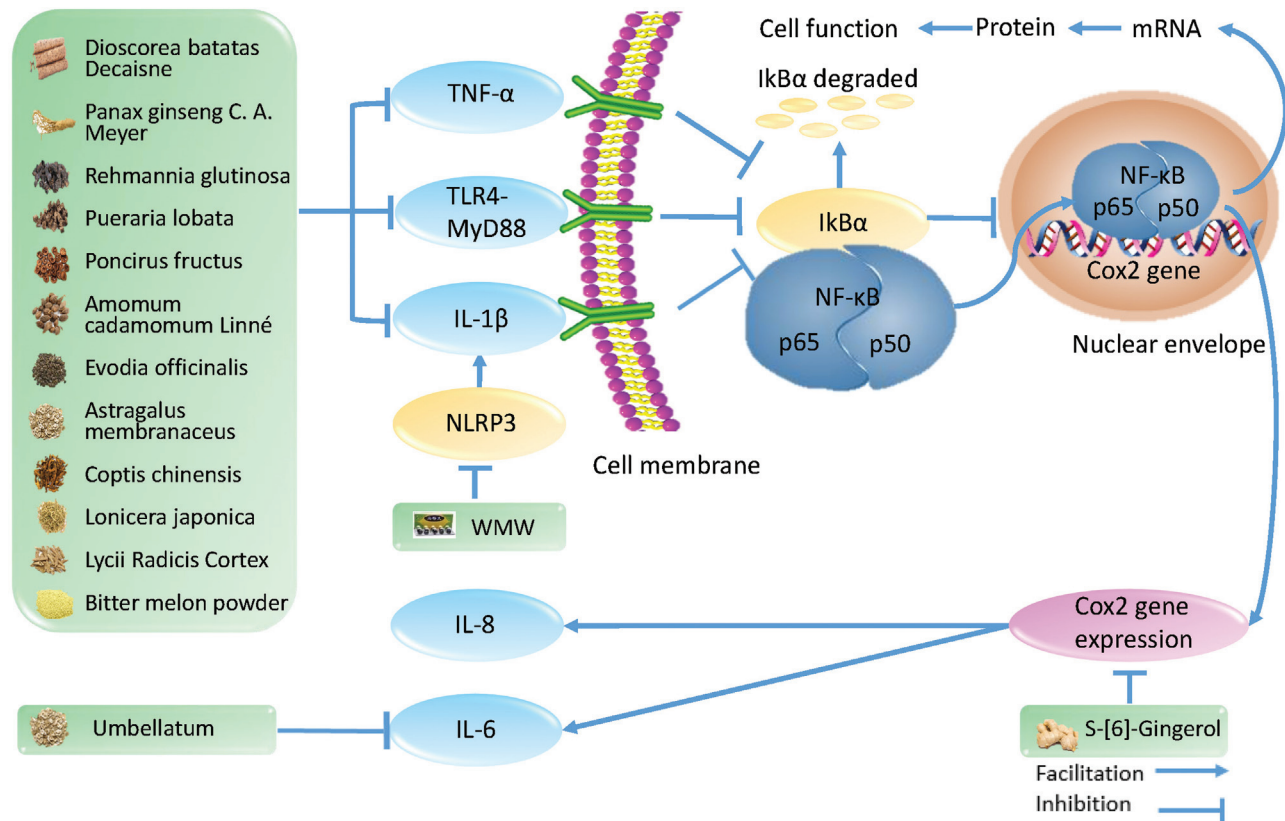


Figure 1: The anti-inflammatory effect of herbal medicine in type 2 diabetes mellitus. TNF- α : tumor necrosis factor- α ; TLR4-MyD88: toll-like receptor 4-myeloid differential protein-88; IL-1 β : interleukin-1 β ; NLRP3: NACHT, LRR, and PYD domain-containing protein 3; WMW: Wu-Mei-Wan; NF- κ B: nuclear transcription factor kappa B; I κ B α : inhibitor of NF- κ B; COX2: cyclooxygenase 2; IL-8: interleukin-8; IL-6: interleukin-6.

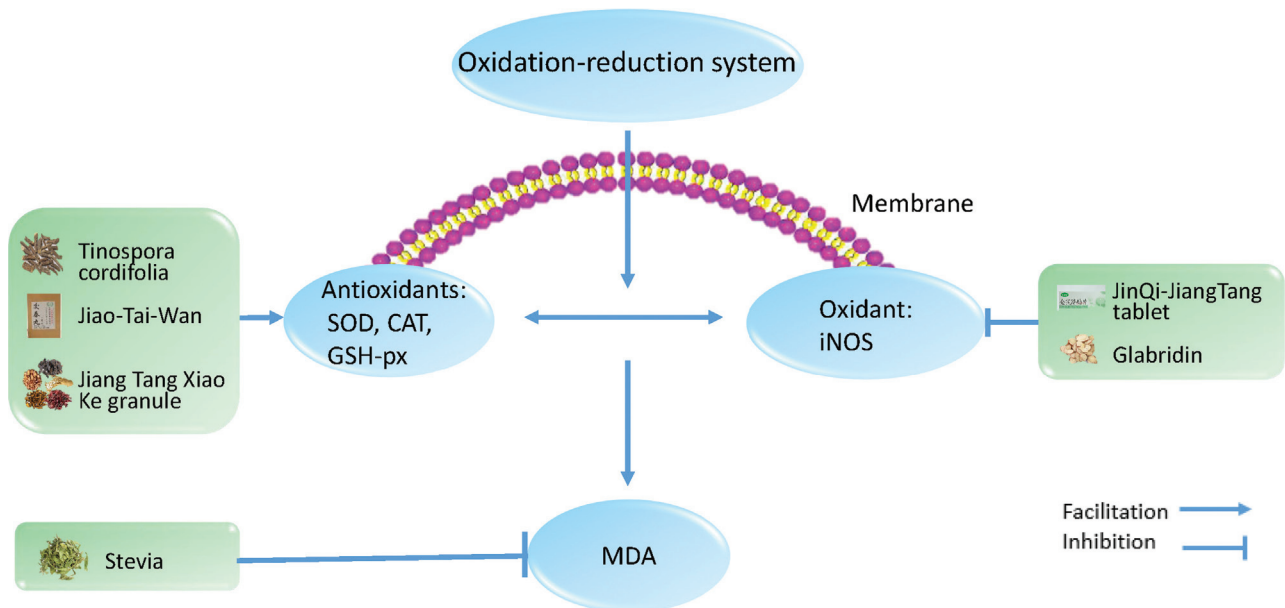


Figure 2: The anti-oxidation effect of herbal medicine in type 2 diabetes mellitus. SOD: superoxide dismutase; CAT: catalase; GSH-px: glutathione peroxidase; iNOS: inducible nitric oxide synthase; MDA: malondialdehyde.

Additionally, in 2017, *M. umbellatum* was used again by Sunil *et al*^[21] for an experiment on mice. Additionally, they found that it clearly reduced the serum IL-6 level and insulin resistance in high-fat diet-induced obese mice,

which fully demonstrated that *M. umbellatum* can treat diabetes by lowering the level of IL-6. The nuclear transcription factor kappa B (NF- κ B) participates in the inflammatory response by controlling gene expression to

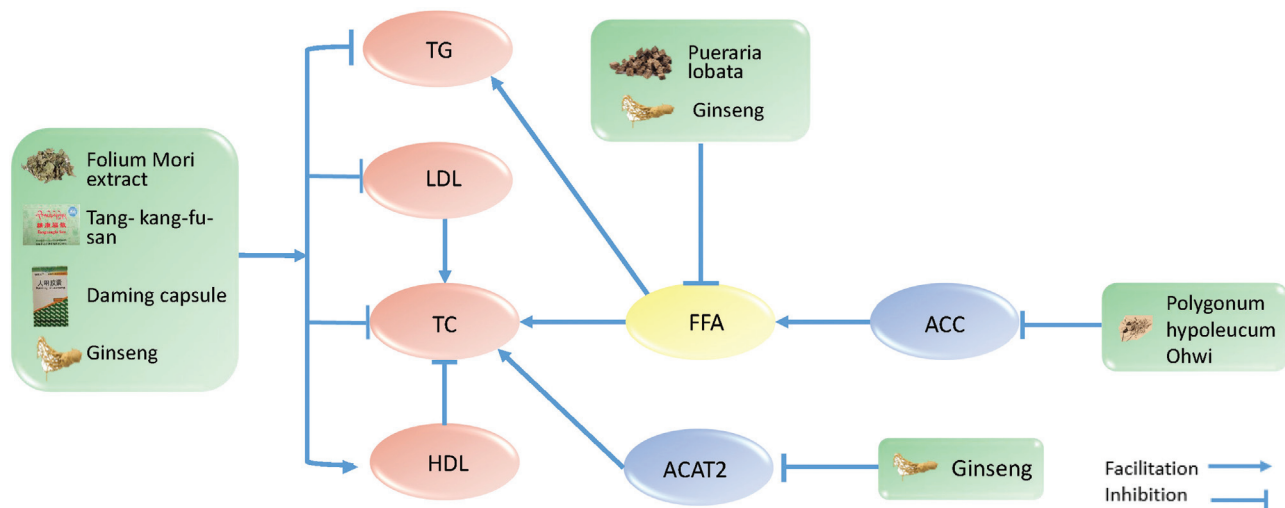


Figure 3: The regulating blood lipids effect of herbal medicine in type 2 diabetes mellitus. TG: triglyceride; LDL: low-density lipoprotein; TC: total cholesterol; HDL: high-density lipoprotein; FFA: free fatty acids; ACC: acetyl-coenzyme A carboxylase; ACAT2: acetyl-coenzyme A acetyltransferase 2.

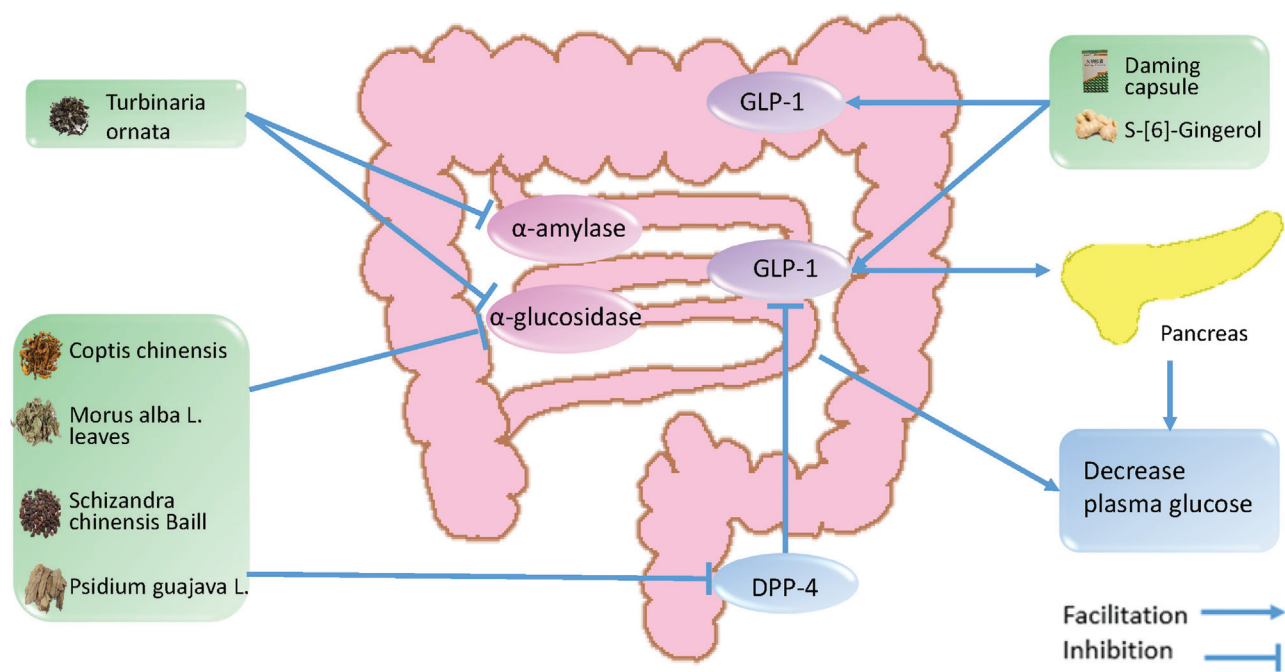


Figure 4: The anti-glucose effect of herbal medicine in type 2 diabetes mellitus. GLP-1: glucagon-like peptide-1 (7–36) amide; DPP-4: dipeptidyl-peptidase 4.

promote immunity. Blocking the NF-κB-mediated signaling pathway can effectively reduce the production of pro-inflammatory cytokines.^[22] *Lycii Radicis Cortex* is the root bark of *Lycium barbarum* Linnaeus or *Lycium chinense* Miller, which can be used to treat inflammation, diabetes, and other diseases. The study by Xie *et al*^[23] has shown that the extracts of *Lycii Radicis Cortex* can effectively inhibit NF-κB activity to inhibit an inflammatory response. In China, ginger is used as both a spice and an herbal remedy for disease. S-[6]-Gingerol is an important substance that causes ginger to produce a pungent smell. It has been found that S-[6]-Gingerol can suppress cyclooxygenase 2 expression via blocking the NF-κB-mediated

signaling pathway to inhibit IL-6 and IL-8 expression in cytokine-stimulated HuH7 cells.^[24] The inhibitor of NF-κB (IκBα) is the inhibitory protein of NF-κB. The inactivation of the IκBα protein can effectively inhibit the expression of NF-κB and reduce the inflammatory response induced by the NF-κB-mediated signaling pathway.^[25] *Momordica charantia* L., often known as bitter melon, is a plant that grows in Asia and can be used as both a food and an herb. Dietary fiber, carbohydrate, protein, and water are the main components of bitter melon, in addition to micronutrients such as calcium, phenolics, flavonoids, and saponins.^[25] As early as 2003, bitter melon's hypoglycemic effect has been confirmed.^[26]

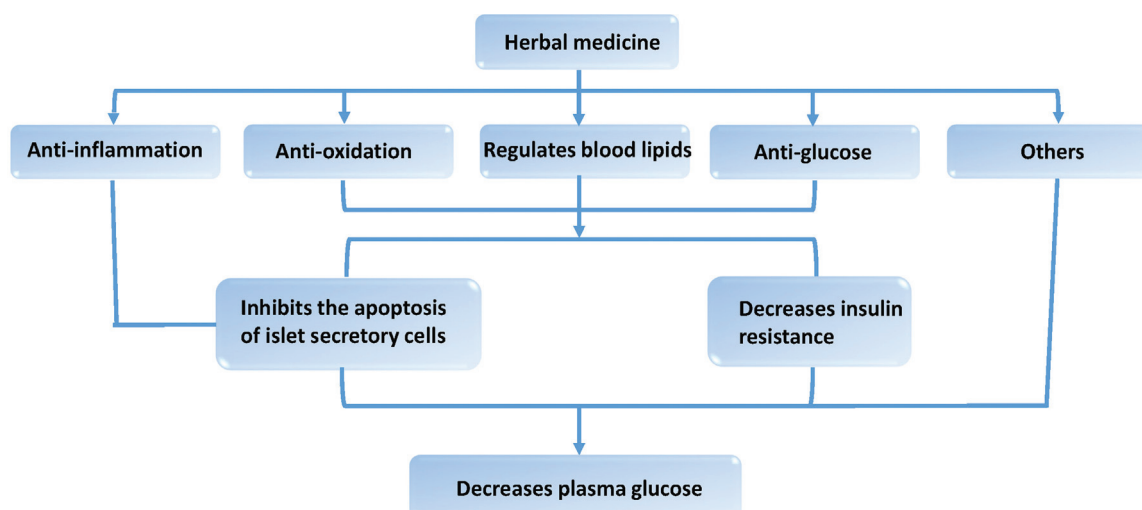


Figure 5: The effect of herbal medicine in type 2 diabetes mellitus.

In 2006, Bai *et al*^[25] found that bitter melon powder can inhibit the activation of NF- κ B by inhibiting I κ B α degradation, thus significantly inhibiting inflammation. JinQi-JiangTang tablets, an effective Chinese patent medicine with anti-glucose properties, containing refined extracts from *Astragalus membranaceus* (Leguminosae), *Coptis chinensis* (Ranunculaceae), and *Lonicera japonica* (Caprifoliaceae), can reduce the degradation of the I κ B α to inhibit the activity of NF- κ B.^[13] The studies have also found that herbal medicine can reduce NF- κ B activation via inhibiting IL-1 β , TNF- α , and toll-like receptor 4 to treat T2DM.^[15,19,27-31]

Anti-oxidation properties

The oxidation–reduction (REDOX) process is an important process in the human body and is closely related to the body's metabolism and functioning. In a physiologic state, the body is in a state of redox homeostasis. When the human body is subjected to various types of harmful stimuli, the homeostasis is broken, causing oxidative stress to damage the human body.^[32] Oxidative stress in patients with T2DM has been confirmed.^[33] Islet secretory cells are naturally weak in antioxidant activity as the activity of various antioxidant enzymes in the islet is lower than that of other tissues.^[34] Therefore, oxidative stress is most harmful to human pancreatic cells, causing diabetes. Moreover, increasing studies^[35,36] have shown that oxidative stress can induce insulin resistance, which makes more evident that oxidative stress is an important factor in the onset or exacerbation of T2DM. Therefore, anti-oxidative therapy is helpful for the treatment of T2DM. Superoxide dismutase (SOD), glutathione peroxidase (GSH-px), and catalase (CAT) are important enzymes that can effectively counter the free radicals in the human body.^[33,37] *Tinospora cordifolia* (Hook and Thomson) is part of the Menispermaceae family. Sangeetha *et al*^[38] showed that *T. cordifolia* can increase SOD and CAT activities in experimentally induced T2DM in rats, and the group treated with 200 mg/kg performs better compared to the group treated with 100 mg/kg. Jiao-Tai-Wan is a

famous herbal formula in China that mainly consists of 2 herbs: *Rhizoma coptidis* and *Cinnamomum cassia*. Chen *et al* have found that this formula has exerted an antioxidant effect by significantly increasing activities of SOD, GSH-px, and CAT.^[39] The Jiang Tang Xiao Ke (JTXK) granule is a type of Chinese patent medicine that contains *Radix Salviae Miltiorrhizae* (Dan Shen), *Radix Rehmanniae* (Di Huang), *Panax ginseng* (Ren Shen), *R. coptidis* (Huang Lian), and *Fructus corni* (Shan Yu Rou) for treating diabetes mellitus. Zhang *et al*^[40] found that giving JTXK in combination with metformin, compared to metformin alone, can significantly improve antioxidant capacity because of suppression of the decrease of SOD activity in diabetic mice. Nitric oxide (NO) is an important bioactive product in the human body that can exacerbate oxidative stress. Additionally, inducible nitric oxide synthase (iNOS) is an important enzyme that promotes the formation of NO.^[41] Therefore, inhibition of iNOS can effectively prevent the further development of oxidative stress. Liu *et al*^[13] have also found that the JinQi-JiangTang tablet not only has anti-inflammatory effects but can also reduce the activity of iNOS by regulating REDOX system in palmitate-induced insulin resistant L6 myotubes. It has been shown by Yehuda *et al*^[42] that glabridin can also regulate the synthesis of iNOS in macrophage-like cells. It is well known that malondialdehyde (MDA) is a product of lipid peroxidation and is widely used to reflect the level of oxidative stress in the body. Assaei *et al*^[43] have found that the aquatic extract of *Stevia* can effectively decrease the concentration of MDA.

Regulating blood lipids effects

Lipotoxicity is a lipid metabolism disorder that causes or aggravates insulin resistance and pancreatic cell dysfunction.^[44] As early as 2001, McGarry^[45] suggested that the fundamental cause of the pathophysiologic changes of T2DM pathogenesis is the disorder of the lipid metabolism, which he suggested naming T2DM diabetes mellipodtus. Therefore, lipid metabolism plays an important role in the pathogenesis of T2DM. Previous studies have found that

herbal medicine plays an important role in reducing blood triglyceride (TG), total cholesterol (TC), and low-density lipoprotein (LDL) levels and increasing the high-density lipoprotein (HDL) level.^[46,47] The Folium Mori extract is an extract of *Morus alba* L., which is an herb used to treat diabetes in China. Cai *et al*^[46] have found that it can effectively reduce serum TG, TC, and LDL levels in a T2DM rat model. Qurs Tabasheer is a polyherbal formulation containing *Portulaca oleracea*, *Rosa damascene*, *Punica granatum*, *Bambusa arundinacea*, and *Lactuca sativa* Linn. Danish Ahmed *et al* found that can reduce TG and TC levels in diabetic rats.^[48] Tang-kang-fu-san is a hypoglycemic formula in Tibetan medicine, in which gallic acid and curcumin are the main active ingredients. Duan *et al*^[47] found that it can effectively reduce the serum TG and LDL level and increase the HDL of mice in T2DM. The Daming capsule is a type of Chinese patent medicine developed under the guidance of traditional Chinese theory. It has been proven by Zhang *et al*^[49] that the Daming capsule can effectively reduce serum TG and LDL levels and increase HDL levels in diabetic mice. Fatty acids are an important ingredient in the synthesis of TG. Therefore, the increase of free fatty acids (FFA) can increase the level of TG in the blood.^[50] Yeo *et al*^[29] have also found that an aqueous extract of herbal compounds containing *Pueraria lobata*, *Panax ginseng* C.A. Meyer, *Rehmannia glutinosa*, *Poncirus fructu*, *Dioscorea batatas* Decaisne, *Evodia officinalis*, and *Amomum cadamomum* Linné can decrease plasma FFA. Acetyl-coenzyme A carboxylase (ACC) is an important substance involved in the metabolism of fatty acids. Additionally, inhibition of ACC can effectively reduce the levels of FFA in the blood.^[51] Therefore, ACC inhibitors have excellent potential for treating diabetes.^[52] Chen *et al*^[51] found that an ethanol extract of *Polygonum hypoleucum* Ohwi can effectively inhibit ACC in C57BL/6J mice that were given a high-fat diet. Acetyl-coenzyme A (CoA) acetyltransferase 2 (ACAT2) is an important enzyme involved in TC generation and metabolism, and inhibiting ACAT2 can reduce TC levels in the blood.^[53] Banz *et al*^[54] have found that ginseng has significantly reduced the levels of TG and TC in male Zucker diabetic fatty rats. In addition, Saba *et al*^[55] have found that ginseng extract ameliorates hypercholesterolemia by attenuating ACAT2.

Anti-glucose effects

According to the American Diabetes Association's (ADA's) "Standards of Medical Care in Diabetes-2018," fasting plasma glucose ≥ 7.0 mmol/L and 2-h post-prandial plasma glucose ≥ 11.1 mmol/L is the important diagnostic basis for T2DM. Chronic hyperglycemia can damage the pancreatic β -cell, which leads to pancreatic β -cell glucotoxicity.^[56] The damage of pancreatic β -cell can lead to a decrease in insulin secretion, which further aggravates hyperglycemia. It is important to stabilize the blood glucose level of T2DM so that it remains in a reasonable range.^[5] Okchun-san is an herbal formula used to treat diabetes in Korea. Chang *et al* have found that it can lower blood glucose in db/db mouse model.^[57] Bofu-tsusho-san is an herbal formula of Kampo, and Morimoto *et al*^[58] have found that it is effective against hyperglycemia in KKAY mice. Under normal physiologic conditions, the body adjusts the insulin secretion of

pancreatic β -cells to fight the hyperglycemia caused by food absorption after eating. The pancreatic β -cell function of T2DM is impaired, and it is difficult to produce enough insulin to fight the hyperglycemia.^[56] Therefore, the post-prandial plasma glucose of in patients with T2DM is higher than normal and can even develop an acute complication of diabetes. A study in the last century^[59] has found that α -amylase and α -glucosidase play important roles in the body to absorb glucose. Inhibiting α -amylase and α -glucosidase can effectively reduce post-prandial hyperglycemia to achieve treat T2DM.^[60,61] In recent years, it has been shown that more types of herbal medicine can inhibit α -amylase and α -glucosidase, which can lower post-prandial hyperglycemia. *Acer pycnanthum* is a type of Aceraceae known as "Hana-noki" in Japan. Honma *et al*^[62] found that the extract of the leaves of *A. pycnanthum* can lower hyperglycemic by inhibiting α -glucosidase. *Lodhrasavam* is an Ayurvedic anti-diabetic formulation that contains 19 herbal ingredients. Butala *et al*^[63] found that *Lodhrasavam* has effectively anti- α -amylase and anti- α -glucosidase properties in a simulation of gastro-intestinal digestion. GLP-1^[64] is a type of peptide secreted by L cells of the gastrointestinal mucosa that promotes insulin synthesis and secretion, thereby reducing blood glucose. Additionally, GLP-1 promotes insulin secretion in a positive correlation with blood glucose concentration: the higher the blood glucose is, the stronger the effect is; the lower the blood glucose is, the weaker the effect is. GLP-1 plays an important role in regulating blood glucose homeostasis.^[65] Samad *et al*^[66] have found that [6]-Gingerol increased insulin secretion by strengthening the GLP-1-mediated secretion pathway in Lepr db/db T2DM mice. Zhang *et al*^[49] have also found that the Daming capsule can increase the secretion of GLP-1 in diabetic mice. Dipeptidyl-peptidase 4 (DPP-4)^[67] is a type of high-specific serine protease that, exists in the form of a dimer. GLP-1 is a natural substrate of DPP-4. Therefore, DPP-4 can rapidly degrade GLP-1 to deactivate the function of GLP-1. As a DPP-4 inhibitor, sitagliptin^[68] has been widely used in the clinical treatment of T2DM and has achieved good results. Wang and Chiang^[69] have found that an herbal formula used to treat diabetes that contains *C. chinensis*, *M. alba* L. leaves, *Schizandra chinensis* Baill, and *Psidium guajava* L. can inhibit α -glucosidase and DPP-4.

Other effects

Herbal medicine can also treat T2DM in other ways. It is well known that the gut microbiome is a large system in the human body. It is estimated that there are more than 1000 types of gut microbiomes in the human body, which is more than 100 times the number of human genes.^[70] In recent years, the association between gut microbiomes and T2DM has attracted more and more attention. It has been preliminarily confirmed that gut microbiome disorders are closely related to insulin resistance and the onset of T2DM.^[71,72] Therefore, can herbal medicine treat T2DM by regulating the gut microbiome? Many people have studied this problem. Wang *et al*^[72] have found that *Ephedra sinica* can effectively reduce the fasting blood glucose by changing the composition of gut microbiota, especially *Roseburia*, *Blautia*, and *Clostridium*. Qijian mixture^[73] is a new herbal formula for treating T2DM that

contains *Ramulus euonymi*, *P. lobata*, *A. membranaceus*, and *C. chinensis*. Gao *et al*^[73] have demonstrated the effectiveness and safety of the Qijian mixture in a T2DM model rat. They found that the Qijian mixture has enormously rich Bacteroidetes, which may be closely related to its role in treating T2DM. Adiponectin is a cytokine that comes from adipocytes and improves insulin resistance.^[74] The use of adiponectin as a treatment strategy for T2DM has been increasingly recognized.^[75] However, up to now, adiponectin biologic agents have not been used in medical practice. However, herbal medicine has been reported to improve the expression of adiponectin in treating diabetes. *Cirsium japonicum* DC is a type of herb used in hemostasis; however, Liao *et al*^[76] found that flavones isolated from *C. japonicum* DC can also exert an anti-diabetic effect by improving severe adiponectin expressions in diabetic rats. Dangguiliuhuang decoction (DGLHD) is an herbal formula that is widely used to treat diabetes. It contains *C. chinensis*, golden cypress, *Radix Rehmanniae* preparata, *Angelica*, *Scutellaria baicalensis*, and *A. membranaceus* and the amount of *A. membranaceus* is twice that of other herbs. Cao *et al*^[77] have found that DGLHD increased the expression of adiponectin.

Conclusion

The T2DM is a global health problem that causes significant distress for patients.^[78] Although many biologic agents have been developed to treat T2DM, attention to herbal medicine in the treatment of T2DM has been growing. In this article, we summarized the roles of some herbs, herbal extracts, and herbal formulas in the treatment of T2DM. Herbal medicine is mainly used to treat T2DM through its anti-inflammatory, anti-oxidation, blood lipid regulation, and anti-glucose properties.

Herbal medicine is superior in its holistic quality, which can treat T2DM through multiple targets, and is a good complementary and alternative treatment for T2DM. However, there are some deficiencies in herbal medicine that need to be studied further. Herbs, especially some herbal formulas, contain a variety of ingredients, and it is difficult to accurately identify the active ingredients and toxic ingredients. Most of the above studies are animal experiments. Large-scale, multicenter clinical studies still lack reliable and detailed information. Furthermore, there have also been few reports on follow-up observations of patients with T2DM treated with herbal medicine. All these questions provide direction for our future research.

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Conflicts of interest

The authors declare no conflict of interest.

Author contributions

Pang GM selected topic and wrote the manuscript, Li FX, Yan Y, Zhang Y, Kong LL, Zhu P, Wang KF, Zhang F, and Liu B retrieved material and Lu C designed and modified the article.

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