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Application of *Monascus* fermentation products in prevention and treatment of diabetes and their potential molecular mechanisms

Jun Wan[a,b,1], Caiyun Meng[a,1], Caiqing Yue[a], Deqing Zhao[a], Shengfa Li[a], Yunxia Gong[a], Yanchun Shao[a,c,*]

[a] *College of Food Science and Technology, Huazhong Agricultural University, Wuhan 430070, China*

[b] *The Third Clinical Medical College of China Three Gorges University, Gezhouba Central Hospital of Sinopharm, Yichang 443002, China*

[c] *Hubei International Scientific and Technological Cooperation Base of Traditional Fermented Foods, Huazhong Agricultural University, Wuhan 430070, China*

ABSTRACT: *Monascus* spp. are important fungal resources used for produce Hongqu (red yeast rice, RYR) with various pharmacological activities. Many studies have suggested that *Monascus* fermentation products have the potential to prevent and treat diabetes because of their hypoglycemic effect. Based on the data from 2019 to 2024 in the SciFinder, PubMed and Web of Science, this article summarized the physiological activities of different metabolites produced by *Monascus* fermentation, the experimental effects in the treatment and prevention of Type 2 diabetes mellitus (T2DM) and its complications. Meanwhile, the molecular mechanisms were reviewed underlying the effectiveness of several substances, including Monacolin K (Lovastatin), γ-aminobutyric acid (GABA), and pigments against T2DM. In addition, *Monascus* strains can ferment a variety of grains and plants to produce hypoglycemic substances, which can be used as a dietary supplement to prevent T2DM, but the underlying mechanisms of most compounds are still unclear. In the future, it is necessary to conduct further research on the structure-activity relationship of bioactive compounds produced by *Monascus* fermentation, contributing to the development of potential anti-T2DM drugs.

Keywords: *Monascus* spp.; secondary metabolites; diabetes mellitus; hypolipidemic activity; research progress

1. Introduction

DM, featuring hyperglycemia, is a disease triggered by endocrine disorder in the body. According to different pathogenesis, it is mainly divided into type 1 and type 2 DM (T1- and T2DM). T1DM is characterized by damage to pancreatic β-cells and absolute insufficiency of insulin secretion, and often involves autoimmune mechanisms. The pathogenesis of T2DM is dominated by insulin resistance, which leads to insufficient utilization of insulin. As a result, a series of symptoms and signs are caused by the relative insufficiency of insulin secretion. Clinically, T2DM accounts for 90%~95% of all DM cases in adults[1]. The prevalence of DM is rising with the increased intake of foods high in sugar and fat. It is estimated that the prevalence of DM will increase to 10.2% (578 million) by 2030 and 10.9% (700 million)

[1] These authors contributed equally to this work.
***Corresponding author**
yanchunshao@mail.hzau.edu.cn

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by 2045, making diabetes a critical "killer" threatening human health[2]. As a chronic metabolic disease, DM usually does not exist independently, but often co-exists with many other non-healthy states or diseases, such as diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, cardiovascular complications, diabetic foot problems, hepatobiliary manifestations and hematological derangements etc. Fig.1 exhibited the DM complications.

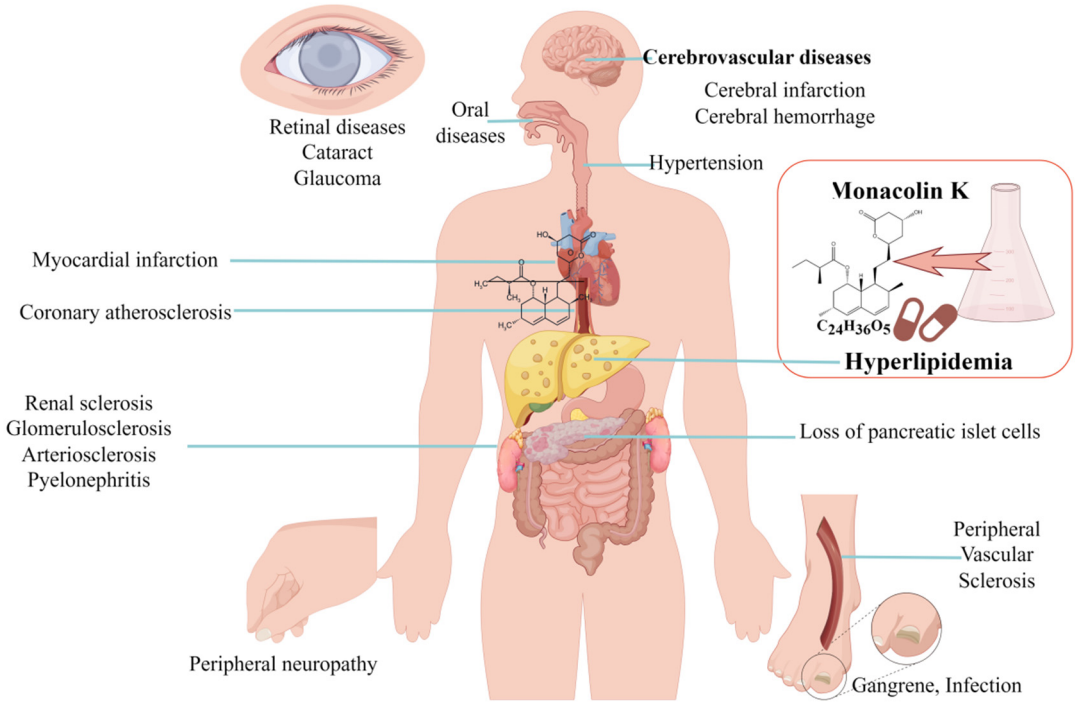

Fig.1 Diabetes and its main complications

Since DM poses such a great threat to human health, prevention and treatment of it are particularly important. The strategies for T2DM treatment generally include dietary control, moderate exercise, taking hypoglycemic and hypolipidemic drugs, etc. Although the drugs for treating T2DM have certain therapeutic benefits, most of them can produce side effects[3,4]. An increasing number of studies have shown that natural products from plants and microorganisms, such as polyphenols, polysaccharides, flavonoids and saponins, have the effects of lowering blood sugar and regulating glucose metabolism disorders[5]. *Monascus* species are filamentous fungi, which belong to the genus of *Monascus*, Monascaceae, Eurotiales, Eumycota, Plectomycetes, Ascomycotina[6,7]. *Monascus* specises can secret many beneficial compounds, such as *Monascus* pigments (MPs), Monacolin K (MK), γ-aminobutyric acid (GABA), ergosterol, *Monascus* polysaccharides, flavonoids, enzymes and organic acids, and some of these metabolites have been demonstrated to play pharmacological activities (summarized in Table 1), such as lipid-lowering activity, central neuron protection, immunoregulation, anti-inflammation, alleviating liver damage, and anti-tumor.

Table 1 Main Chemical Constituents of *Monascus* Metabolites and Their Pharmacological Effects

Main Components	Pharmacological Effects
Statins	Lowering lipid, glucose and blood pressure, anti-tumor, bacteria inhibition, anti-inflammation, anti-oxidation, anti-fatigue, anti-Alzheimer's, relieving liver injury, immunoregulation, and protecting rat cranial nerves

MPs	Anti-oxidation, anti-atherosclerosis, prevention of fatty liver and accumulation of cardiac aortic plaque, inhibition of lipogenesis, promotion of lipolysis, anti-obesity, reduction of hyperglycemia, protection of liver ischemia- reperfusion injury, and protection of hemorrhagic brain injury
Monascus polysaccharides	Enhancing immunity, anti-tumor, and anti-protein oxidative damage
GABA	Anti-tumor, reducing blood glucose and pressure, anti-fatigue, and protection of central neurons
Stigmasterol	Reducing blood lipid, anti-tumor, antiinflammation
Ergosterol	Reducing blood pressure, anti-oxidation, anti-tumor, prevention of osteoporosis

Monascus species are traditionally used to make Hongqu, a folk medicine component and natural food colorant, which has been widely used for thousands of years in China and Southeast Asian countries[8]. There are so many ancient literature in China recording the efficacy of Hongqu, which was summarized in Table 2.

Table 2 Main Efficacy and Functions of Hongqu in Chinese Ancient Books

Dynasty, principal author	Ancient book	Record
Yuan Dynasty, R. Wu	*Daily Materia Medica*	The liquor brewed with *Monascus* species can eliminate blood stasis, expedite qi and blood, and facilitate the effect of Hongqu, and also play a role in the treatment of "miasma" and traumatic injuries.
Yuan Dynasty, S.H. Hu	*Principle of Correct Diet*	Hongqu has sweet taste, mild medicinal properties and no toxicity, and can nourish and tonify the spleen qi, and tonify the spleen and stomach.
Yuan Dynasty, D.X. Zhu	*Supplement to the Extension of the Materia Medica*	Hongqu encourages the restoration of qi and blood, digestion of food, strengthens the spleen and qi, tonify the spleen and stomach, and can be urilized in the treatment of dysentery with pus and blood in the stool and indigestion.
Ming Dynasty, S.Z. Li	*Compendium of Materia Medica*	Hongqu can be taken in a bowl with liquor, ground up, wherever women experience abdominal pain from stagnant blood as well as the discharge of necrotic decidua and haemophilia.
Ming Dynasty, X.Y. Miao	*Shen Nong's Classic of the Materia Medica*	Hongqu promotes digestion of food, strengthens the spleen and stomach, and is as effective as Medicated Leaven. It is the only medicine that can promote blood circulation and reduce stasis. Therefore, it is an important medicine for treating dysentery with blood.
Qing Dynasty, A. Wang	*Essentials of Materia Medica*	Hongqu can invigorate ying blood circulation and eliminate stasis with strong effect, treating stomach fire to promote food digestion and invigorate blood circulation to remove stasis. It treats dysentery with blood in the stool and traumatic injuries.
Qing Dynasty, B.C. Wang	*Xin'an Medical Book Series · Discussion Collection*	Hongqu enters the blood system to eliminate blood stasis and treat food indigestion. It can be incorporated into the spleen and stomach as a medicine for removing food retention.
Qing Dynasty, unknown	*Origin of Materia Medica*	Hongqu can be used as an adjunct for anyone with blood stasis. It can treat dysentery caused by dampness and cold gathering in the intestines, traumatic injuries, amenorrhea, and postpartum hemorrhage.
Qing Dynasty, B.C. Zhang	*Convenient Reader on Materia Medica*	Promoting blood circulation to replenish nutrient qi and cure dysentery. Strengthening the spleen and digestion to harmonize the middle Jiao.
Qing Dynasty, unknown	*Compilation of Materia Medica*	Hongqu is gentle, sweet and red. It can promote food digestion and regulate the middle Jiao, strengthen the spleen, stomach and nutrient blood. It can be used for postpartum recovery.
Qing Dynasty, L. Zhang	*Origin of Herbal Classic*	Hongqu can be used for women with menstrual stasis and dysentery.
Qing Dynasty, H.X. Wang	*Life-saving Manual of Diagnosis and Treatment of External Diseases*	Hongqu is taken together with liquor to cure postpartum hemorrhage.
Qing Dynasty, M. Zhang	*Debate on Diet for Regulating Diseases*	Ground and decocted with liquor, Monascus can be used to treat hematocele in the abdomen as well as postpartum blood congestion.
Qing Dynasty, Y.L. Wu	*New Compilation of Materia Medica*	Hongqu removes stomach fire and eliminates food stagnation, and treats dysentery with blood in stools.

Qing Dynasty, A. Wang	*Easy Understanding of Materia Medica*	Hongqu can treat dysentery with blood in stools, stabbing pains of blood and qi, postpartum hemorrhage, and eliminate bruises from traumatic injuries.
Qing Dynasty, A. Wang	*Essentials of Materia Medica*	Hongqu can be used for the treatment of dysentery with blood in stools, traumatic injuries and postpartum hemorrhage.
Qing Dynasty, Z.Y. Lu	*Bencao Chengya Banjie*	Hongqu is mainly used to promote food digestion, invigorate blood circulation, tonify the spleen and stomach, and treat dysentery with pus and blood in stools and indigestion.
Qing Dynasty, Q.R. Chen	*Essentials of Materia Medica*	Hongqu mainly invigorates ying blood circulation and eliminates stasis, removes stomach fire and promotes food digestion.
Qing Dynasty, L. Yao	*Classic of Materia Medica*	Hongqu treats nutrient blood in the spleen and stomach, removes blood stasis and invigorates blood circulation.
Qing Dynasty, G. Ye	*Classic Explanation of Materia Medica*	Hongqu has the main functions of promoting digestion and blood circulation, tonifying the spleen and regulating stomach, and treating dysentery with pus and blood in stool.
Qing Dynasty, J. Yan, W. Shi, W. Hong	*Supplement of Materia Medica*	Hongqu promotes food digestion and blood circulation, and treats dysentery with pus and blood in stool.
Qing Dynasty, D.C. Xu	*Practical Use of Drug Properties*	Hongqu can enter the blood system to eliminate blood stasis and is a specialized medicine for treating dysentery with thick and sticky stools.
Qing Dynasty, Z.Z. Feng	*Feng's Secret Collection of Know How*	The main functions of Hongqu are promoting digestion and blood circulation, tonifying the spleen and regulating stomach, and treating dysentery with pus and blood in stool.
Qing Dynasty, J.Y. Gu	*Gu Songyuan's Medical Mirror*	Hongqu is used to invigorate blood circulation and promote digestion.

It is worth mentioning that since Japanese scholar Endo proved that *Monascus* strain can produce the lipid-lowering ingredient MK (also named lovastatin) in 1979, *Monascus* species have received unprecedented attention. In 1985, American doctors Brown and Geldstein were awarded the Nobel Prize for elucidating the mechanism of MK inhibiting cholesterol biosynthesis. In addition to preventing and treating cardiovascular disease, there are also many reports on the hypoglycemic effect of *Monascus* metabolites[9,10]. In this review, we summarized the applications of the secondary metabolites from *Monascus* fermentation to the prevention and treatment of DM and its complications, as well as the molecular mechanisms by which they exert pharmacological activity, providing some references for the development and utilization of *Monascus* resources.

2. Preventive care functions of major metabolites of Monascus species on DM combined with hyper-lipidemia

2.1 MK

The mechanism by which MK, regulates dyslipidemia has been clarified, and the drugs derived from it, such as “Xuezhikang” and “Zhibituo”, have been proven to bring good therapeutic effects for patients with hyperlipidemia, together with statins, niacins and fibrates. “Xuezhikang” consists of 13 natural statins, unsaturated fatty acids, ergosterol, amino acids, flavonoids, alkaloids, trace elements and other substances, and has long been regarded as a natural lipid-lowering drug[11]. This drug can effectively reduce cardiovascular events in patients with DM and coronary heart disease (CHD). It has been reported that “Xuezhikang” can significantly reduce triglycerides (TG), a potential risk factor for myocardial infarction. Compared with simvastatin (SIM) in the treatment of patients with T2DM combined with dyslipidemia,

"Xuezhikang" can significantly reduce the levels of total cholesterol (TC), TG, fasting plasma glucose (FPG), 2hPG and low-density lipoprotein cholesterol (LDL-C) and help to increase the level of high-density lipoprotein cholesterol (HDL-C), with a low rate of adverse reaction. It is more effective than SIM in improving TC and TG in blood glucose and lipids in patients with T2DM combined with dyslipidemia[12]. In the treatment of stage III diabetic kidney disease (DKD), "Xuezhikang" was found to improve patients' blood lipid, especially LDL level, and further alleviate the urinary protein excretion, as well as reduce the inflammatory response of the body and improve renal blood flow, with few adverse effects. In a multicenter, randomized controlled study designed to evaluate the effects of "Xuezhikang" and pravastatin on TG and other lipid parameters in patients with T2DM and dyslipidemia, it was found that 6 weeks of treatment with "Xuezhikang" and pravastatin resulted in a significant reduction in fasting and postprandial TG levels in patients with T2DM and no atherosclerotic cardiovascular disease (ASCVD), which would provide additional clinical support for optimizing primary prevention of ASCVD in DM patients for lipid control[13].

2.2 ANKASCIN 568 plus

Hyperglycemia can also lead to macrovascular disease, small vessel disease (retinopathy, nephropathy), and neuropathy. As was reported in a previous study (Fig. 2), patients who took two capsules of ANKASCIN 568 plus (*Monascus* fermentation product) daily for 12 weeks showed a decrease in fasting blood glucose, LDL-C and TC levels by 8.5%, 10.3% and 7.5%, respectively[14]. This result suggests that ANKASCIN 568 plus produced by the fermentation of *Monascus* strain NTU 568 may be a potential drug for the regulation of blood glucose and lipids as well as the treatment of coronary artery disease (CAD). In addition, MK significantly reduced plasma alanine aminotransferase, cholesterol, TG, and homeostasis model assessment (HOMA) index, and improved insulin sensitivity[15,16]. Meanwhile, through the study of *Monascus* NTU 568 fermentation products on the effects of fasting blood glucose and oral glucose tolerance test (OGTT) of streptozotocin induced diabetes rats, it was found that oral *Monascus* fermentation products could delay the development of blood glucose levels, and significantly reduce the levels of urine glucose and urine protein in rats after 8 weeks of feeding at a dose of 200 mg/kg. This study scientifically validates the widely claimed use of *Monascus* fermentation products as a folk drug for DM treatment[17].

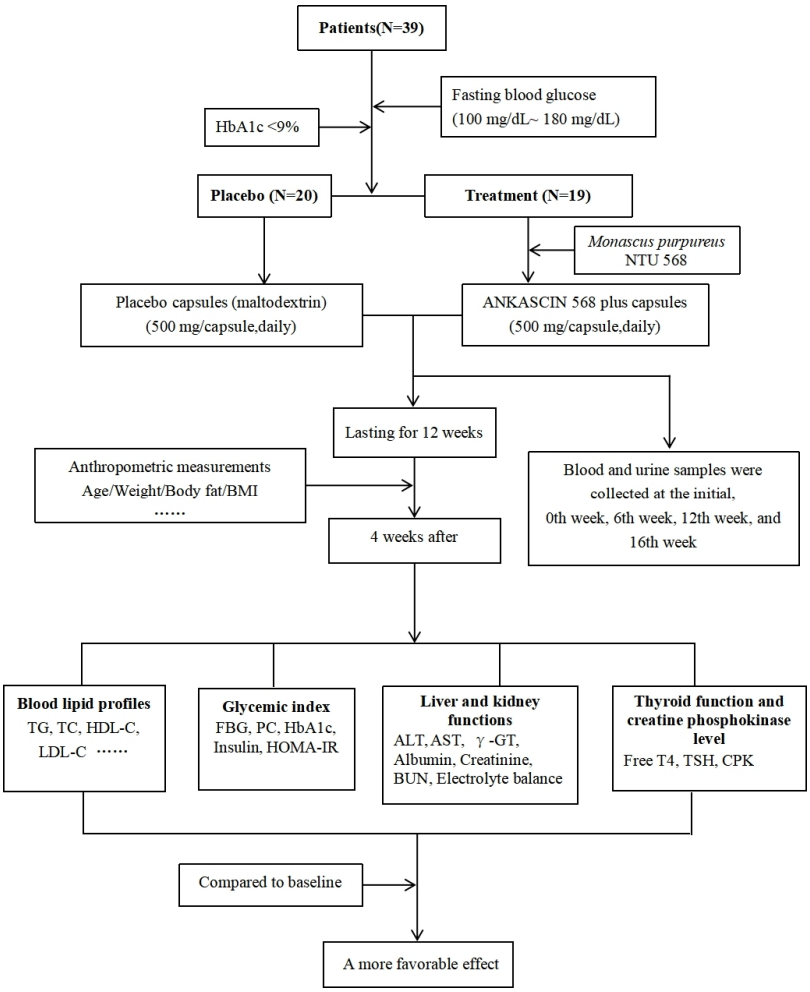

Fig.2 A randomized, double-blind clinical study to determine the effect of ANKASCIN 568 plus on blood glucose regulation[11]

2.3 Monascus fermented products

The treatment of DM and its complications with metabolites secreted by *Monascus* strains has also been reported in animal models (Table 3). Rajasekaran et al [18]. used streptozotocin (STZ)-induced DM model rats to assess the antidiabetic activity and nephroprotective effects of *Monascus* fermented rice produced (MFR) by mutant *M. purpureus* 254 (MMFR). After treatment with the fermentation products of *Monascus* strain, the relevant biochemical indices of the DM rats were significantly reduced, lipids were restored to normal level, blood glucose was significantly reduced, body weight was decreased, and renal antioxidant level was increased. MFR not only has antidiabetic activity, but also prevents DM-induced nephropathy and hypercholesterolemia. The other example is that Yoshizaki et al [19] fed Hongqu to mice on a high-fat diet for 4 weeks. The blood glucose level of the mice in the feeding group was significantly lower, and their body mass, epididymal white adipose tissue and total adipose tissue mass were all significantly lower than the common rice group, proving that Hongqu has the function of weight loss and DM treatment. Further experimental studies showed that Hongqu extract reduced BG and insulin levels and increased glucose transporter type 4(GLUT4) protein expression levels in skeletal muscle but did not affect GLUT2 levels in liver in streptozotocin- and high-fat diet-induced insulin-deficient and insulin-resistant mouse models[20].

Table 3 Hypoglycemic Effects of *Monascus* Fermentation Products in Animal Experiments

First author, year	Compound	Research objectives	Study design	Duration	Main outcomes/ Results
A. Rajasekaran 2013	*Monascus* fermented rice (MFR) made by mutant *M. purpureus* 254 (MMFR)	Protective effect of *Monascus* fermented rice against STZ-induced diabetic oxidative stress in kidney of rats	Anti-diabetic activity and neph-roprotective effect of MFR was evaluated by using STZ-induced diabetic rats	14 days	MFR, not only possess anti- diabetic activity but also prevents nephronpathy and hypercholesterolemia due to diabetes.
T. Yagi, 2020	Red rice koji (RRK) extract	Examine the mechanism underlying the hypoglycemic action of RRK extract in two diabetic animal models	Low and high doses of RRK extract were orally administered to the mice for 10 successive days. Blood glucose levels of STZ-treated mice in insulin tolerance test and BG and insulin levels of HFD-fed mice in IPGTT were investigated.	10 days	Orally administered RRK extract lowered the BG and the homeos- tasis model assessment index for insulin resistance.
Y.C. Shi, 2010	*purpureus* NTU 568 fermented products	Examine the effect of *M. purpureus* NTU 568 fermented products on fasting blood glucose and oral glucose tolerance testing (OGTT) in streptozotocin-induced diabetic rat	8 weeks of being fed with red-mold-fermented products at a dose of 200 mg/kg.	8 weeks	Oral administration of red-mold- fermented products can delay the development of the plasma glucose level in rats.
W.H. Hsu, 2013	*Monascus*-fermented metabolite monascin (MS)	Prove the *Monascus*-fermented metabolite MS acts as a novel natural peroxisome proliferator-activated receptor-γ (PPARγ) agonist that improves insulin sensitivity	Investigated the metabolic, bio- chemical, and molecular abnor- malities characteristic of type 2 diabetes in MG-treated Wistar rats treated with oral administration of MS or rosiglitazone.	28 days	MS acts as an anti-diabetic and anti-oxidative stress agent to a greater degree than rosiglitazone and thus may have therapeutic potential for the prevention of diabetes.
X.H. Hsu, 2013	*Monascus*-fermented products (MS and MK)	Confirm the protective effects of MS and MK on pancreatic function	BALB/c mice were treated with AGEs via intraperitoneal injection for 22 weeks to induce hyperglycemia, and the pancre-asprotecting mechanism of MS and MK from AGE induced damage was investigated.	22 weeks	MS strongly improved perfor- mance in the oral glucose tolerance test (OGTT) and the insulin tolerance test (ITT). Both MS and MK elevated pancreatic insulin expression when compared to the AGE-treated group.
C.W. Lin, 2023	MS and ankaflavin (AK)	The effects of MS and AK onpreventing metabolic disorder with type 2 diabetes induced by long-term high fat and high fructose diet	MS and AK were orally administered to HFFD-fed rats for 10 weeks.	10 weeks	MS had a more potent effect on lowering blood glucose, fruc- tosamine, and insulin resistance, and increasing hepatic GLUT2, adipocyte GLUT4, and hypoxia-inducible factor 1-α.

B.H. Lee, 2013	*Monascus*-fermented products	The attenuation of hyperglyc- emia by MS treatment in vivo	Hyperglycemic C57BL/6 mice were given MS and pioglitazone (PPARg agonist), with or without GW9662 (PPARg antagonist)	8 weeks	MS improves diabetes and dyslipi- demia by regulating PPARγ and inhibiting lipogenesis in fructose- rich diet-induced C57BL/6 mice.
S. Wu, 2021	*Monascus*-fermented products (MS and AK)	The anti-glycation potential of *Monascus*-fermented products rich in MS and AK (denoted as MPs) were assessed	Measuring the changes in the formation of fructosamine (Amadori product), α-dicarbonyl compounds and total fluorescent- AGEs.	/	MPs significantly inhibited the formation of fructosamine, α-dicarbonyl compounds, and advanced glycation end products (AGEs) in the human serum albumin (HSA)-glucose in vitro glycation model.
B.C. Chen, 2006	*M. pilosus* and *M. purpureus*	Screen the effect of Hon-Chion plasma glucose and investigate the possible mechanisms	The powder of Hon-Chi was dissolved in saline solution for oral administration at the desired doses (50,100 and 150 mg/kg) into fasting Wistar rats.	/	Hon-Chi has an ability to raise the release of ACh from nerve terminals, which in turn to stimulate muscarinic M3 receptors in pancreatic cells and augment the insulin release to result in plasma glucose lowering action.

3. Effect and molecular mechanism of secondary metabolites produced by *Monascus* species on regulating blood sugar

Due to the complex composition of secondary metabolites produced by *Monascus* species, further study is required on the main components and molecular mechanisms of their hypoglycemic effects. Currently, the therapeutic effects and signaling pathways of MK, γ-aminobutyric acid and monascorubin, on DM have been studied.

3.1 Effect and molecular mechanism of MK and statins on regulating blood sugar

MK, or lovastatin[21], is a secondary metabolite with cholesterol-lowering activity by inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase[22,23], a key substance in the rate-limiting step of cholesterol biosynthesis. MK effectively reduces LDL-C concentrations, thereby reducing the risk of cardiovascular disease. Due to their safety and effectiveness, drugs such as lovastatin, SIM, and pravastatin, are currently available on the market, are isolated or structurally modified from fungal metabolites[24]. Meanwhile, HMG-CoA reductase inhibitors (statins) have been used as first-line agents in the treatment of diabetic dyslipidemia[25].

3.1.1 MK alleviates DM by improving insulin resistance

In DM treatment alone, the effect of statins, represented by MK, on glucose metabolism and the risk of DM remains a controversial issue, despite the proven hypoglycemic effect of *Monascus* metabolites. Previous study showed that statins can block the opening of the electric-gated voltage-controlled L-shaped channel, thereby inhibiting insulin secretion and leading to elevated blood glucose; they also control the production of some intermediates by interfering with the relevant cellular signaling pathways, thereby reducing the expression and translocation of GLUT4 to the cell membrane, and promoting insulin resistance, leading to elevated blood glucose[26]. However, its triglyceride-lowering ability, endothelium- dependent increase in islet blood flow, anti-inflammatory properties, and the ability that statins have to alter the circulating levels of several adipokines known to affect glucose homeostasis, including adiponectin, leptin, visfatin and resistin, can effectively lower blood glucose levels[27]. Currently, an increasing number of studies have demonstrated the hypoglycemic function of statins, especially in the context of DM complications.

The study on the ameliorative effects of MK from *Monascus* fermentation on insulin resistance and DM showed that MK increased the uptake of fluorescent glucose (2-[N-(7- Nitrobenz-2-oxa-1,3-diazol -4-yl) amino] -2-deoxy-D-glucose, 2-NBDG) in FL83B cells, and ameliorated insulin resistance by increasing the phosphory- lation of Insulin Receptor Substrate-2 (IRS-2), which increased the phosphorylation of Akt and the expression of glucose transporter protein 2 (GLUT2). In addition, MK increased the ratio of NADPH to NADP(+). This suggests that MK has antioxidant effects and can keep NADPH in a reduced state. These findings suggest that MK not only has the function of regulating blood

lipids, but also improves insulin resistance in hepatocytes, which is expected to be developed as a DM drug[28].

3.1.2 MK ameliorates DM by suppressing inflammation and protecting the pancreas

In DM patients, the level of advanced glycosylation end products (AGEs) is high and pancreatic damage caused by AGEs has been identified in recent studies. In contrast, MS and MK from *Monascus* fermentation, inhibit inflammation and improve insulin resistance. Administration of MS or MK to AGE-treated mice could restore the expression of pancreatic and duodenal homebox-1 (PDX-1) and GLUT2, suggesting that MS and MK have protective effects on the pancreas by attenuating AGE-induced pancreatic dysfunction (Fig. 3). A histopathologic study demonstrated that peritoneal injection of AGEs did not result in pancreatic injury[29]. These findings confirm the potential mechanisms of AGEs on pancreatic dysfunction, including induction of inflammation and inhibition of PDX-1 and GLUT2 expression, suggesting that MS and MK may be developed as an antidiabetic drug in the future.

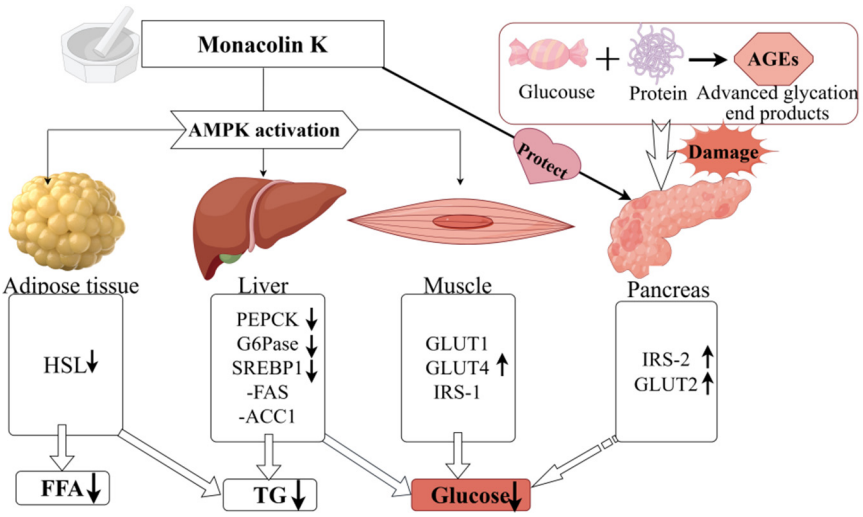

Fig. 3 Potential molecular mechanism of MK regulating diabetes through AMPK

(AMPK, adenosine monophosphate-activated protein kinase; HSL, hormone sensitive lipase; FFA, free fatty acids; PEPCK, phosphoenol- pyruvate carboxykinase; G6Pase, glucose-6-phosphatase; SREBP1, sterol regulatory element binding protein 1c; FAS, fatty acid synthase; ACC1, acetyl-CoA carboxylase 1; TG, triglyceride; GLUT, glucose transporters; IRS, insulin receptor substrate)

3.1.3 Role of statins represented by MK in DM and its complications

SIM, synthesized by methylation of MK, has been shown to be useful in DM complications[30]. Structurally, the two differ by only one methyl group; pharmacologically, they are extremely similar. Al-Rasheed et al. showed that SIM significantly improved body weight, reduced hyperglycemia and hyperlipidemia, improved Creatine Kinase-Myocardial Band and troponin I in rats, and prevented histological changes and collagen deposition in the hearts of DM animals[31]. SIM also reduced the expression of serum inflammatory mediators and NF-κB and decreased cardiac caspase-3 in DM hearts, suggesting that SIM alleviates diabetic cardiomyopathy (DCM) by alleviating hyperglycemia/

hyperlipidemia- induced oxidative stress, inflammation, and apoptosis. These results shed some lights on the molecular mechanisms of MK in DM treatment.

A recent study on the efficacy of, SIM in diabetic nephropathy (DN) demonstrated that SIM prevented DN by attenuating hyperglycemia, renal injury, fibrosis, inflammation and OS, and up-regulating antioxidants, FXR and Nrf2/HO-1 signaling[32]. An animal experiment showed that SIM improved creatinine clearance and urinary creatinine, urea and albumin levels, and decreased lipid peroxidation and NO levels in STZ-induced rats, and it could prevent DN by attenuating oxidative stress and apoptosis[33]. Activation of RhoA/ROCK1 by high glucose disrupted occludin/ZO-1 expression and translocation, in which SIM alleviated occludin-ZO-1 dysregulation and proteinuria by inhibiting RhoA/ROCK1 signaling during early DN[34]. These results suggest that SIM could be used to prevent and treat early DN.

Also, statins have a role in the treatment of DM-related depression. A study on the effect of lovastatin (LOV) on the depressive phenotype of streptozotocin-induced DM mice showed that 3 weeks of LOV treatment at a dosage of 10 or 20 mg/kg significantly prevented DM-associated depressive behaviors. Further investigation indicated that these treatments improved hippocampal neurogenesis, with an increase in the number of bromodeoxyuridine-positive cells in the dentate gyrus, the expression of mature brain-derived neurotrophic factor, and the phosphorylation of cAMP responsive element-binding protein[35].These results once again illustrate the potential for statins to be used as therapeutic agents for DM-related depression.

According to a study of statins on memory impairment and neurotoxicity in DM mice, SIM treatment led to a significant increase in peroxisome proliferator-activated receptor γ (PPAR-γ) and a decrease in NF-jBp65 in the hippocampus and cerebral cortex, ameliorated the neuroinflammatory response through a decrease in Iba-1-positive cells and a decrease in inflammatory mediators, including IL-1b, IL-6 and TNF-a, and inhibited neuronal apoptosis by decreasing TUNEL-positive cells, increasing the Bcl-2/Bax ratio, and decreasing caspase-3 activity in the hip and cortex. In addition, SIM significantly attenuated amyloid production by decreasing amyloid-b, amyloid precursor protein (APP) and β-site APP-cleaving enzyme-1[36]. The findings reveal a new potential for statins to treat DM-related cognitive impairment.

Hyperglycemia leads to disruption of the blood-retinal barrier by impairing the function of endothelial nitric oxide synthase (eNOS). Increased L-arginine uptake induced by SIM treatment in the presence of high glucose levels is associated with increased levels of CAT-1 and eNOS mRNA, leading to increased NO production in TR iBRB cells[37]. Thus, SIM may be a good regulator in diabetic retinopathy treatment by increasing L-arginine uptake and improving endothelial function in retinal capillary endothelial cells. SIM treatment also inhibited the formation of retinal superoxide in diabetes rats and reduced the expression of VEGF, angiopoietin-2 and erythropoietin[38].

The risk of cardiovascular complications in DM patients is likely to be increased by fluctuating hyperglycemia. In a rat model of T2DM with glucose variability, SIM was found to reduce glucose

variability and limit glucose fluctuation-induced changes in the expression of angiogenic factors in the cardiovascular system[39].

The above studies have confirmed at different levels that MK, as well as statins modified from MK, represented by SIM, have the potential for the prevention and treatment of DM and its complications, but the specific regulatory mechanisms need to be further investigated. In recent years, a series of studies around the anti-diabetic function of *Monascus* secondary metabolites have shown that other metabolites produced by *Monascus* can also exhibit hypoglycemic activity, and its mechanism of action is more clarified.

3.2 Potential mechanism of GABA in DM treatment

GABA is a natural nonprotein amino acid[40] available from a wide range of food sources and tends to be more abundant in plant foods than in animal foods, and more abundant in fruits and vegetables than in grains[41]. In 1987, Kohama et al[42]. found that the blood pressure-lowering function of Hongqu is attributed to the GABA produced by *Monascus* strains. A clinical study suggested that GABA also has a potential therapeutic role in DM and its complications[43]. As an autocrine of islet cells, the secretion of GABA is significantly reduced in DM state[44]. It is an important neurotransmitter in the organism and plays a crucial part in maintaining normal blood glucose by increasing insulin secretion and protecting β-cells, inhibiting α-amylase and α-glucosidase activities, alleviating oxidative stress, inhibiting inflammatory factors and regulating intestinal flora (Fig. 4).

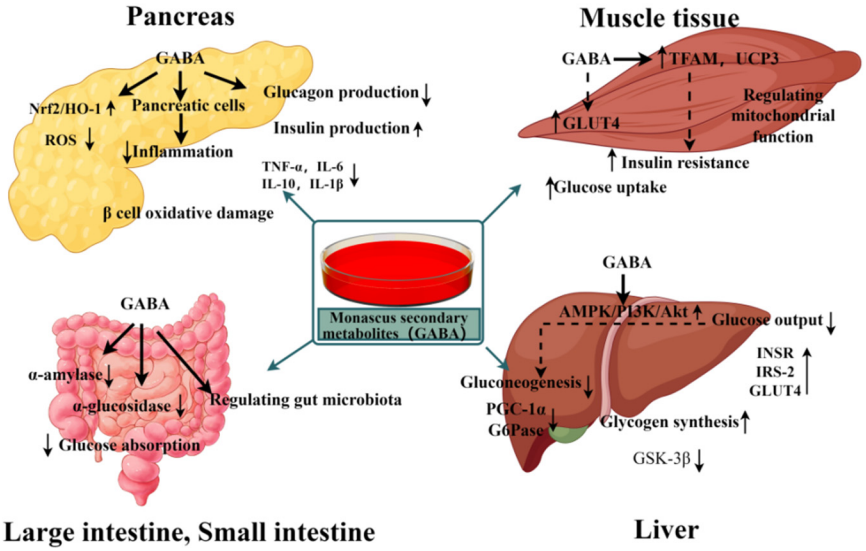

Fig. 4 Mechanism of blood glucose regulation by GABA

(Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase 1; ROS, reactive oxygen species; IL, interleukin; TNF, tumor necrosis factor; TFAM, mitochondrial transcription factor A; UCP3, uncoupling protein 3; GLUT4, glucose transporter-4; GSK-3β, glycogen synthase kinase-3β; PGC-1α, peroxisome proliferator activated receptor γ coactivator-1α; G6Pase, glucose-6-phosphatase; IRS, insulin receptor substrate; INSR, insulin receptor)

3.2.1 Lowering blood glucose by inhibiting α-amylase and α-glucosidase activity

Carbohydrates are hydrolyzed to monosaccharides by α-amylase and α-glucosidase, which increase blood glucose when absorbed into the blood stream, and inhibition of these two enzymes may reduce glucose uptake and thus improve blood glucose. In an in vitro study, GABA or GABA-riched foods were

found to inhibit α-amylase and α-glucosidase activities[45], but this was yet to be confirmed by in vivo studies, and the mechanism by which GABA inhibits α-amylase and α-glucosidase is unknown.

3.2.2 Regulation of α-cells and β-cells to exert hypoglycemic effects

Elevated blood glucose stimulates β-cells to produce insulin, activates intracellular protein kinase B (PKB), which rapidly phosphorylates and translocates the GABAA receptor to the cell membrane, increasing Cl-efflux and causing β-cells to depolarize, while the voltage-gated calcium channels are opened, and extracellular Ca^{2+} flows inward, thus further activating phosphatidylinositol 3 kinase (PI3K) and Akt signaling pathways, inducing β-cells to secrete insulin and GABA[46]. GABA binds to GABAA receptors on α-cell membranes, increasing Cl-inward flow, causing α-cell hyperpolarization, inhibiting glucagon transport to the β-cell surface, and leading to sustained insulin secretion, which lowers blood glucose (Fig. 5)[47].

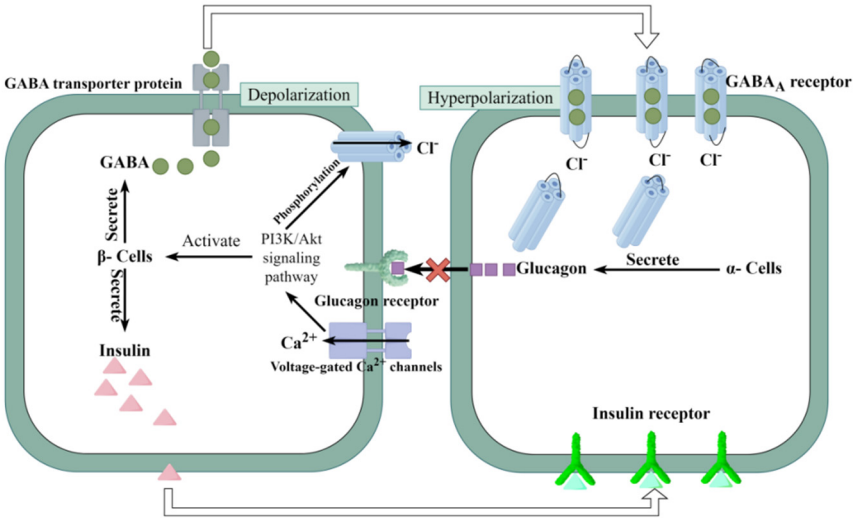

Fig. 5 Mechanism of Blood Glucose Regulation by GABA

(PI3K/Akt, phosphoinositide 3-kinase/protein kinase B)

Animal experiments have shown that GABA is able to induce β-cell proliferation, the main mechanisms of which are enhancement of the content and cycling of Klotho (a natural antidiabetic agent) in the pancreatic islets, activation of the PI3K/Akt pathway in the cells, up-regulation of some anti-apoptotic and down-regulation of some pro-apoptotic proteins, and induction of α-cell to β-cell transformation. Some studies suggest that GABA may increase insulin secretion by increasing the production of klotho[48] and upregulating the expression of PDX1 in the pancreas of DM mice.[49]

GABA leads to reduced glucagon levels in DM mice by reducing α-cell proliferation[50] and the mass of α-cells in the pancreas[51], glucagon secretion can be increased by 2-3 times after treatment of pancreatic islet cells with a GABAA receptor antagonist[52], suggesting that GABA may inhibit glucagon secretion by α-cells.

3.2.3 Improvement of glucose tolerance and insulin resistance to exert hypoglycemic effects

GLUT4 is an insulin-sensitive glucose transporter found in adipose tissue, and abnormal GLUT4 function can lead to insulin resistance or impaired glucose tolerance[53]. GABA up-regulates the expression of insulin receptor substrate (IRS)1, IRS2, Akt, Akt2 and GLUT4-related genes, and decreases forkhead box protein O1 (FOXO1) and phosphoenolpyruvate carboxykinase (PEPCK) gene expression, ameliorating insulin resistance and impaired glucose tolerance in DM rats and their offspring[54].

3.2.4 Regulation of blood glucose by inhibiting the production of inflammatory cytokines

DM is a metabolic disease closely related to inflammation, and therefore anti-inflammatory therapy may be a potential treatment. Different animal models as well as in vitro models have confirmed that GABA inhibits the production of various inflammatory cytokines. In addition, transforming growth factor β1 (TGF-β1) secreted by T cells has potent immunosuppressive and anti-inflammatory effects. GABA can also inhibit inflammation by stimulating the production of TGF-β1 by T cells[55], thus exerting a potential hypoglycemic effect.

3.2.5 Regulation of blood glucose by reducing oxidative stress

Reactive oxygen species (ROS) are a major marker of oxidative stress and are closely related to glucose secretion, insulin resistance and β-cell apoptosis. Superoxide dismutase (SOD), catalase (CAT), peroxidase, glutathione peroxidase (GPx) and glutathione together form an antioxidant defense system to scavenge ROS from the body. The activity and expression of this antioxidant defense system is inhibited in DM patients. GABA attenuates DM-associated oxidative stress through activation of antioxidant enzyme, inhibition of pro-oxidant factor expression, and regulation of oxidative equilibrium[56].

3.2.6 Improvement of DM by regulating the intestinal microbiota

The intestinal microbiota plays a key role in maintaining the physiological equilibrium of the host. In DM mice, the ratio of Firmicutes to Bacteroidetes (F/B) in the intestinal tract was significantly increased, and GABA reduced the F/B ratio and increases the relative abundance of anti-obesity flora (e.g., Bacteroidetes, Verrucomicrobia, and Akkermansia), leading to an improvement in glycolipid metabolism[57]. Plasma GABA levels were significantly higher in obese patients after transplantation of fecal microbiota from healthy lean populations, which may account for their improved insulin resistance. Some microbiota such as *Lactobacillus* ameliorated insulin secretion in DM mice by synthesizing GABA.

3.2.7 Amelioration of DM through regulation of mitochondrial function and epigenetic modifications

Mitochondrial dysfunction is induced by high glucose status, which triggers apoptosis and promotes the progression of DM. GABA promotes the expression of mitochondrial transcription factor A (TFAM) and uncoupling protein 3 (UCP3), which maintains normal mitochondrial function in skeletal muscle and improves glucose metabolism[58]. Epigenetic modifications (e.g., DNA methylation, histone modifications, and RNA changes) play crucial roles in maintaining gene transcription and homeostasis. GABA ameliorates insulin resistance by down-regulating DNA methylation and regulating histone acetylation, but the exact mechanism is yet to be clarified[59].

In conclusion, the hypoglycemic mechanism of GABA can be summarized as follows: regulation of pancreatic α and β cells, improvement of glucose tolerance and insulin sensitivity, inhibition of inflammation, improvement of immune cell function, attenuation of oxidative stress, maintenance of the normal mitochondrial function, and regulation of the balance of the intestinal microbiota[60]. However, there is insufficient clinical evidence to confirm the efficacy of GABA or GABA-riched foods in DM patients, and further studies are needed to explore their effectiveness and safety in lowering glucose in humans. Combinations of GABA with glucose-lowering drugs, chemicals or natural products may be a potential approach to improve the effectiveness of DM treatments, but the range of safe therapeutic dose needs to be fully evaluated. In the future, more clinical trials are needed to confirm the potential therapeutic effects of GABA in improving glucose metabolism and to explore its mechanism of action.

3.3 Molecular mechanisms of MPs in DM treatment

MPs produced by *Monascus* strains are intrinsically polyketide compounds primarily consisting of red, orange, and yellow pigments[61], and there are more than 100 pigment components. Monascorubin, one of orange pigments, has been demonstrated to play a role in preventing and treating DM to some extent[62,63]. MS and AK are typical yellow fat-soluble pigments identified from the fermentation products of *Monascus* strain, and it has been proven that MPs significantly reduces the formation of fructosamine, α-dicarbonyl compounds and AGEs, making it a promising source of antiglycation agents for food products[64].

Cellular experiments demonstrated that MS also acted as a PPAR-γ agonist and promoted insulin sensitivity in C2C12 cells. Animal experiments suggested that both MS and pioglitazone significantly down-regulated blood glucose and hyperinsulinemia in C57BL/6 mice induced by fructose-riched diet (FRD) for 8 weeks. In addition, GW9662 (PPARγ antagonist) attenuated the inhibitory effects of MS and pioglitazone on inflammatory cytokine production, serum dyslipidemia, and hepatic fatty acid accumulation. These results were mediated by MS inhibition of FRD-elevated adipogenic transcription factors, including sterol regulatory element-binding protein-1c (SREBP-1c), carbohydrate response element-binding protein (ChREBP), PPARγ coactivator-1α, and PPAR-γ coactivator-1β. The findings further confirm that MS may inhibit FRD-induced adipogenesis in mice and has therapeutic potential as an antidiabetic agent for DM prevention[65].

In a recent study, Hsu et al. found that MS, a PPAR-γ agonist, inhibited inflammation in rats treated with methylglyoxal (MG), prevented pancreatic injury leading to AGEs, promoted insulin expression in vitro and in vivo, and weakened the activation of hepatic stellate cell (HSC) induced by carboxy methyl lysine (CML). Furthermore, studies demonstrated that MS activated nuclear factor erythroid 2-related factor 2 (Nrf2) in pancreatic RIN-m5F cells, thereby alleviating methylglyoxal-induced pancreatic dysfunction via Nrf2-dependent antioxidant pathways[66]. MS and AK were shown to have a significant inhibitory capacity against α-glucosidase, with IC50s of (126.5 ± 2.5) and (302.6 ± 2.5) μmol/L, respectively, compared to the glucose-lowering drug Acarbose (IC50=341.3 ± 13.6 μmol/L)[67]. Monascorubin exerts hypoglycemic

effects mainly by protecting pancreatic β-cells, boosting insulin secretion, inhibiting gluconeogenesis and improving insulin resistance.

3.3.1 Protection of pancreatic β cells

Pancreatic β cells are the site of insulin synthesis and secretion, and their integrity is a prerequisite for the body to maintain normal blood glucose levels. When the level of ROS increases in the body, it is easy to damage the β cells and reduce the secretion of insulin, which leads to the increase of blood glucose level, and even causes DM. Monascorubin not only up-regulates the activities of antioxidant enzymes such as GPx, SOD and CAT, but also the expression of Nrf2, PPARγ, and forkhead box protein O1 (FoxO1), which in turn inhibits the phosphorylation of protein kinase C (PKC) related to insulin synthesis[68], reduces the ROS content, and protects the islet β cells (Fig.6).

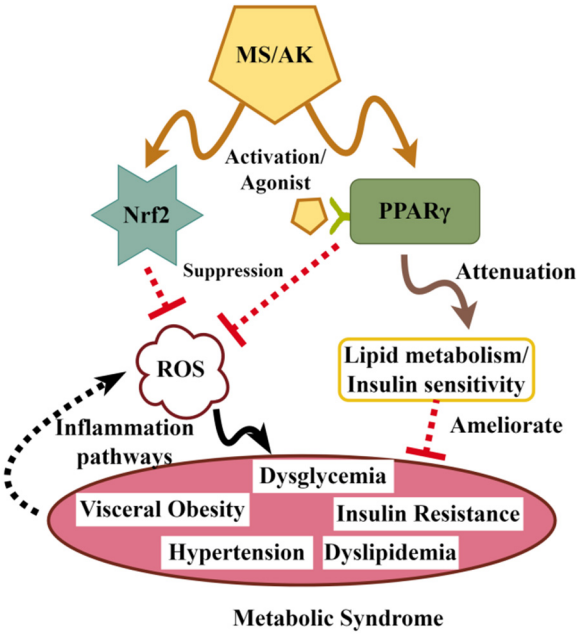

Fig. 6 Monascin and ankaflavin exhibit multiple beneficial effects against metabolic syndrome via the PPARγ/Nrf2 pathways.

(MS/AK, Monascin/Ankaflavin; Nrf2, nuclear factor erythroid 2-related factor 2; PPARγ, peroxisome proliferator-activated receptor Gamma; ROS, reactive oxygen Species)

3.3.2 Promoting insulin secretion

Excess glucose enters the islet β cells through GLUT4 and is transformed to glucose 6-phosphate by glucokinase (GCK), which stimulates β cells to secrete insulin. In contrast, AK acts as a PPARγ agonist and upregulates the expression of GCK and GLUT4, thereby promoting insulin secretion[69].

3.3.3 Inhibition of gluconeogenesis

Gluconeogenesis is the process of converting non-carbohydrates (e.g., amino acids, lactate, glycerol and pyruvate) into glucose (Fig.5). Hongqu reduces the glucose content of gluconeogenesis by inhibiting the expression of phosphoenolpyruvate carboxykinase (PEPCK), the rate-limiting enzyme in gluconeogenesis, and thus has a hypoglycemic effect (Fig.6)[70].

3.3.4 Amelioration of insulin resistance

Monascorubin has a good effect on insulin resistance (IR) and thus play a hypoglycemic role. Insulin resistance is a physiological state caused by decreased insulin sensitivity in target organs such as liver and adipose tissue, and decreased glucose uptake and utilization, resulting in increased compensatory insulin secretion[71]. It has been found that the phosphorylation of c-Jun N-terminal kinase (JNK) is activated by inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleu kin-1β (IL-1β) and ROS, which then inhibits the phosphorylation of insulin receptor (IR) and insulin receptor subsutrate 1 (IRS-1) and reduces the translocation of GLUT4, thus decreasing glucose uptake by the target cells and causing insulin resistance[72]. AK and MK inhibit JNK phosphorylation by enhancing PPAR-γ mRNA expression or acting as PPAR-γ agonists, improving insulin sensitivity and glucose uptake in target cells[73,74]. Monascorubin up-regulates the activities of SOD, CAT and other antioxidant enzymes to inhibit ROS production in vivo, reduces the damage of target cells and target tissues, and thus improves their insulin sensitivity. *Monascus* yellow pigments and *Monascus* orange pigments down-regulate the expression of inducible nitric oxide synthase (iNOS) to reduce the levels of inflammatory factors such as TNF-α, IL-6 and NO, which in turn inhibit the activation of JNK, promote the translocation of GLUT4, and ultimately increase the rate of glucose uptake (Fig.7)[75].

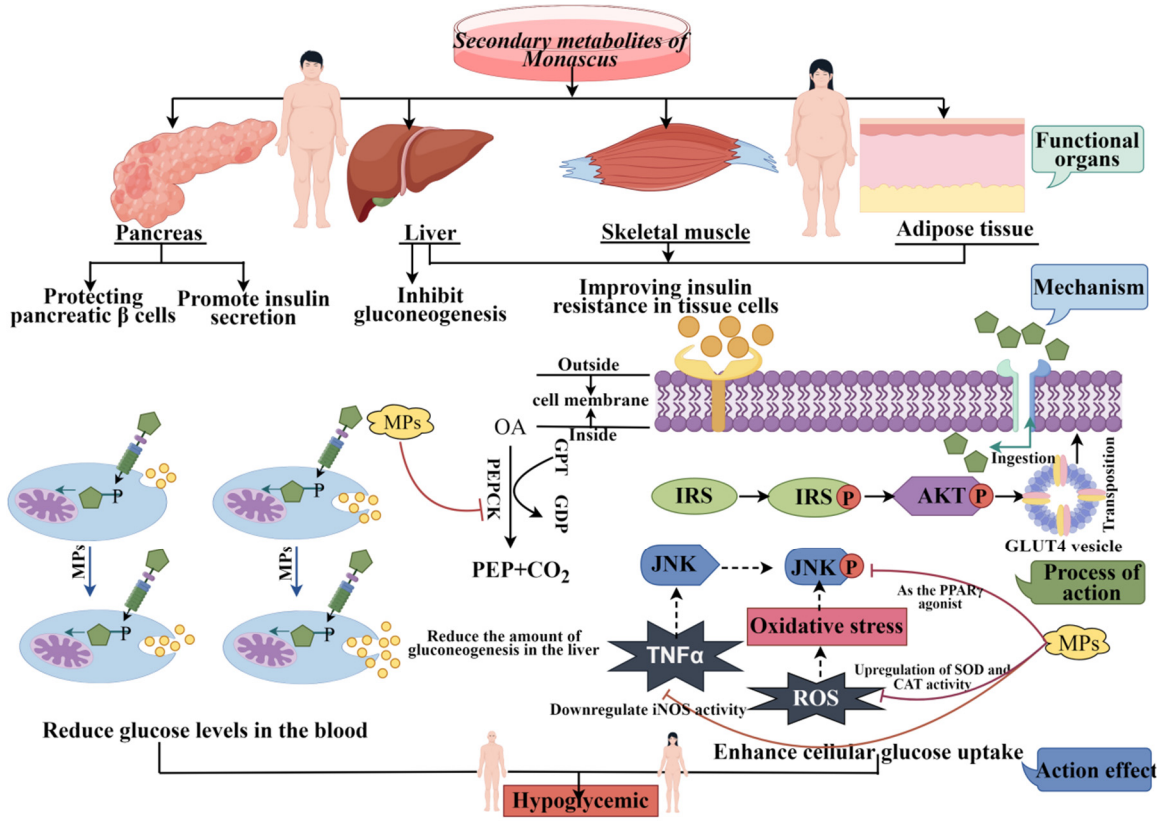

Fig.7 The underlying regulatory mechanisms of MPs on hyperglycemia

(OA,oleic Acid; PEP, phosphoenol pyruvate; PEPCK, phosphoenolpyruvate carboxykinase; GPT, glutamic-pyruvic transaminase; GDP, guanosine diphosphate; IRS, insulin receptor substrate; AKT, protein kinase B; JNK,c-Jun N-terminal kinase; TNFα,tumor necrosis factor alpha)

Moreover, monascorubin can synergize its hypoglycemic activity in different tissues and organs through different pathways. In pancreatic tissues, it plays a role in protecting islet cells and promoting insulin secretion; in the liver, it inhibits gluconeogenesis; in insulin-targeted tissues (liver, skeletal muscle, and adipose tissue), it improves insulin resistance, thus exerting hypoglycemic effects[76].

4. The biotransformation process of hypoglycemic substances driven by *Monascus* strains

As mentioned above, several metabolites produced by *Monascus* species have the potential to prevent and treat diabetes and its complications, and the mechanism of their functions has also been explored. In addition, *Monascus* species can ferment various plants and their components, as well as food raw materials, to produce various active substances with hypoglycemic properties, not only enriches the variety of hypoglycemic substances, but also lays a foundation for the development and utilization of functional foods or preventive care drugs for DM. Here are some typical research cases.

4.1 Monascus-fermented grain vinegar contains hypoglycemic active substances

Monascus vinegar (MV) is produced from grain fermented with several microorganisms including *Monascus* species, which has potential biological activities in antioxidant, anti-diabetic and anti-obesity. It was found that MV exhibited inhibitory activity against pancreatic lipase, α-amylase, and α-glucosidase with IC50 values of 0.48, 0.10, and 0.09 mg/mL, respectively. MV inhibits key enzymes associated with T2DM and obesity, and can be used for the prevention of obesity and T2DM[77]. Pyo et al. alidated the hypoglycemic effect of acetic acid vinegar (AAV, which contains only 4% acetic acid) and MV containing multiple bioactive compounds on 3T3L1 cells and C57BL/KsJ db/db mice (db). Mice in the AAV or MV groups had lower levels of fasting blood glucose, insulin, leptin, and glycosylated hemoglobin (HbA1c), and higher levels of GLUT4 expression in skeletal muscle[78]. Detection of the antidiabetic mechanism of *Monascus*-fermented grain vinegar using HepG2 cells and C57BL/KsJ-db/db mice showed that MV increased insulin sensitivity by promoting insulin-dependent glucose uptake and activating glycogen accumulation in HepG2 cells. In addition, it enhances glucose homeostasis by activating the IRS-1/PI3K/Akt and AMPK pathways in skeletal muscle and liver tissues. MV also promotes glycogen synthesis by regulating key enzymes, such as GSK-3β and GS, and inhibits gluconeogenesis by suppressing mRNA expression of G6pase and PEPCK. These results suggest that MV simultaneously regulates signaling pathways to improve glucose metabolism disorders[79]. Therefore, MV may be an alternative functional food or nutrient to improve T2DM.

4.2 Monascus strain can ferment ginger to produce hypoglycemic active substances

The potential antioxidant and antidiabetic activities of *Monascus* ginger extract (MGE) were also demonstrated. The ethyl acetate fraction of MGE had a higher potential to inhibit key digestive enzymes (α-amylase, α-glucosidase) associated with T2DM compared to ginger extract (CGE) ($P < 0.05$). The IC50 of the α-amylase inhibitory activity of MGE (3.40 ± 0.88) mg/mL was better than that of acarbose (7.01 ± 0.23) mg/mL, which is currently used as a DM treatment. In addition, the ethyl acetate fraction of MGE

increased the expression of GLUT4, glucokinase (GCK), and AMP-activated protein kinase (AMPK) in HepG2 cells. The ethyl acetate fraction of MGE significantly improved glucose uptake in HepG2 cells through activation of the PI3K/Akt and AMPK phosphorylation pathways, and MGE showed potential for the development of anti-diabetic nutrients[80].

4.3 Monascus strain can ferment durian seeds to produce hypoglycemic active substances

Study on the in vitro α-glucosidase inhibitory activity of *Monascus*-fermented durian seed extracts was carried out by inoculating the spore suspension of *Monascus* sp. KJR2 into boiled durian seed cuts and then incubated at room temperature for 14 days. The durian seed (DS) and powdered *Monascus*-fermented durian seed (MFDS) were extracted with distilled water and ethanol. The extracts were analyzed for the in vitro α-glucosidase inhibition activity and total phenol content. The results show that DS and MFDS ethanolic extracts have α-glucosidase inhibitory activity with IC50 of 199.1 μg/mL and 70.7 μg/mL, respectively[81]. MFDS is potential for diabetes mellitus management. This study lays the foundation for the preventive health effects of DM, but the composition and molecular mechanism of the active substances that specifically exert hypoglycemic effects need to be further elucidated.

4.4 Monascus strain can ferment mulberry leaf to produce hypoglycemic active substances

Mulberry leaves (MLs) are considered to have great hypoglycemic potential due to their high flavonoid content. In order to enhance the hypoglycemic effect of MLs, *Monascus* species were used to ferment MLs for obtaining more flavonoid. Significantly high flavonoid contents and enhanced antidiabetic properties were observed in both solid state fermentation (SSF) and submerged fermentation (SMF), and active substances enhancing α-glucosidase inhibition were detected in fermented MLs. The IC50 values for α-glucosidase inhibitory activity reached (112.80 ± 1.29) μg/mL and (123.9 ± 0.96) μg/mL for SSF-MLs and SMF-MLs, respectively. Enzyme inhibition kinetics revealed the inhibitory types of seven major flavonoids on α-glucosidase, and molecular docking indicated the interaction mechanism of α-glucosidase inhibition[82].The results showed that SMF optimized the bioavailability of flavonoids during in vitro digestion, suggesting a new direction for the development of DM therapeutic drugs by fermentation of MLs with *Monascus* strain.

4.5 Co-fermentation of guava leaves by M. anka and Bacillus sp. BS2 promotes the release of hypoglycemic active substances

A recent study suggested that Co-fermentation of guava leaves by *M. anka* and *Bacillus* sp. BS2 promotes the release of phenolic compounds, and in vitro simulated gastrointestinal digestion experiments suggested that the bioavailability of total polyphenolic compounds amounted to 51.18%[83]. These phenolic compounds have the abilities to inhibit α-glucosidase activity and antioxidant capacity, mainly attributed to their abundance of ellagic acid, isoquercitrin, quercetin-3-O-α-L-pyranoside, quercetin-3-0-α-L-arabino-furanosidase and abamectin[84]. In addition, phenolic-rich extract from fermented guava leaves (PE-fgl) significantly improved serum glucose and lipid levels as well as antioxidant capacity in DM mice, and

alleviated hepatic, renal and pancreatic injuries[83]. These results suggested that PE-fgl could be a nontoxic candidate for DM treatment.

4.6 M. pilosus-fermented black soybean can ameliorative high-fat diet-induced obesity and hyperglycemia

Administration of *M. pilosus*-fermented black soybean (F-BS) on high-fat diet-induced C57BL/6 mice inhibited the growth of epididymal, retroperitoneal and perirenal fat pads by preventing an increase in adipocyte size. In addition, F-BS significantly reduced blood glucose, total cholesterol and leptin levels in a dose-dependent manner. These results suggest that F-BS is a beneficial food supplement for obesity prevention, glycemic control and cholesterol lowering, but its mechanism of action needs to be further investigated[85].

4.7 Hypoglycemic effect of Artemisia argyi H. under liquid-state fermentation driven by M. purpureus

In a study on the effect of Artemisia argyi H. under liquid-state fermentation by *M. purpureus* (AAFM) on cognitive impairment, it was found that AAFM significantly improved glucose tolerance and ameliorated cognitive deficits, including passive avoidance, Morris water maze, and Y maze tests[86]. It showed that the fermentation products of *Monascus* have a role in DM and its complications. Another study from Taiwan confirmed that nutrients consisting of Hongqu, bitter melon, and chromium could be used as an ancillary drug in the treatment of T2DM and in delaying the disease by maintaining pancreatic β cell function[87].

In recent years, there has been an increasing researches on obtaining active substances for the prevention and treatment of chronic diseases through microorganisms-driven fermentation. Table 4 summarizes relevant examples of *Monascus*-fermented different substrates to obtain active components with hypoglycemic effects.

Table 4 *Monascus* Strains-driven Fermentation with Different Substrates to Produce Hypoglycemic Components

First author, Year	*Monascus*-fermented products and related components	Research objectives	Study design	Main outcomes/ Results
Y.H. Noh, 2021	*Monascus*-fermented grain vinegar (MV)	Identify the potential biological activities of *Monascus*-fermented grain vinegar (*Monascus* vinegar, MV) with respect to its anti-oxidant, anti-diabetic, and anti-obesity effects.	Using *Monascus*-fermented grain vinegar as sample for research and evaluating it physiological activity in vitro.	MV can inhibit the key enzymes related to T2DM and obesity.
Y.H. Pyo, 2022	Acetic Acid and *Monascus*-fermented grain vinegar	Compared the hypoglycemic and hypolipogenic effects of acetic acidvinegar and *Monascus*-fermented grain vinegar (MV) containing various bioactive compounds in 3T3L1 cells and C57BL/KsJ-db/db mice (DB).	The DB were divided randomly into three treatment groups containing nine mice each; DB-, AV-, and MV-groups were orally administered 1 mL/kg/day of distilled water, aceticacid vinegar, and *Monascus* vinegar, respectively, for 8 weeks.	Lower levels of fasting blood glucose, insulin, leptin, and the glycosylated hemoglobin (HbA1c) as well as higher levels of the skeletal muscle GLUT4 expression were obtained in the AV- or MV-groups than levels determined in the control DB-group.
K.Y. Lu, 2020	Red yeast rice, bitter gourd, and chromium	Test whether a nutraceutical combi-nation of these 3 materials prevented dedifferentiation of pancreatic β cells.	Male db/db mice were allocated into four groups and fed a high-fat diet Containing 0%, 0.2%, 0.4%,or 1% nutraceutical, respectively，dietary therapy for 8 weeks.	A combination of *M. purpureus*, momordica charantia, and chromium, could be used as an adjunct for T2DM treatment and delay disease progression by sustaining β-cell function.
I. Srianta, 2013	*Monascus*-fermented durian seed	Study on the in vitro α-glucosidase inhibitory activity of *Monascus*-fermented durian seed.	*Monascus* sp. KJR2 into boiled durian seed cuts and then incubated at room temperature for 14 days. The durian seed (DS) and powdered *Monascus*- fermented durian seed (MFDS) were extracted with distilled water and ethanol. The extracts were analyzed for the α-glucosidase inhibition activity in vitro and total phenol content.	DS and MFDS ethanolic extracts have α-glucosidase inhibitory activity with IC50 of 199.1μg/mL and 70.7μg/mL, respectively. Water extract of DS and MFDS have low α-glucosidase inhibitory activity (<10%).
G. Oh, 2014	*Monascus pilosus*-fermented black soybean (F-BS)	Examine the antiobesity effects of *M.* pilosus-fermented black soybean (F-BS) in C57BL/6 mice with high-fat diet (HFD)-induced obesity.	BS (oral, 0.5 and 1.0 g/kg per Body weight, twice per day) ameliorated obesity by reducing body and liver weight increases, andregulating blood glucose and cholesterol levels in C57BL/6 mice fed a control or HFD with oral administration of F-BS for 12 weeks.	The levels of blood glucose, total cholesterol, and leptin were significantly lowered by F-BS administration in a dose-dependent manner.

M. Yoon, 2021	*Monascus*-fermented ginger extract *M. pilosus* KCCM 60084	Investigated the potential antioxidant and antidiabetic activity of *Monascus*-fermented ginger extract (MGE).	Ginger was fermented with *M.pilosus* KCCM 60084 for 2 weeks at 30℃ and extracted with 95% ethanol，test the key digestive enzymes linked to T2DM(a-amylase, a-glucosidase) and the expression of GLUT4, glucokinase (GCK), and AMP-activated protein kinase (AMPK) in HepG2 cells.	The ethyl acetate fraction of MGE significantly improved glucose uptake in HepG2 cells by activating both PI3K/Akt and AMPK phosphorylation pathways
Wang, 2023	*M. purpureus*-fermented Mulberry leaves	Exploited the fermentation potentialof *M. purpureus* to improve the flavonoid profile of Mulberry leaves.	Optimized flavonoid composition by subjecting MLs to *M. purpureus* Fermentation.	Enhanced α-glucosidase (AG) inhibitory activities were identifie fermented MLs, which are essential for diabetes management.The IC50 values for the inhibitory activities of SSF-MLsand SMF-MLs against AG reached (112.80 ± 1.29) μg/mL and (123.90 ± 0.96） μg/mL, respectively.
C.W. Lin, 2023	*Monascus purpureus*-fermented red mold dioscorea (RMD)	Effects of RMD on preventing metabolic disorder with type 2 diabetes induced by long-term high fat and high fructose diet (HFFD).	RMD, MS, and AK were orally administered to HFFD-fed rats for 10 weeks.	Orally administered MS, AK, and RMD were able to prevent the development of diabetes. MS had a more potent effect on lowering bloodglucose, fructosamine, and insulin resistance, and increasing hepatic glucose transporters-2, adipocyte glucose transporters-4, and hypoxia-inducible factor 1-α.
C.J. Lee, 2017	*M. purpureus*-fermented *Artemisia argyi* H.	The effect of Artemisia argyi H. under liquid-state fermentation by *purpureus* (AAFM) on cognitiveimpairments has been studied in a mice model of diabetes-associated cognitive decline induced by streptozotocin (STZ).	C57BL/6 mice (9 weeks of age, male) were separated into four groups: a normal control, STZ-induced diabetic mouse group (STZ group), Artemisia argyi H. (AA) 10 group (diabetic mouse+AA 10 mg/kg/day), AAFM 10 group (diabetic mouse+AAFM 10 mg/kg/day).	Administration of AA and AAFM significantly improved glucose tolerance, as shown by the intraperitoneal glucose tolerance test (IPGTT), and ameliorated cognitive deficit, as shown by the behavioral tests including passive avoidance, Morris water maze, and Y-maze tests.
C.C. Chen, 2006	*M.pilous* and *M. purpureus*	Screen the effect of Hon-Chi on plasma glucose and investigate the possible mechanisms.	The powder of Hon-Chi was dissolved in saline solution for oral administration at the desired doses (50,100 and 150 mg/kg) into fasting Wistar rats.	Hon-Chi has an ability to raise the lease of ACh from nerve terminals, which in turn to stimulate muscarinicM3 receptorsin pancreaticcells and augment the insulin release to result in plasma glucose lowering action.
Z.F. Huang, 2021	*M. anka* and *Bacillus* sp. BS2. fermented Guava leaves	Evaluate the bioaccessibility, safety and antidiabetic effect of phenolic -riched extract from fermented guavaleaves (PE-fgl) using *M. anka* and *Bacillus* sp. BS2.	The phenolic compounds in guava leaves were released and biotransformed through fermentation, and were used to treat diabetes mice to evaluate the levels of blood sugar and lipid, antioxidant capacity, and liver, kidney and pancreas injuries.	PE-fgl significantly improved serum glucose and lipid levels as well as antioxidant capacity in diabetic mice.

5. Summary and Prospect

DM, one of the most serious chronic diseases in the world, can lead to a series of associated complications, causing a huge health and economic burden. Although a variety of medications that can effectively control blood glucose are available on the market, there is a high incidence of adverse effects, such as gastrointestinal symptoms, hypoglycemia and weight gain. Therefore, there is an urgent need to develop safe, economical and effective natural health foods to prevent and delay the occurrence of DM complications. *Monascus* species are filamentous fungi capable of producing diverse metabolites with pharmacological activities including lipid regulation, atherosclerosis inhibition, glucose reduction, anti-inflammation, and anti-tumor effects. In particular, it is characterized by few adverse reactions, wide pharmacological effects, and obvious regulation of dyslipidemia[88], which has a good potential to prevent and control DM and its complications. This article reviews the effect and potential application of *Monascus*-fermented products in the treatment and prevention of DM and its complications by combining the research progress at home and abroad, which provides new therapeutic targets and strategies for the prevention and treatment of DM, which also indicates the expanded use of functional Hongqu in the DM domain. However, a small sample size of clinical cases on the hypoglycemic effect of *Monascus* metabolites is limited to the level of case indicators and lacks in-depth mechanism analysis. In the future, it is necessary to expand the sample size to include more clinical cases and conduct multicenter clinical trials on the hypoglycemic function of *Monascus* metabolites. Meanwhile, the main active ingredient and molecular mechanism of the hypoglycemic effect of *Monascus*-fermented products need to be further studied.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All participants were informed and gave written consent.

Availability of data and material

No datasets were generated or analysed during the current study.

Competing interests

The authors declare no competing interests

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