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Bioactive Components of Chinese Herbal Medicines in the Treatment of Glucose and Lipid Metabolism Disorders: Evidence and Potential Mechanisms



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ABSTRACT

Disturbed cholesterol and glucose homeostasis play crucial roles in the development of various diseases such as cardiovascular diseases, cerebrovascular diseases, central nervous system diseases, and cancer. An increasing number of studies have shown that excessive body fat accumulation is associated with type 2 diabetes or insulin resistance in a vicious cycle. This vicious cycle promotes the occurrence and development of the aforementioned diseases. Therefore, stabilizing the blood lipids and blood glucose of patients is the predominant strategy for improving the symptoms of patients with cardiovascular, cerebrovascular, and central nervous system diseases. Traditional Chinese medicine, mainly Chinese herbal medicine (CHM), has a history of more than 2000 years in China, which has established a unique theory and accumulated a great wealth of clinical experience. Moreover, CHM has been widely used in China and other countries for the treatment of cardiovascular and cerebrovascular diseases, with the advantages of preventing and curing hyperlipidemia, diabetes, hypertension, and other diseases. However, the use of CHM in Western countries remains rather limited, partly because of the incomplete understanding of multiple complex components and uncertain pharmacological mechanisms. Herein, we review and discuss the benefits, molecular mechanisms, and clinical research progress of bioactive components of CHM and their preparations as therapeutics for hyperlipidemia and hyperglycemia.

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1. Introduction

With the rapid aging of the global population, the incidence of cardiovascular and cerebrovascular diseases (CVD) continues to increase, which have outranked cancer and communicable diseases as the most common causes of death globally [1]. Glucose and lipid metabolism disorders are the most important detrimental conditions that promote the development of atherosclerosis, coronary heart disease, myocardial infarction, heart failure, and stroke. Therefore, using hypolipidemic and hypoglycemic drugs can be of great significance in protecting cardiovascular and cerebrovascular functions, thereby reducing CVD mortality.

The control of blood lipids and glucose in patients has improved with the successful development of statins and fibrates for lowering blood lipids and the widespread applications of sulfonylureas and biguanides to reduce blood glucose. However, many issues remain regarding the long-term use of these medicines. For example, some compounds cause serious adverse reactions that can damage the liver, kidneys, and other organs of the body. Therefore, it is of great significance to develop drugs that lower blood glucose and lipids with high efficiency and low toxicity.

Chinese herbal medicine (CHM), which is based on a unique theory and a wealth of clinical experience of over 2000 years, has been widely used for the treatment of CVD in China [2]. The advantages of CHM in CVD treatment are mainly manifested in its anti-hyperlipidemic and antihyperglycemic properties. Based on the principles of polypharmacology, CHM protects the cardiovascular and cerebrovascular systems using multiple mechanisms and

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multiple targets. For example, flavonoids, alkaloids, and terpenoids (TPs) can protect the cardiovascular and cerebrovascular systems by regulating blood lipids; enhancing immunity; providing autophagy antioxidant, antithrombotic, and anti-inflammatory capacities; protecting endothelial cells; reducing blood pressure and blood lipids; and maintaining homeostasis and the microbiome [3]. Currently, several CHM compounds such as the compound Danshen dripping pill, compound Danshen tablet, and Naoxintong capsule have been widely used for patients with CVD. However, owing to the presence of uncertain components and the lack of understanding of underlying pharmacological mechanisms, CHM is considered a complementary or alternative medicine in most Western countries.

Studies in the past decades have shown that it is important to explore the pharmacological effects and molecular/signaling mechanisms of the active components of CHM on the cardiocerebral vascular system. With advances in bioinformatics, next-generation sequencing, synthetic biology, network pharmacology, and artificial intelligence, rapid progress has been made in the extraction or synthesis of effective components of CHM, identification of CHM functions, and establishment of CHM-based gene regulatory networks.

In this review, we summarize the efficacy and molecular mechanisms of multiple CHM monomers and compounds (Fig. 1) in treating hyperlipidemia and hyperglycemia, with the aim of promoting the worldwide clinical application of CHM in the prevention and treatment of CVD.

2. Methods

Electronic databases (PubMed and CNKI) were searched for studies between January 1, 2010 and January 1, 2022, to evaluate the effects of CHM on hyperlipidemia and hyperglycemia. The keywords used in our search were “traditional Chinese medicine” or “Chinese herbal medicine” in combination with each of the following terms: “hyperlipidemia,” “hyperglycemia,” “diabetes,” “blood lipid,” “blood glucose,” “gut microbiota,” “clinical trial,” and “mechanism.” The review was conducted based on the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

3. Results

By searching the terms defined in the Methods section in the PubMed and CNKI databases, we identified a total of 2831 results, 1189 of which were related to hyperlipidemia and the others were related to hyperglycemia. Eight clinical trials and 21 original studies that clearly identified bioactive components and molecular mechanisms of CHM, such as studies that included anthraquinones, saponins, and flavonoids in hyperlipidemia, were included in the review. Six clinical trials and 25 original studies with defined bioactive components and molecular mechanism of action of CHM in hyperglycemia were included, such as studies that identified anthraquinones, TPs, flavonoids, and alkaloids. Clinical trials that did not compare CHM to placebo or lack sufficient statistical analysis were excluded from the review (Fig. 2).

3.1. Bioactive components of CHMs regulate hyperlipidemia

As a strong risk factor for CVD, hyperlipidemia is characterized by elevated concentrations of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C), and/or decreased concentrations of high-density lipoprotein cholesterol (HDL-C) in the blood [4]. In China, the morbidity of dyslipidemia is as high as 41.9%, but the overall compliance rate for LDL-C is only 37.3%. Hyperlipidemia is an independent predictor of atherosclerosis and other CVD, and hypolipidemic agents can effectively prevent and treat CVD [5].

Currently, lipid-lowering drugs in the market include chemical drugs and CHM. However, the emergence of toxicity or resistance to lipid-lowering drugs limits their applications for the long-term treatment of hyperlipidemia. Statins are the most important lipid-lowering drugs that inhibit the production of low-density lipoproteins and have beneficial effects on cardiovascular health. However, statin-associated muscle symptoms and neuropsychiatric adverse effects have been frequently reported in patients using

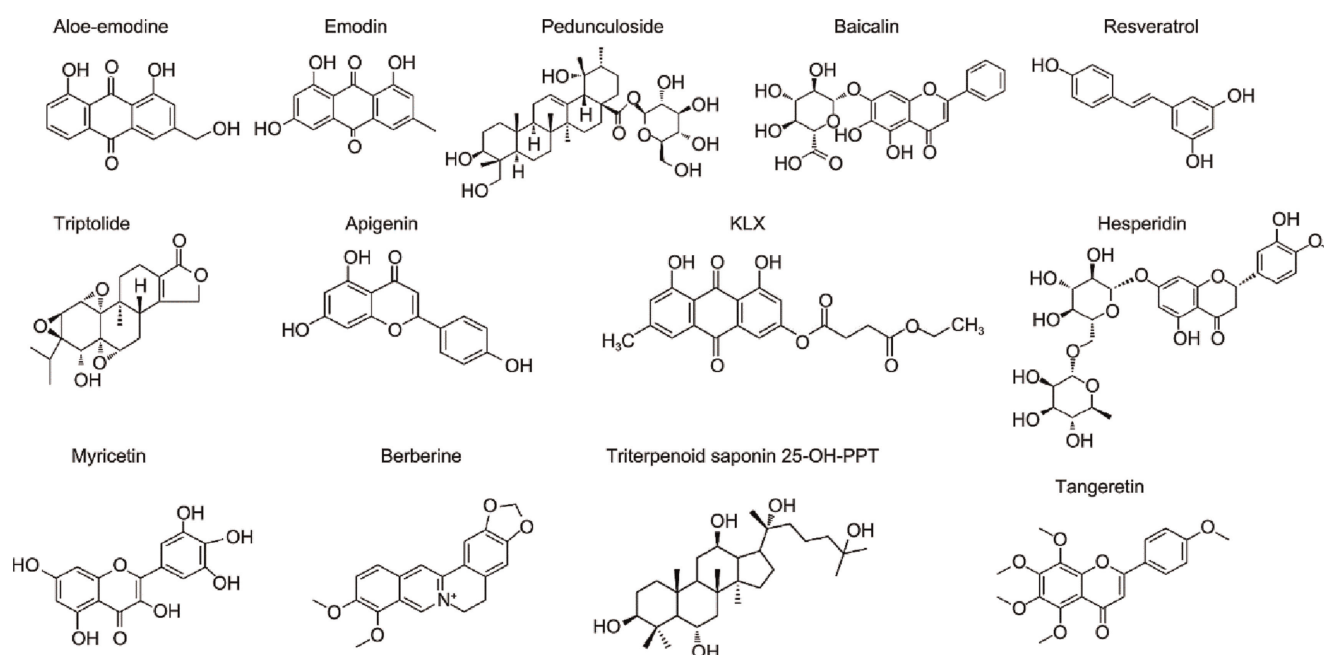


Fig. 1. The chemical structure of bioactive components of CHMs. KLX: 1,8-dihydroxy-3-succinic acid monoethyl ester-6-methylantraquinone; 25-OH-PPT: 25-hydroxy-1-protopanaxatriol.

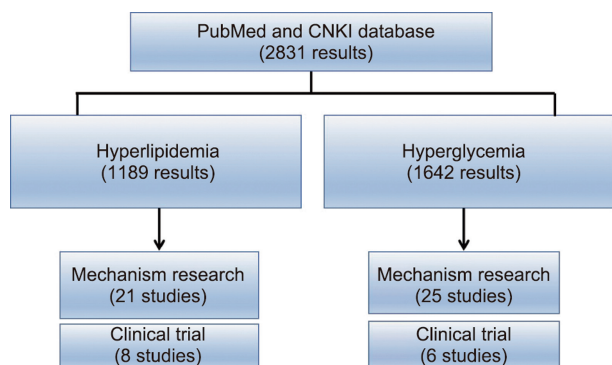


Fig. 2. PRISMA flow chart for the database search, screening, inclusion, and exclusion studies for the systematic review.

statins [6,7]. This subsection reviews the therapeutic potential of CHM in treating hyperlipidemia, with the aim of providing clinicians with therapeutic and safety profiles characterized by low toxicity, few side effects, and suitability for long-term anti-hyperlipidemic treatment.

At present, most traditional Chinese medicine doctors divide dyslipidemia syndromes into the following four categories: qi stagnation and blood stasis syndrome, phlegm turbidity and internal obstruction syndrome, spleen deficiency and dampness syndrome, and liver–kidney Yin deficiency syndrome. Consequently, lipid-lowering drugs in CHM can also be divided into four classes: dampness and phlegm-reducing drugs, blood circulation and stasis-removing drugs, qi-removing drugs, and tonic drugs [8]. Based on the active ingredients, hypolipidemic CHM can be divided into anthraquinones, saponins, and flavonoids.

Anthraquinone, which exists in the metabolites of higher and lower plants such as lichens and fungi, has various pharmacological effects, including homeostatic, antibacterial, antidiarrheal, and diuretic activities. We previously developed a new anthraquinone compound, 1,8-dihydroxy-3-succinic acid monoethylester-6-methylanthraquinone (KLX), which reduces lipid accumulation by activating the 5'-adenosine monophosphate-activated protein kinase (AMPK)/sterol regulatory element-binding protein (SREBP)-2/protein convertase subtilisin kexin type 9 (PCSK9)/LDL-C receptor (LDLR) signaling pathway in the liver [9]. We also developed Daming capsule (DMC), which is composed of *Rheum palmatum*, *Cassia obtusifolia* L., *Salvia miltiorrhiza*, *Panax ginseng* C.A., *Citri Reticulatae Pericarpium*, and *Poria cocos*. DMC has a lipid-lowering action and exhibits little adverse side effects; it has been widely used in China as an anti-hyperlipidemic agent. In a previous study, we revealed that DMC shows clear lipid-lowering and hepatoprotective effects by activating the AMPK signaling pathway, which in turn activates peroxisome proliferator-activated receptor (PPAR)- α and LDLR in hyperlipidemic rats and oleic acid-treated HepG2 cells [10]. In addition, we reported that DMC could protect the aorta from high-fat diet-induced endothelial dysfunction by upregulating endothelial nitric oxide synthase (eNOS) expression [11]. Moreover, we found that aloe emodin (AE), another bioactive component of DMC, can reduce cholesterol content by inhibiting the hepatic PCSK9/LDLR pathway in hyperlipidemic rats [12]. Emodin, an anthraquinone derivative isolated from the rhizomes of rhubarb, has antioxidant, anti-aging, anti-inflammatory, and antiviral effects. He et al. [13] found that emodin could alleviate lipid metabolism disorders by enhancing LDL-C uptake, reversing cholesterol transport, and inhibiting cholesterol synthesis in zebrafish larvae fed a high-cholesterol diet. All published studies point to the effective antihyperlipidemic properties of anthraquinones.

Saponins are glycosides whose aglycones include triterpenes or spiral steranes, which are widely distributed in plants of the

Rosaceae and Cucurbitaceae families. Studies have shown that saponins can significantly lower blood lipid levels. Xu et al. [14] discovered a naturally occurring, rare triterpenoid saponin, 25-hydroxyl-protopanaxatriol (25-OH-PPT) in ginseng stems and leaves, which has a substantial blood lipid-lowering effect. Pedunculoside (PE) is a triterpenoid saponin extracted from the dried bark of *Ilex rotunda* Thunb. Liu et al. [15] showed that PE could improve lipid disorders by regulating lipogenesis and fatty acid (FA) β -oxidation in hyperlipidemic rats induced by high-fat diet. Therefore, saponins are considered novel lipid-lowering drugs. *Gynostemma pentaphyllum* is a gourd plant that has phlegm elimination, heat clearance, and detoxification effects. The main components responsible for its lipid-lowering efficacy of this plant include the total saponins. Xu [16] found that the polyherbal formulation of *Gynostemma pentaphyllum* reduced the levels of TC, TG, and LDL and increased the level of HDL in the peripheral blood of patients with hyperlipidemia.

Flavonoids generally refer to a series of compounds that include two benzene rings connected by three carbon atoms in other words, these are compounds with a C6–C3–C6 structure. Flavonoids are widely present in nature and account for the largest proportion of natural phenolic compounds. Researchers have found that citrus peel is rich in flavonoids and has anti-hyperlipidemic properties. Su et al. [17] reported that citrus flavonoids regulate lipid metabolism by modulating the expression of micro RNA (miR)-122 and miR-33. In a prospective study of 80 volunteers over a period of six months, Toth et al. [18] found that bergamot considerably reduced TC, TG, and LDL levels, and increased HDL level. Khaerunnisa et al. [19] used an imprinting process to isolate and identify flavonoids from cogon grass roots and found that the flavonoids significantly reduced TC and LDL levels but had no effect on HDL levels in rats with hypercholesterolemia. Flavonoids extracted from sea buckthorn can ameliorate obesity and hyperlipidemia. A study conducted by Xiao et al. [20] demonstrated that sea buckthorn flavonoids (SF) promote the conversion of cholesterol into bile acids and cholesterol efflux, inhibit cholesterol synthesis, and accelerate FA oxidation to improve hyperlipidemia. Zhang and Shen [21] found that SF oral liquid effectively reduced TC and TG levels and increased HDL.

Baicalin, a flavonoid compound isolated from *Scutellaria baicalensis georgi*, has antibacterial, diuretic, anti-inflammatory, anti-allergic reaction, and spasmodic effects; it is also used in cancer therapy. Studies have shown that baicalin lowers blood lipid levels. Wu et al. [22] revealed that baicalin can produce anti-adipogenic, antioxidant, and anti-inflammatory effects in patients with atherosclerosis by inhibiting the nuclear factor- κ B (NF- κ B) and p38 mitogen-activated protein kinase (MAPK) signaling pathways.

Gut microbes exert hypolipidemic effects by regulating the metabolism of bile acids. A β -D-fructan polysaccharide (MDG-1) extracted from the roots of *Ophiopogon japonicus*, can prevent obesity and hyperlipidemia. Wang et al. [23] revealed that MDG-1 restores the gut microbiota balance by increasing the abundance of beneficial bacteria, especially short-chain FA-producing bacteria; it also increases the contents of acetic acid and valeric acid, thereby regulating inflammatory responses and hepatic lipid metabolism. *Rhizoma Coptidis* alkaloids remarkably increase the levels of farnesoid X receptor (FXR) and G-protein coupled bile acid receptor (TGR5) by ameliorating the gut microbiota to ameliorate hyperlipidemia [24]. The comparison between drugs with lipid-lowering effects was shown in Table 1.

At present, a variety of CHM are clinically used to treat hyperlipidemia. Our group previously conducted a randomized, multicenter, open-label, parallel-group clinical trial to study the efficacy and tolerability of the DMC in Chinese patients with hyperlipidemia. Sixty enrolled patients with hyperlipidemia, allocated to

Table 1
Comparison between drugs with lipid-lowering effects.

Kind of compound	Name	Dose	Drug efficacy	Molecular mechanism
Anthraquinone	Kanglexin	80 mg.kg ⁻¹ , <i>in vivo</i> ; 10 μmol.L ⁻¹ , <i>in vitro</i>	Reduce lipid accumulation	Activate the hepatic AMPK/SREBP-2/PCSK9/LDLR signalling pathway
	DMC	162 mg.kg ⁻¹ , <i>in vivo</i> ; 100 mg.kg ⁻¹ , <i>in vivo</i>	Alleviated hepatomegaly, hepatic lipid deposition, and hepatic steatosis; protects the aorta from HF-induced endothelial dysfunction	Activate the AMPK signalling pathway; improve the relaxation of the aortic rings by upregulation of the expression of eNOS
	Emodin	0.5 μg.mL ⁻¹ , <i>in vivo</i>	Regulate the enhancement of LDL-C uptake; reverse cholesterol transport; inhibit cholesterol synthesis	Reduce lipid accumulation in blood vessels and liver; alleviated hepatic histological damage by AMPK/SREBP-2/PCSK9/LDLR signal pathway
Triterpenoids	Triterpenoid saponin 25-OH-PPT	40 mg.kg ⁻¹ , <i>in vivo</i>	Increase insulin sensitivity and hypolipidemic effects	Up-regulate GLUT4 and AMPK in skeletal muscle; activate insulin signaling pathways
	PE	30, 15, or 5 mg.kg ⁻¹ , <i>in vivo</i> ; 25, 50, 100, and 200 μmol.L ⁻¹ , <i>in vitro</i>	Decrease serum TC and LDL-C; reduce liver TC	Down-regulate of genes involved in lipogenesis; up-regulate of genes involved in FA β-oxidation by interaction between PE with proteins involving PPAR-γ, C/EBPα, and SREBP-1
	Gynostoglypha compound preparation	10–20 mL per time, two times per day, <i>in vivo</i>	Reduce the levels of TC, TG, and LDL; increase the level of HDL in peripheral blood	—
Flavonoids	Sanqi tablets	50 mg per tablet, two tablets each time, three times a day orally, 12–15 days of treatment	Decrease the level of TG and TC	—
	Citrus flavonoids	10 μmol.L ⁻¹ , <i>in vitro</i>	Beneficial for lipid metabolism	Down-regulate the miR-122 and miR-33 expression; affect the expression FAS and CPT1α
	Bergamot	Bergamot-derived extract (Bergavit R [®]) for six months, <i>in vivo</i>	Reduce TC, TG, and LDL levels; increase HDL levels	—
	Flavonoids from cogon grass roots	15 mg per 200 g body weight, <i>in vivo</i>	Lower the TC levels and LDL levels	—
	SF	20 μg.mL ⁻¹ , <i>in vitro</i>	Promote cholesterol transformation into bile acids and cholesterol efflux; inhibit cholesterol <i>de novo</i> synthesis; accelerate FAs oxidation; reduce TC and TG; increase HDL levels	Increase the messenger RNA expression of PPAR-γ, PPAR-α, ABCA1, CPT1α, etc.; decrease SREBP-2 and its target gene <i>LDLR</i>
Western medicine	Baicalin	50 and 100 mg.kg ⁻¹ , <i>in vivo</i>	The anti-adipogenic effect; the anti-oxidant effect	Exert anti-lipogenic, antioxidant, and anti-inflammatory effects through inhibiting the NF-κB and p38 MAPK signaling pathways
	Atorvastatin	10 mg.kg ⁻¹ , <i>in vivo</i>	Decrease blood TC and LDL-cholesterol	Inhibit the HMG-CoA reductase
	Acarbose	5 mg acarbose in 100 g of diet	Decrease the postprandial blood glucose levels	α-glucosidase inhibitor
	Fenofibrate	150 mg.kg ⁻¹ , <i>in vivo</i>	Decrease the plasma levels of TC and LDL-C; increase the plasma level of HDL-C	A PPAR-α agonist

HF: high-fat diet; C/EBPα: CCAAT/enhancer binding protein α; GLUT4: glucose transporter 4; FAS: FA synthetase; CPT1α: carnitine palmitoyltransferase 1α; ABCA1: adenosine triphosphate binding cassette subfamily a member 1.

six medical centers, were randomly divided into two groups of 30 individuals each. One group received DMC 2 g twice a day for six weeks, and the other received pravastatin 10 mg orally once a day for six weeks. The results showed that serum TC and LDL-C levels significantly decrease in the DMC-treatment group compared to the levels before the treatment, whereas no significant change was observed in TG and HDL-C levels [25]. Zhibitai capsule, composed of hawthorn, *Alisma*, *Atractylodes macrocephala* Koidz, and red yeast, also showed effects on patients with hyperlipidemia. A total of 169 subjects with moderate to high cardiovascular risk were recruited and randomly divided into the Zhibitai group (85 subjects), which received 480 mg of Zhibitai orally twice daily, and the atorvastatin group (84 subjects), which received 10 mg of atorvastatin orally once a day. In both groups, the TC and LDL-C levels decreased significantly after four weeks of treatment, whereas HDL-C levels increased significantly after eight weeks. Interestingly, plasma TG levels decreased in the Zhibitai group after four weeks of treatment, but the decrease did not occur until eight weeks after atorvastatin treatment, suggesting that CHM has the potential advantage of fewer side effects than Western medicine in the treatment of hyperlipidemia [26]. Liu et al. [27] assessed the effects of inulin-type fructans on human blood lipids across 20 randomized controlled trials with 607 adult participants and found

that these fructans are beneficial in LDL-C reduction. Oleanolic acid (OA), a pentacyclic triterpenoid compound extracted from *Olea europaea*, showed effects to ameliorate hyperlipidemia. Luo et al. [28] demonstrated that patients with hyperlipidemia who received OA for four weeks (4 tablets once, three times a day) exhibited decreased levels of TC, TG, and HDL-C. Red yeast rice (RYR) is a fermented product of rice and red yeast (*Monascus* species), and monacolin K is an active component of RYR. Wang et al. [29] assessed the serum TC and LDL-C levels in monacolin K-treated patients (16 subjects) and found that the levels decreased significantly after a three-month intervention with daily monacolin K intake of 8 mg compared with the placebo group (17 subjects), whereas the serum TG level declined steadily but was not statistically significant. Ankascin 568 plus and *Monascus*-fermented products have numerous biological effects. Liu et al. [30] conducted a double-blind clinical study to evaluate the effects of Ankascin 568 plus on blood lipid regulation. They demonstrated that the subjects (40 subjects aged 18–65 years, 20 in the treatment and placebo groups, respectively) who received one 500 mg capsule of Ankascin 568 plus for more than four weeks exhibited significant reductions in serum TC and LDL-C levels. Huang et al. [31] found that Sanqi tablets significantly reduced TG and TC levels in inpatients with primary hyperlipidemia. Xuezhitong (XZT), also

known as Xie Bai, is a single-prescription traditional Chinese medicine that is enriched, purified, and refined from the natural edible and medicinal plant, *Allium macrostemon* Bunge. A total of 358 subjects with hypertriglyceridemia were enrolled and randomly assigned to receive XZT (2700 mg daily), Xuezhikang (XZK; 1200 mg daily), or placebo. Daily use of XZT for 12 weeks resulted in statistically significant (65.2% for XZT, 38.3% for XZK,

and 25.0% for placebo; $P < 0.0167$) as well as clinically meaningful increases in HDL-C levels by $\geq 4 \text{ mg}\cdot\text{dL}^{-1}$ compared to XZK and placebo. Hence, XZT is safe and well tolerated in patients with hypertriglyceridemia [32].

Evidence indicates that some CHM exhibit significant efficacy in treating hyperlipidemia via explicit molecular mechanisms (Fig. 3). Exploring the synergistic effects of various CHM components using

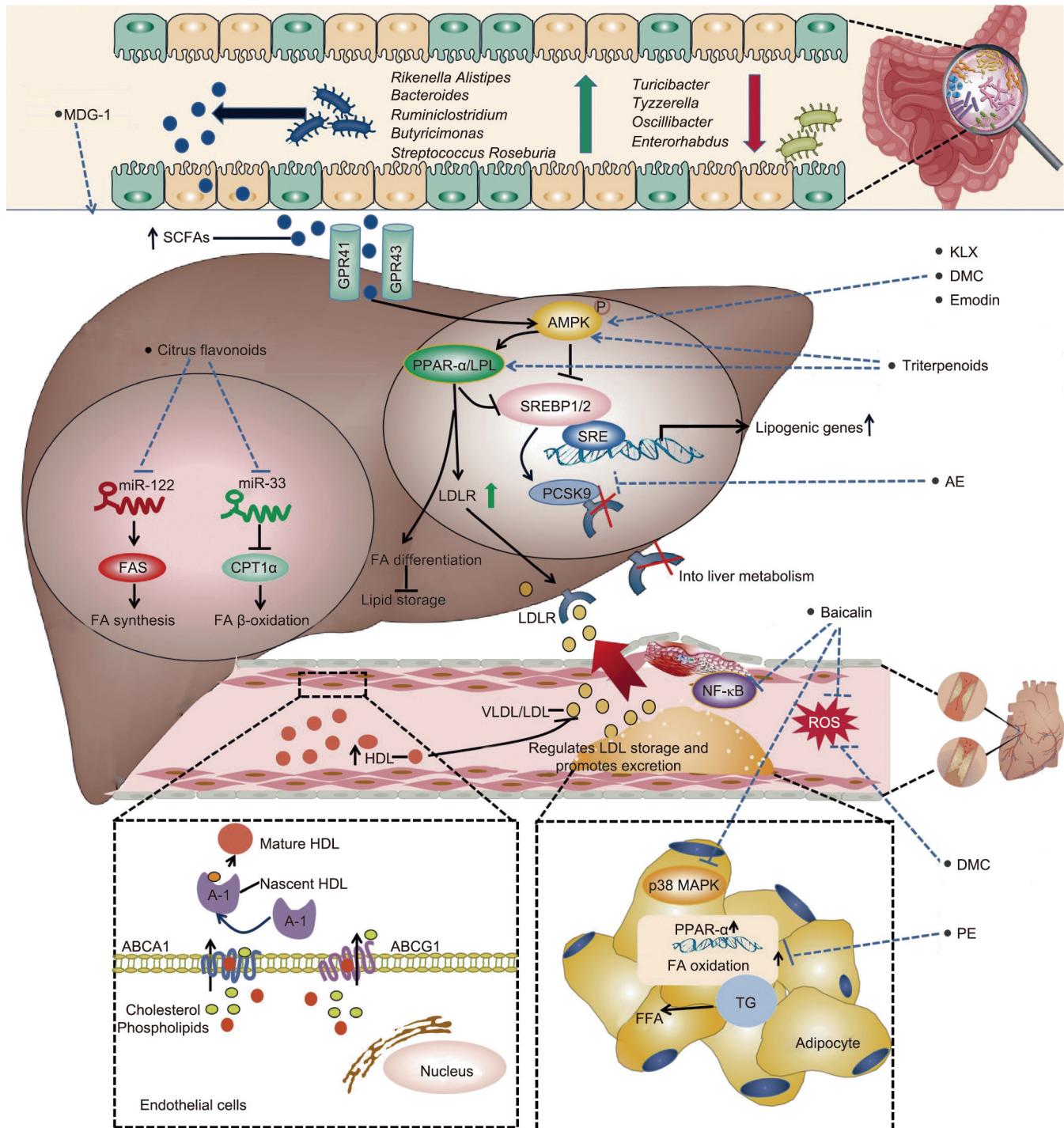


Fig. 3. The effects and mechanisms of CHM in lowering hyperlipidemia. MDG-1 restores the balance of gut microbiota and increases the relative abundance of beneficial bacteria, especially short chain FA (SCFA)-producing bacteria by regulating AMPK signaling pathway. Citrus flavonoids down-regulate the miR-122 and miR-33 expression and affect the expression FAS and CPT1 α . KLX, DMC, emodin, and triterpenoids reduce lipid accumulation by activating the AMPK signaling pathway in liver. AE reduce cholesterol content by inhibiting the hepatic PCSK9/LDLR pathway. PE improve lipid disorders by regulating lipogenesis and FA β -oxidation. Baicalin exerts anti-lipogenic, antioxidant, and anti-inflammatory effects through inhibiting the reactive oxygen species (ROS), NF- κ B, and p38 MAPK signaling pathways. GPR41: G-protein coupled receptor 41; SRE: serum response element; ABCG1: adenosine triphosphate binding cassette subfamily G member 1; FFA: free FA; A-1: apolipoprotein-1; VLDL: very low-density lipoprotein.

advanced chemical separation and analysis methods combined with modern pharmacological experiments and developing novel hypolipidemic agents are the focus of future research. Furthermore, the mechanisms of action of CHM components in the regulation of hyperlipidemia must be elucidated.

In summary, the application of CHM to regulate blood lipids and protect homeostasis of the cardiovascular system has broad prospects for clinical treatment.

3.2. Bioactive components of CHMs regulate hyperglycemia

Hyperglycemia is a high-risk factor for various tissue and organ injuries. Patients with diabetes suffer from long-term hyperglycemia due to glucose metabolism disorders, insulin resistance, or impaired insulin secretion, which eventually results in cardiovascular, neurological, urinary, and other complications [33]. Moreover, the mortality rate of patients with diabetes mellitus who have by CVD complications is increasing significantly. The regulation of glucose homeostasis is important to protect the cardiovascular system.

CHM has a long history of use in regulating blood glucose homeostasis by promoting insulin secretion, improving insulin sensitivity, and protecting β -cells and other molecular mechanisms. Compared with Western medicines, CHM preparations not only reduce blood glucose but also regulate physiological functions and effectively prevent or delay the cardiovascular complications of diabetes [34]. Owing to the advantages of better safety profiles and multiple pharmacological effects, CHM has attracted the attention of pharmacologists and clinicians [35]. Traditional Chinese medicine practitioners believe that diabetes is caused by excessive heat and deficiency in Yin and Jin. CHM ingredients with hypoglycemic effects can be divided into four categories: anthraquinones, TPs, flavonoids, and alkaloids.

In addition to their antihyperlipidemic effects, anthraquinones also have impressive hypoglycemic effects. Our group previously demonstrated that emodin, an anthraquinone derivative, can downregulate miR-20b and increase the expression of its target gene, mothers against decapentaplegic homolog 7 gene (*Smad7*) to produce an anti-insulin resistance (IR) effect in a type 2 diabetes mellitus (T2DM) model [36]. Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a natural polyphenol present in plants such as grapes and blueberries, can be classified as an anthraquinone TP with the ability to ameliorate hyperglycemia. Guo et al. [37] showed that resveratrol mediated the AMPK-related signaling pathway to inhibit reactive oxygen species (ROS) generation and protect against cardiomyocyte apoptosis induced by high glucose.

TPs, compounds derived from meglutaric acid with isoprene as the basic structural unit, have important hypoglycemic activities and are important sources for the study of natural products and development of new drugs. A TP belonging to TPs in CHM is an epoxide diterpene lactone compound extracted from the roots, leaves, flowers, and fruits of *Tripterygium wilfordii*. It has been used for centuries to treat autoimmune and inflammatory diseases for centuries [38]. Wen et al. [39] showed that triptolide inhibited the expression of cardiac NF- κ B to attenuate cardiac inflammation and fibrosis in a rat model of diabetic cardiomyopathy. The *Ginkgo biloba* extract contains bioactive components such as flavonoid glycosides and TPs. Yu [40] found that *Ginkgo biloba* extract (Shuxuening) significantly reduces fasting blood sugar and two-hours postprandial blood glucose levels in patients with diabetes. Fitzl et al. [41] reported that *Ginkgo biloba* extract (EgB 761) protected of cardiac mitochondrial function in diabetic rats. Additionally, it is also reported that EgB761 can improve hypoxia tolerance of myocardial microvessels and reduce the deposition of collagen in the cardiac interstitium of diabetic rats [42].

Many flavonoids, including apigenin, hesperidin, myricetin, salicin, and anthocyanin, exhibit substantial hypoglycemic effects. Apigenin (4,5,7-trihydroxyflavone), which mainly exists in vegetables, has preventive and therapeutic effects on metabolic diseases. Mahajan et al. [43] demonstrated that apigenin protects against myocardial infarction in diabetic rats by activating the PPAR- γ pathway. Hesperidin is a citrus bioflavonoid with anti-inflammatory, lipid-lowering, and hypoglycemic effects. Akiyama et al. [44] documented that hesperidin decreases blood glucose by normalizing the activity of key enzymes involved in glucose metabolism, such as glucokinase, glucose-6-phosphatase, and adiponectin. Myricitrin is one of the most important flavonoids primarily found in the root bark of *Myrica cerifera* and *Ampelopsis grossedentata*. Zhang et al. [45] found that myricetin protects against dilated cardiomyopathy (DCM) through anti-inflammatory effects and inhibits oxidative stress and cardiomyocyte apoptosis. Mechanistically, myricetin up-regulates nuclear factor erythroid-derived 2-like 2 (Nrf2) expression and suppresses the NF- κ B signaling pathway. Therefore, myricetin has the potential to be developed as an agent against DCM. Anthocyanins are naturally active components that are found in several plants [46]. They are well-known for their strong antioxidant, anti-inflammatory [47], anti-hyperglycemic [48], and anti-fibrosis properties [49]. Fallah et al. [50] conducted a meta-analysis to evaluate the effects of dietary anthocyanins on the biomarkers of glycemic control and glucose metabolism. They found that anthocyanin consumption significantly reduces fasting blood sugar levels, two-hours postprandial glucose levels, and glycated hemoglobin. Our group previously revealed that anthocyanin not only reduces blood glucose but also has cardioprotective effects against myocardial inflammation and fibrosis in DCM by targeting interleukin (IL)-17 in cardiac fibroblasts [51].

Alkaloids, also known as vegetative alkaloids, are nitrogenous basic organic compounds that exist in nature and exert regulatory effects on blood glucose. Vindogentianine, an indole alkaloid isolated from *Catharanthus roseus*, produces a hypoglycemic effect by inhibiting the activity of protein tyrosine phosphatase 1B [52]. Berberine (BBR) is an isoquinoline alkaloid isolated from *Coptis chinensis* that has hypoglycemic and insulin-sensitizing effects in T2DM. Chang et al. [53] showed that BBR improves insulin resistance in cardiomyocytes by activating AMPK activity. Zhang et al. found that BBR treatment changed the bacteria in the gut of insulin-resistant rats, and short chain FA (SCFA)-producing bacteria such as *Blautia* and *Allobaculum* were selectively enriched [54]. Additionally, Liu et al. [55] demonstrated that BBR increased beneficial gut bacteria species or probiotics such as *Bifidobacterium* and decreased Gram-negative bacterial species such as *Escherichia coli* by regulating the lipopolysaccharide (LPS)/toll-like receptor 4 (TLR4)/tumor necrosis factor (TNF)- α signaling pathway in the liver.

One of our published studies revealed that DMC has a significant hypoglycemic effect as it promotes the secretion of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) by activating the glycogen synthase kinase-3 β (GSK-3 β)/ β -catenin pathway and upregulating transcription factor 7 like 2 (TCF7L2) levels [56]. Shensong Yangxin capsule (SSYX) is composed of ginseng, *Ophiopogon japonicus*, *Cornus officinalis*, *Salvia miltiorrhiza*, sour jujube kernel, sago, red peony, woodlouse worm, *Rhizoma Coptidis*, *Fructus Schisandrae Chinensis*, and keel; it possesses remarkable beneficial effects on CVD. Another study from our group found that SSYX ameliorates myocardial fibrosis in diabetic cardiomyopathy by inhibiting the transforming growth factor- β 1 (TGF- β 1)/Smad signaling pathway, thereby restoring cardiac function [57]. The comparison between drugs with hypoglycemic effect was shown in Table 2.

Emerging clinical evidence has shown that CHM is effective in treating hyperglycemia. TM81 is a formulation derived from a clas-

Table 2
Comparison between drugs with hypoglycemic effect.

Kind of compound	Name	Dose	Drug efficacy	Molecular mechanism
Anthraquinone	Emodin	20 and 40 mg·kg ⁻¹ , <i>in vivo</i> ; 20 μmol·L ⁻¹ , <i>in vitro</i>	Improve insulin resistance; improve glucose metabolism	Inhibit miR-20b; increase Smad7; improve glucose metabolism
	Resveratrol	200 mg·kg ⁻¹ ·d ⁻¹ , <i>in vivo</i> ; 50 μmol·L ⁻¹ , <i>in vitro</i>	Improve glucose tolerance and insulin sensitivity; protect cardiomyocytes in diabetic cardiomyopathy	Improve glucose tolerance and insulin sensitivity; activate AMPK signaling pathway; inhibit NADPH derived ROS production; increase cardiac antioxidant enzyme activities
Triterpenoids	Triptolide	100, 200, or 400 μg·kg ⁻¹ ·d ⁻¹ , respectively, <i>in vivo</i> ; 20 ng·mL ⁻¹ , <i>in vitro</i>	Inhibit high glucose-induced inflammation; inhibit myocardial fibrosis	Inhibit NF-κB signaling pathway
	<i>Ginkgo biloba</i> extract	<i>Ginkgo biloba</i> extract (Shuxuening), two tablets per time, three times a day for three months; <i>Ginkgo biloba</i> extract (EGb761), 100 mg·kg ⁻¹ , <i>in vivo</i>	Improve insulin sensitivity; reduce blood glucose; improve the hypoxia tolerance of myocardial microvessels in diabetic rats; reduce the deposition of collagen	—
Flavonoids	Apigenin	75 mg·kg ⁻¹ ·d ⁻¹ , <i>in vivo</i>	Improve diabetes-related cardiovascular complications	Activate PPAR-γ pathway
	Hesperidin	10 g·kg ⁻¹ diet (fed with hesperidin containing diet), <i>in vivo</i>	Lower the blood glucose and blood lipid	Inhibit serum and liver TC, TG, and serum LDL + VLDL-C concentrations; alter the activity of glucose-regulating enzymes
	Myricetin	75, 150, 300 mg·kg ⁻¹ ·d ⁻¹ , <i>in vivo</i> ; 25 μg·mL ⁻¹ , <i>in vitro</i>	Cardioprotective effects against DCM	Inhibit NF-κB signaling pathway; activate phospho-Akt; inhibit phospho-ERK; activate Nrf2 signaling; attenuate oxidative stress, inflammation, and apoptosis
	Anthocyanin	250 mg·kg ⁻¹ , <i>in vivo</i> ; 250 μg·mL ⁻¹ , <i>in vitro</i>	Improve cardiac function; alleviate inflammation and fibrosis	Inhibit IL-17, IL-1β, IL-6, and collagen I and III
Alkaloids	Vindogentianine	12.5, 25.0, 50.0, 100.0, and 200.0 μg·mL ⁻¹ , <i>in vitro</i>	Increase glucose uptake	Inhibit PTP-1B
	BBR	10 μmol·L ⁻¹ , <i>in vitro</i>	Improve insulin resistance in H9c2 cardiomyocytes	Increase AMPK activity
Chinese herbal compound	DMC	200 mg·kg ⁻¹ ·d ⁻¹ , <i>in vivo</i> ; emodin (100 μmol·L ⁻¹), <i>in vitro</i>	Anti-hyperglycemic	Activate GSK-3β/β-catenin signaling pathway; promote TCF7L2 expression; stimulate the secretion of GLP-1 and GIP
	SSYX	50, 100, and 200 mg·kg ⁻¹ ·d ⁻¹ , <i>in vivo</i>	Improve the impaired cardiac function of T2DM rats; improve diabetic cardiomyopathy; alleviate fibrosis	Inhibit TGF-β/Smad signaling pathway

NADPH: nicotinamide adenine dinucleotide phosphate; VLDL-C: VLDL cholesterol; Akt: serine-threonine protein kinase; PTP-1B: protein tyrosine phosphatase-1B; ERK: extracellular signal-regulated kinase; Nrf2: nuclear factor erythroid-derived 2-like 2.

sis formula described in the *Treatise on Exogenous Febrile Diseases* over 1000 years ago. The TM81 formula contains *Rhizoma Coptidis*, *Radix Paeoniae Alba*, *Radix Scutellariae*, *Pericarpium Citri Reticulata*, *Rhizoma Rhei*, and other Chinese herbs. Tong et al. [58] conducted a randomized double-blind placebo-controlled trial with 480 overweight patients with type 2 early stage diabetes who received 6 g TM81 or placebo three times daily for 12 weeks and found that TM81 was more effective for patients with higher baseline glycosylated hemoglobin, type A1c (HbA1c) levels. They found that TM81 improves β-cell function, increased homeostatic model assessment (HOMA)-β, and reduced body weight, body mass index (BMI), waist circumference, and symptoms related to diabetes [58]. Xiaohe Pill comprises 0.25 mg of glibenclamide per pill and herb components includes *Radix Puerariae*, *Radix Rehmanniae*, *Radix Astragali*, *Radix Trichosanthis*, *Stylus Zeae Maydis*, *Fructus Schisandrae Sphenantherae*, and *Rhizoma Dioscoreae*. Ji et al. [59] conducted a double-blind, randomized controlled trial of 800 patients with unsatisfactory glycemic control. They were randomly assigned to receive Xiaohe Pill or glibenclamide in two study groups, and the results showed that patients with type 2 diabetes treated with Xiaohe Pill exhibited significant reduction in the risk of hypoglycemia and showed improvements in their glycemic control after 48 weeks compared to patients who were administered glibenclamide. This indicates that CHM has the potential advantage of fewer side effects than Western medicine [59]. Moreover, Pang et al. [60] performed a retrospective analysis of 183 patients with 678 clinical visits and found that Dahuang Huanglian Xiexin decoction (DHXD) decreased blood glucose, improved T2DM symptoms, and reduced body weight. Liu et al. [61] found that resveratrol consumption

significantly reduces fasting blood sugar levels and insulin resistance in 388 participants with diabetes. Jinlida is a CHM composed of danshensu sodium salt, puerarin, salvianolic acid B, epimedin B, epimedin C, icariin, and the ginsenosides Rb1, Rc, and Rb2. Pan et al. [62] demonstrated that Jinlida granules improved glycemic control and glycemic variability in 138 patients with newly diagnosed T2DM. The Tianqi capsule consists of ten CHMs, namely *Astragali Radix*, *Coptidis Rhizoma*, *Trichosanthis Radix*, *Ligustri Lucidi Fructus*, *Dendrobii Caulis*, *Ginseng Radix*, *Lycii Cortex*, *Ecliptae Herba*, *Galla Chinensis*, and *Corni Fructus*. Lian et al. [63] conducted a clinical trial for 420 enrolled subjects with impaired glucose tolerance over the course of a 12-month treatment with Tianqi and found that it reduces the risk of diabetes by 32.1% compared with placebo.

These studies indicate that CHM must be subjected to more investigation to identify its potential in treating diabetes and other associated cardiovascular complications (Fig. 4).

4. Discussion

In recent years, CHM has gained increasing attention because of its efficacy in the treatment of various diseases. Several studies have confirmed that the bioactive components of CHM can prevent hyperlipidemia and diabetes and produce protective effects in the cardiovascular and cerebrovascular systems. Researchers have clarified the pharmacological effects and specific molecular mechanisms of some bioactive components of CHM. These studies not only provide drug candidates for the clinical prevention of CVD

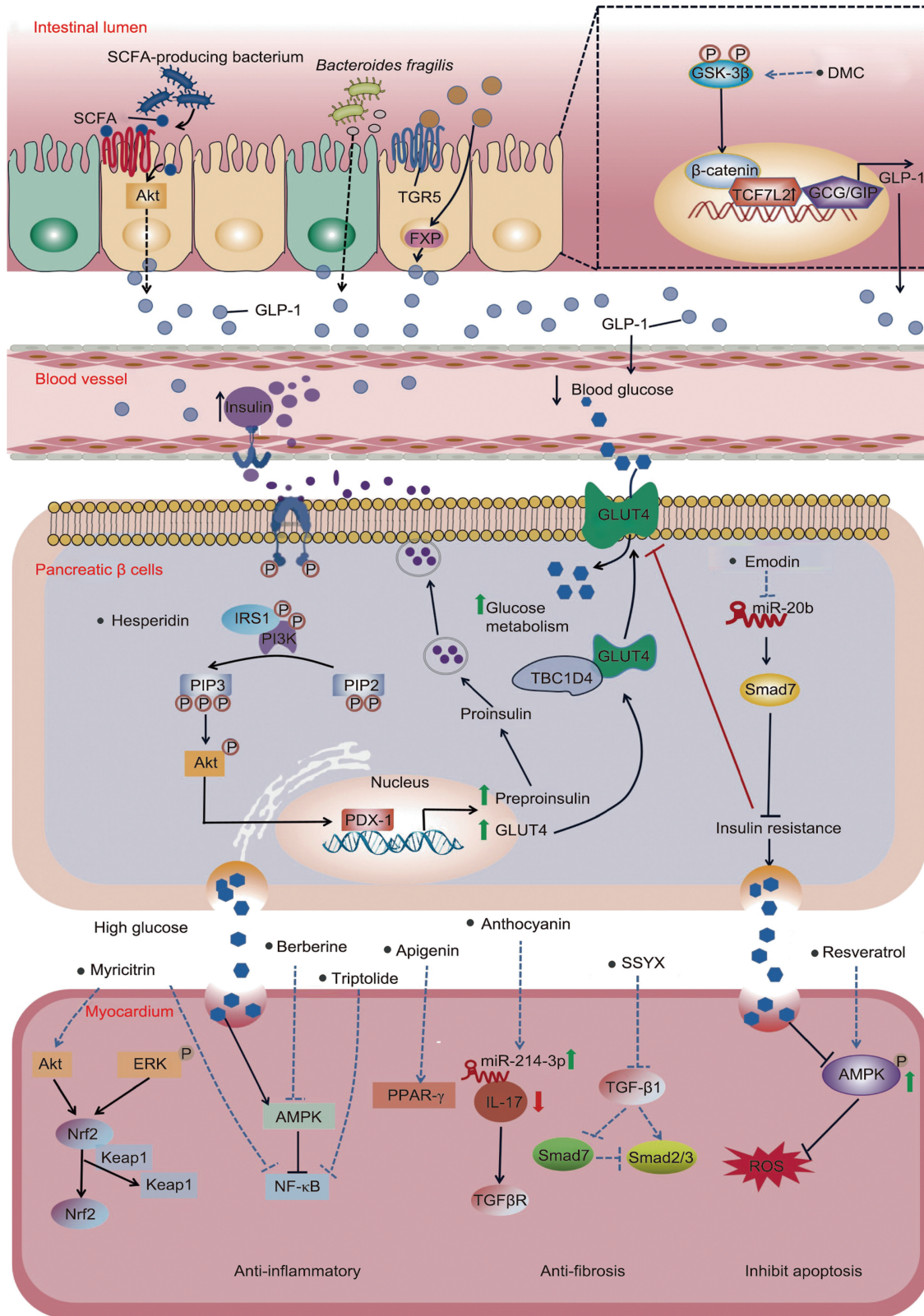


Fig. 4. The effects and mechanisms of CHM in regulating hyperglycemia. SCFA activates Akt and increases the secretion of GLP-1. DMC shows hypoglycemic effect via promoting the secretion of GLP-1 and GIP by activating the GSK-3β/β-catenin pathway and upregulating the level of TCF7L2. Hesperidin decreases blood glucose by normalizing the activity of key enzymes involved in glucose metabolism. Insulin promotes the expression of pancreatic and duodenal homeobox-1 (PDX-1), which promotes the transcription of GLUT4 and proinsulin, thus promoting insulin production and glucose metabolism. Emodin inhibits miR-20b, increases Smad7 and improves glucose metabolism. Myricitrin shows anti-inflammatory effects by up-regulating Nrf2 expression and suppressing the NF-κB signaling pathway. BBR increases AMPK activity. Anthocyanin protects cardiac function and cardiac fibroblasts from high-glucose induced inflammation and myocardial fibrosis by increasing miR-214-3p and inhibiting IL-17. SSYX improve myocardial fibrosis in diabetic cardiomyopathy by inhibiting the TGF-β1/Smad signaling pathway. Apigenin improve diabetes-related cardiovascular complications by activating the PPAR-γ pathway. Resveratrol activates AMPK to inhibit ROS generation and protected against cardiomyocytes apoptosis induced by high glucose. IRS1: insulin receptor substrate 1; PI3K: phosphoinositide 3-kinases; TBC1D4: CDC16 domain-containing protein family member 4; Keap1: kelch like ECH associated protein 1; TGFβR: TGF-β receptor; GCG: glucagon; PIP2/3: plasma membrane intrinsic protein 2/3; P: phosphorylation.

but also provide a theoretical basis for the promotion of CHM globally.

In general, CHM appears to have better safety profiles (lower toxicity), therapeutic outcomes (curative), disease-preventive power, and diverse applications. These advantages could be partially ascribed to the multitargeting property of CHM, which contains multiple bioactive components at a concentration lower than its toxic threshold and has a unique action. For example, Xiaoke Pill has the potential advantage of fewer hypoglycemic side effects than glibenclamide [59]. DMCs exert hypolipidemic and hypoglycemic effects by targeting the AMPK and GSK-3 β / β -catenin pathways, respectively. Nonetheless, the multitargeting property is naturally occurring or non-rationally designed, and is therefore often not optimal for a specific disease entity. In this sense, one of the directions for future research on CHM is to combine scientific guidance and empirical knowledge and formulate more rational medications. In this regard, the currently available computational technologies and databases provide a wealth of resources for the rational design of CHM formulas based on modern polypharmacological principles and methodologies. Another advantage of CHM is its potential for use in personalized or precision medicine by modifying formulas according to each individual's specific etiology and symptoms, despite the fact that such superiority also creates difficulties for large-scale clinical trials. Resolving this issue will be a prerequisite for CHM to overcome its current dilemma and limitations, thereby being one of the directions for future research. Intriguingly, single compounds derived from CHM, such as resveratrol and BBR, also known as natural products, possess multitargeting properties in general, but have mild efficacy accompanied by lower toxicity, relative to Western medicines. One way to enhance the therapeutic efficacy of natural products is to chemically modify their structure. Alternatively, natural products could be used as components of combinational drug therapy or as adjunct therapies. The multitargeting properties of natural products have recently become a hot topic for researchers worldwide and will continue to be an active field of future research.

Compared to the published review [64], our review mainly discusses the dose, drug efficacy, molecular mechanisms, and clinical research progress of bioactive components or preparations from CHM on hyperlipidemia and hyperglycemia.

5. Conclusion

In this review, we discuss the benefits, molecular mechanisms, and clinical treatment progress of bioactive components from CHM in hyperlipidemia and hyperglycemia. We believe that there are two clear requirements for the global application of CHM. One of the needs is to integrate empirical knowledge about the pharmacological properties of CHM with modern scientific principles and methodologies and adopt rigorous and rational experimental approaches to understand the effects and mechanisms of CHM. Second, more randomized clinical trials are being conducted to validate the therapeutic efficacy and safety profile of CHM observed and experienced through CHM doctors' individual practice.

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Compliance with ethics guidelines

Ying Zhang, Jiaming Ju, Lei Jiao, and Baofeng Yang declare that they have no conflict of interest or financial conflicts to disclose.

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