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Bitter Melon and Diabetes Mellitus

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ABSTRACT

Bitter melon *(Momordica charantia*) has traditionally been used in the management of diabetes in many countries and territories. However, standardized information on the use of this vegetable as an antidiabetic drug is still very limited. Many animal studies and clinical trials have showed the remarkable effect of bitter melon on diabetes. The research results showed that bitter melon could enhance insulin sensitivity, repair damaged pancreas islet β-cells and stimulate insulin secretion. What's more, bitter melon could reduce hyperglycemia by regulating intestinal flora, inhibiting glucosidase and amylase, scavenging free radicals, enhancing the activity of AMP-activated protein kinase (AMPK) and increasing expression of peroxisome proliferator-activated receptors (PPARs). In addition, it could also act as the glucagon-like peptide 1 receptor (GLP-1 R) agonist and the 11-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor to exert hypoglycemic effects. Therefore, we will discuss the hypoglycemic mechanisms of crude extracts and different phyto-metabolites derived from bitter melon in the paper.

KEYWORDS

Bitter melon; diabetes mellitus; crude extracts; phyto-metabolites; hypoglycemic mechanism

Abbreviations:

AEBM, aqueous extract of bitter melon; AGEs, total advanced glycation end products; Akt, protein kinase B; ALT, alanine aminotransferase; ALX, alloxan; AMPK, adenosine monophosphate-activated protein kinase; aPKC, atypical protein kinase C; AST, aspartate aminotransferase; AUC, areas under the curve; β-CD, β-cyclodextrin; BCAAs, branched-chain amino acids; BM, bitter melon; BMI, body mass index; BMJ, bitter melon juice; BMP, bitter melon powder; BW, body weight; DBP, diastolic blood pressure; DM, diabetes mellitus; Erk1/2, extracellular signal-regulated kinase 1/2; FBG, fasting plasma glucose; FP, fermented polysaccharide; FPG, fasting plasma glucose; GLP-1R, glucagon-like peptide 1 receptor; GLUT4, glucose transporter 4; GSK-3, glycogen synthase kinase-3; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; HFD, high-fat diet; IKK, IkB kinase; IL, interleukin; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; LDL, low-density lipoprotein; M, male; MC, *Momordica charantia*; polysaccharide; MCS, *Momordica charantia* saponin; MDA, malondialdehyde; MET, metformin; NA, nicotinamide; NF-κB, nuclear factor κB; PDK-1, phosphoinositide-dependent protein kinase-1; PI3-K, phosphoinositide 3-kinase; PIP_3, phosphatidylinositol (3,4,5)-trisphosphate; PPAR, peroxisome proliferator-activated receptor; PPG, post-prandial plasma glucose level; PTP, phosphatase; SBP, systolic blood pressure; SCFAs, short-chain fatty acids; SOCS-3, suppressor of cytokine signaling-3; SOD, superoxide dismutase; STZ, streptozotocin; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-α; TPC, total phenolic content; TTC, total triterpene content; UACR, urine albumin-to-creatinine ratio; WC, waist circumference; 11β-HSD1, 11-hydroxysteroid dehydrogenase type 1.

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Introduction

Plants of the genus Cucurbitaceae have long been used as a medical and edible products in developing countries for its high medicinal value and health benefits. Among them, *Momordica charantia*, also named bitter melon (BM), bitter gourd, karela, balsam pear and pare, is in widespread used .[1] The fresh buds, leaves and fruits of bitter melon are often used as vegetables for eating, and dried fruits are used in the production of tea .[2] Meanwhile, bitter melon is widely used for treating diabetes, abortion, parasite, wound, toothache, dysmenorrhea, hypertension, gout, rheumatism, liver diseases, cancer, as well as measles .[2,3]

Diabetes mellitus (DM) is a group of chronic metabolic diseases characterized by hyperglycemia due to defects in insulin production, insulin use, or both .[4] DM mainly consists of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), where, T2DM is the most common form, accounting for more than 90% of whole diabetes cases .[5] The International Diabetes Federation diabetes atlas estimates that, about 463 million people suffered from diabetes globally in 2019 and 10% of the worldwide health expenditure (about 760 USD billion) was spent on the treatment of diabetes .[6] In modern medicine, insulin is the main treatment for patients with T1DM. And therapy for T2DM must improve its pathophysiology, marked by reduced insulin secretion and/or insulin insensitivity .[7]

As a traditional food-drug plant, bitter melon can reduce blood glucose levels in diabetic patients, which is a widely used to remedy for hyperglycemia, and there is evidence of its protective effects on patients in some clinical studies .[8,9] Bitter melon contains many phyto-metabolites with hypoglycemic potential, including charantin, insulin-like peptides, vicine, polypeptide-p, sterol glycosides, triterpenoids, saponins, polysaccharides, alkaloids, water-soluble crude peptides, flavonoids and phenols .[1,2,10–12] Therefore, bitter melon can exert the effect of lowering blood glucose through multiple mechanisms of action. In this review, we will focus on the literature of the recent 5 years, summarizing the following three aspects: 1) the animal models and clinical studies of bitter melon in treating DM; 2) the various hypoglycemic mechanisms of different crude extracts of bitter melon; 3) the multiple hypoglycemic mechanisms of phyto-metabolites from bitter melon.

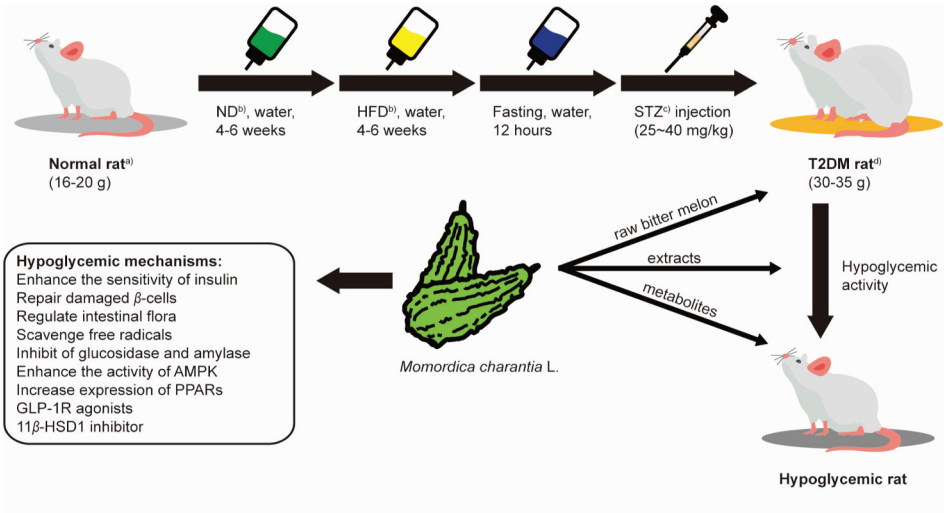

Figure 1. Establishment of a mouse model of T2DM and the hypoglycemic mechanisms of BM. a) Male animals are generally used, females contain hormones to influence modeling efficiency. b) ND, normal diet, acclimatization; HFD, high-fat diet (Lard 18%, sucrose 20%, egg yolk 3%, base feed 59%), inducing insulin resistance. c) STZ, an antibiotic derived from *Streptomyces achromogenes*, and it is selectively toxic to pancreatic β-cells; Utilization rate in chemical induction: 80%. d) The successful model was established when fasting blood glucose of animals is greater than 16.7 mmol/L.

Table 1. Characteristics of clinical studies on bitter melon and DM.

Method, country	Volunteers (n) Time[b)]	Dose of BM (I, II, III) and Control (C)	Primary outcome	Antidiabetic mechanism	Refs.
RCT[a)], Thailand	n = 129 T = 4	I = BM 500 mg/d II = BM 1000 mg/d III = BM 2000 mg/d C = MET 1000 mg/d	Decrease: Fructosamine, FPG (III), 2-h serum glucose Increase: FPG (I, II) Hypoglycemic effect of MC was less than MET	Not reported	[23]
RCT, German	n = 124 T = 16	I = BM 1 g/d II = BM +Cr +Zn 1 g + 100 μg+10 mg/d C = Placebo 1 g/d	Decrease: HbA1c, TC, LDL-c,TG Increase: HDL-c	Inhibit the body's key enzymes (DPP-IV)[c)]	[24]
RCT, Thailand	n = 38 T = 16	I = BM 6 g/d C = Placebo 6 g/d	Decrease: AGEs, FPG, UACR, BW, BMI, SBP, DBP Increase: AST, ALT	Not reported	[25]
RCT, Pakistani	n = 90 T = 10	I = BM 2 g/d II = BM 4 g/d C = Glibenclamide 5 mg/d	Decrease: HbA1c, 2-h serum glucose, FPG, TC, LDL-c, TG, SBP, Weight Increase: HDL-c	Not reported	[26]
RCT, India	n = 85 T = 13	I = BM 1.2 g/d C = Placebo 1.2 g/d	Decrease: FPG, PPG, HbA1c, Serum cholesterol, HDL-C, LDL-C, VLDL-C, TG	Not reported	[27]
RCT, India	n = 123 T = 15	I = BM 1.2 g/d C = MET 1 g/d	Decrease: FPG, HbA1c Hypoglycemic effect of Mc was less than metformin	Promotes glycogen synthesis	[28]
RCT, Tanzania	n = 52 T = 8	I = BM 2.5 g/d C = Placebo 3.25 g/d	Decrease: FPG, HbA1c, Chol, HDL, TG, SBP, DBP Increase: Insulin, BMI	Ower elevated blood glucose levels with prediabetes	[29]
RCT, Mexico	n = 24 T = 12	I = BM 2 g/d C = Placebo 2 g/d	Decrease: HbA1c, 2-h serum glucose, AUC-glucose, Weight, BMI, Fat mass, WC Increase: AUC-insulin, Insulinogenic index, Stumvoll index	Improves Insulin Secretion	[30]

a) RCT = randomized clinical trial. b) Time = follow up duration in weeks. c) DPP- IV = dipeptidyl peptidase IV

Animal models and clinical studies of BM

Many animal models of diabetes have been established to further study the pathogenesis of human diabetes. Methods for establishing animal models of T2DM include diet-induced obese models, chemical-induced diabetic non-obesity models and surgical diabetic models, among them, chemical induction is the most commonly used strategy .[13] For the chemical-induced diabetic non-obesity models, streptozotocin (STZ) and alloxan (ALX) are usually selected as inducers, and the successful model was established when fasting blood glucose of animals is greater than 16.7 mmol/L (the STZ-induced models accounted for 80%). The modeling process of T2DM induced by STZ is shown in Fig. 1. Animal species commonly used in modeling: Kunming mice, [4] CD-1 mice, [14] Wistar rats, [15] Sprague Dawley rats, [16] Japanese white rabbits, [17] Long-Evans rats, [18] KK-Ay mice[19] and Rattus norvegicus rat .[20]

Bitter melon has the effect of lowering blood glucose in normal animals, diabetic animals and obese animals fed with high fat diet (HFD), meanwhile, improving the oral glucose tolerance .[2,21] At present, chemical induction models are commonly used in experiments, but this often damages the liver and kidney function of the animal, which is different from the human pathogenesis. However, the spontaneous diabetes model and the model prepared by the method of high glucose and high cholesterol have low model formation rate, easy death of animals and high cost, which still need further improvement .[22] Therefore, with the development of biotechnology, more and better animal models need to be developed to promote human diabetes research.

In recent years, there are some clinical studies on monoherbal of bitter melon (Table 1) .[23–30] The results of these clinical trials also show some effects of bitter melon on lowering blood glucose in diabetic patients, but not as convincing as animal studies. Clinical studies have shown that longer than 4 weeks after treatment can produce meaningful change in blood glucose control .[31] About the generation of random sequences, only two studies described specific methods for generating random sequences. One uses a simple number list, [30] the other uses a Mersenne Twister random number generator, [29] so the two studies were given lower risk of bias than other studies. Current clinical studies have shown that oral administration of bitter melon preparations at a dose of 2–6 g/day for more than 4 weeks can reduce the FPG, PPG and HbA1c levels in T2DM .[9] However, many of these clinical studies suffer from insufficient sample size, poor research design, and differences in bitter melon formulations, these factors contribute to the instability of the research results. Therefore, well-designed and placebo-controlled randomized clinical trials must be performed prior to the presentation of recommendations for human use to determine the effective dose, method of preparation, and safety of bitter melon .[21]

Crude extracts of BM and their hypoglycemic mechanisms

Bitter melon is the most commonly used vegetable for lowering blood glucose. People with high blood glucose levels can restore normal blood sugar by eating fresh bitter melon directly. And the crude extract of BM is the key part of the research, the BM is extracted with different solvents to obtain crude extracts of different polarities. Among them, there are relatively more studies on aqueous extracts, methanol extracts and ethanol extracts of bitter melon (Table 2).

Raw BM and its hypoglycemic mechanisms

The intestinal flora gets nutrients from the host while regulating and balancing the immune and metabolic functions, the imbalance of the intestinal flora is related to the occurrence and development of diabetes .[62] In the gut, the short-chain fatty acids (SCFAs) are not only the source of energy but also an important signaling molecule for the host, which could stimulate hypothalamic neurons to drive satiety, trigger intestinal gluconeogenesis gene expression, improve glucose and lipid metabolisms and enhance insulin sensitivity .[49] Many studies directly take raw bitter melon as the research

Table 2. Different mechanisms of BM lowering blood glucose.

Object	Detail	Model	Intervention/Control	Antidiabetic mechanism	Refs.
Raw BM	BMP	SD rat (M, HFD)	I = BMP (300 mg/kg BW)[a)] C = Pioglitazone (PGT) (10 mg/kg BW)[a)]	Anti-inflammatory Modulating gut microbiota Enhancing the sensitivity of insulin	[16,32]
	BMJ	Rattus norvegicus rat (M, STZ-induced)	I = Fresh BMJ (71.1 mg/rat/day)[a)] C = Standard diet	Regulating blood lipid	[20]
	Fermented BMJ	Wistar rat (M, HFD, STZ-induced)	I = FBMJ (10 mL/kg BW)[a)] C = No-fermented BMJ (10 mL/kg BW)[a)]	Modulating gut microbiota	[15]
	Fresh BM flesh	α-Amylase inhibitory assay	I = Fresh BM flesh (more effective) C = Freeze-drying BM flesh	Inhibition of α-amylase	[33]
	BMJ + β-CD	Total antioxidant capacity assay	I = β-CD (1.5%)[a)] C = β-CD (0%)[a)]	Antioxidation	[34]
	BMJ	Albino rat (M, STZ-induced)	I = BMJ (10 mL/kg BW)[a)] C = Standard diet	Repairing damaged β-cells Increasing glucose uptake	[35]
	BMP	Rat (STZ-induced)	I = BMP (20%)[a)], (Blood glucose level: 170 mg/dl) C = Standard diet, (Blood glucose level: 500 mg/dl)	Repairing damaged β-cells Protecting liver tissue	[36]
Crude extracts of BM	Aqueous	Wistar rat (M, STZ-induced)	I = AEBM (300 mg/kg BW)[a)], (GLP-1 level, 10.80 ± 0.600)[b)] C = 0.9% normal saline, (GLP-1 level, 5.82 ± 0.311)[b)]	GLP-1 R agonists	[37]
		C57/B6 mice (M, HFD)	I = AEBM (1.0 g/kg/day)[a)] C = Normal diet	Enhancing the sensitivity of insulin	[38]
	Methanolic	DPPH free radical scavenging assay	I = Methanol extract of BM (30.48 ± 2.49 mg of AAE/g of FD)[b)] C = Other solvent extracts	Antioxidation and scavenging free radicals	[39]
		Albino rat (M, ALX -induced)	I = Methanol extract of BM (120 mg/kg)[a)] + sucrose C = sucrose (4 g/kg)[a)]	Regulating blood lipid	[40]
		Wistar rat (M, ALX-induced)	I = Methanol extract of BM (500 mg/kg)[a)], (SOD: 5.83 ± 0.3, MDA: 36.17 ± 0.7)[b)] C = Glibenclamide ((0.6 mg/kg), (SOD: 5.49 ± 0.1, MDA: 32.50 ± 0.9)[b)]	Stimulating insulin secretion Antioxidation Regulating blood lipid	[41]
	Ethanolic	α- glucosidase activity kit	I = Ethanol extract of BM (1000 μg/mL)[a)] α-glucosidase inhibitory activity (18.14 ± 1.3 U/L)[b)] C = Other solvent extracts	Inhibition of α-glucosidase	[42]
		SD rat (M, HFD, STZ-induced)	I = Ethanol extract of BM (400 mg/kg)[a)] C = MET (50 mg/kg)[a)]	Enhancing the sensitivity of insulin	[43]
		SD rat (M, STZ-induced)	I_1 = Ethanol extract of BM (200 mg/kg)[a)], (SOD: 0.10 ± 0.02, MDA: 2.00 ± 0.63)[b)] I_2 = Ethanol extract of BM (400 mg/kg)[a)], (SOD: 0.14 ± 0.08, MDA: 0.98 ± 1.27)[b)] C = Normal diet, (SOD: 0.15 ± 0.12, MDA: 2.02 ± 0.21)[b)]	Antioxidation Anti-inflammatory	[44]
		Wister rat (M, STZ-induced)	I_1 = Glibenclamide (5 mg/kg)[a)] I_2 = Ethanol extract of BM (500 mg/kg)[a)] I_3 = Glibenclamide (5 mg/kg) + Ethanol extract of BM (500 mg/kg) [a)] C = Normal diet	PPAR α activator Repairing damaged β-cells	[45]
	Other solvents	α-Amylase inhibitory assay	I = Acetone extract of BM (357 μg/mL)[a)] (94.62 ± 1.68%)[b)] C = Acarbose (80 μg/mL)[a)] (88.02 ± 1.74%)[b)]	Inhibition of α-amylase	[39]
		α-Glucosidase inhibitory assay	I_1 = Chloroform extract (250 μg/mL)[a)] (102.0 ± 2.4%)[b)] I_2 = Hexane extract (250 μg/mL)[a)] (101.6 ± 6.7%)[b)] C = Acarbose (80 μg/mL)[a)] (81.9 ± 3.0%)[b)]	Inhibition of α-glucosidase	[39]
		ob/ob mice (M, γ-ray- irradiated CRF-1 diet)	I = diet with 1% EtOAc-soluble fraction[a)] C = diet without EtOAc-soluble fraction	Stimulating insulin secretion Enhancing the sensitivity of insulin	[46]

(*Continued*)

Table 2. (Continued).

Object	Detail	Model	Intervention/Control	Antidiabetic mechanism	Refs.
MC polysaccharides	MCPIIa, (13029 Da)	Kunming mice (M, STZ-induced)	I = M-MCPIIa (200 mg/kg)[a] C = MET (40 mg/kg)[a]	Repairing damaged β-cells	[47]
	Se-MCPIIa-1, (4.0038×10^4 Da)	Kunming mice (M, STZ-induced)	I = M-MCPIIa (20 mg/kg/d)[a] C = MET (200 mg/kg/d)[a]	Repairing damaged β-cells	[48]
	From the FMCJ	Wistar rat (M, HFD, STZ-induced)	I = FP (100 mg/kg)[a] C = NFP (100 mg/kg)[a]	Modulating gut microbiota	[49]
	MCPIIaC (8.3×10^4 Da) (purity 79.12%)	Kunming mice (M, STZ-induced)	I = MCPIIaC (30 mg/kg BW)[a] C = MET (200 mg/kg BW)[a]	Promoting hepatic glycogen synthesis Enhancing the sensitivity of insulin Repairing damaged β-cells	[4]
	Crude MCP, (purity 97.84%)	Kunming mice (M, HFD, STZ-induced)	I = MCP (500 mg/kg BW)[a], (SOD: 169.46 U/mL, MDA: 0.63 nmol/mg prot)[b] C = MET (200 mg/kg BW)[a], (SOD: 168.12 U/mL, MDA: 0.88 nmol/mg prot)[b]	Repairing damaged β-cells Antioxidation	[50]
Saponins and Terpenoids	Crude MCS, (purity 77.79%)	Kunming mice (M, HFD, STZ-induced)	I = MCS (40 mg/kg BW)[a] C = MET (200 mg/kg BW)[a]	Regulating lipid control Enhances the activity of AMPK	[50]
	MCS	Wistar rat (M, HFD, STZ-induced)	I_1 = MCS (100 mg/kg/d)[a]; I_2 = MCS (200 mg/kg/d)[a] I_3 = MCS (400 mg/kg/d)[a];C = normal diet	Regulating lipid control Regulating insulin signaling pathway Antioxidation	[51]
	Saponin-rich fraction of BM	MIN6 β-cells	I = Saponin-rich fraction (125 μg/ml)[a] C = Glipizide (50 μM)[a]	Stimulating insulin secretion	[52]
	Cucurbitane triterpenes	MIN6 β-cells	I_1 = Compound (23) (10 μg/ml)[a] I_2 = Compound (24) (10 μg/ml)[a] C = Glipizide (50 μM)[a]		
		C57BL/6 J mice (M, ALX-induced)	I = Compounds 1 (50 mg/kg BW)[a] C = MET (10 mg/kg BW)[a]	Regulating insulin signaling pathway	[53]
		PTP1B inhibition assay	I_1 = Compound 2 (IC_{50} = 51.80 ± 3.91 μM)[b] I_2 = Compound 3 (IC_{50} = 51.80 ± 3.91 μM)[b] C = Na_3VO_4 (IC_{50} = 22.8 ± 0.8 μM)[b]	Enhancing the sensitivity of insulin	[54]
			I = Compounds 1, 4–7 (30 μM)[a] (60–77%)[b] C = Na_3VO_4 (20 μM)[a] (44%)[b]		[55]
		MCF-7 human breast cancer cells	I = Compounds 8 (500 mg/ml)[a] C = Troglitazone (50 μM)[a]	PPAR γ activator	[56]
		α-Amylase inhibitory assay	I = Compounds 12–17 (0.87 mM)[a] (63.5–70.5%)[b] C = Acarbose (0.13 mM)[a] (88%)[b]	Inhibition of α-amylase	[57]
		α-Glucosidase inhibitory assay	I = Compounds 12–17 (1.33 mM)[a] (35.1–49.4%)[b] C = Acarbose (0.13 mM)[a] (88%)[b]	Inhibition of α-glucosidase	
		Murine macrophage RAW 264.7 cell line	I = Compounds 12, 14, 17 (25 μM)[a] C = Lipopolysccharide (1 μg/mL)[a]	Anti-inflammatory	
		FL83B cell line (TNF-α- induced)	I = Compound 18 (in DMSO) (20 mM)[a] C = Compound C (in PBS) (20 mM)[a]		[58]
		Rat (alloxan- induced)	I = Compound (11) C = Compound (9), compound (10)	GSK-3 inhibitor	[59]
		L6 myotubes 3T3-L1 adipocytes C57BL/6 mice (M, HFD)	I = Compounds 17, 19–22 C = Acadesine or MET	Enhances the activity of AMPK	[60]

(*Continued*)

Table 2. (Continued).

Object	Detail	Model	Intervention/Control	Antidiabetic mechanism	Refs.
Phenols	Methanol extract	α-Amylase inhibitory assay	I = Compound 25 (0.87 mM)[a] (60.7%)[b] C = Acarbose (0.13 mM)[a] (88%)[b]	Inhibition of α-amylase	[57]
		α-Glucosidase inhibitory assay	I = Compound 25 (1.33 mM)[a] (56.4%)[b] C = Acarbose (0.13 mM)[a] (88%)[b]	Inhibition of α-glucosidase	
		Murine macrophage RAW 264.7 cell	I = Compound 25 (25 μM)[a] C = Lipopolysccharide (1 μg/mL)[a]	Anti-inflammatory	
Other metabolites	Protein	α-Amylase inhibitory assay	I_1 = MCC (2.5 mg/ml)[a] (66.5%)[b] I_2 = MCM (2.5 mg/ml)[a] (67%)[b] C = Acarbose (2.5 mg/ml)[a] (68%)[b]	Inhibition of α-amylase	[61]
		α-Glucosidase inhibitory assay	I_1 = MCC (2.5 mg/ml)[a] (68.8%)[b] I_2 = MCM (2.5 mg/ml)[a] (69.2%)[b] C = Acarbose (2.5 mg/ml)[a] (70%)[b]	Inhibition of α-glucosidase	

a) The experimental concentration of study subjects and controls. b) The activity of study objects and controls.

object. Two studies by Bai et al. suggested that bitter melon powder (BMP) could restore the intestinal flora and gut-generated metabolites to affect obesity-associated inflammatory responses, thus relieve HFD-induced insulin resistance .[16,32] For another, bitter melon juice (BMJ) is also a hot spot in hypoglycemic research and the fermentation can affect the physicochemical characterization of it .[49] The fermented BMJ could regulation of intestinal flora and production of SCFAs, thus enhancing the anti-diabetes properties of BMJ .[15] Therefore, the raw bitter melon can reach the goal of regulating blood glucose through beneficial regulation of intestinal flora of diabetic patients.

Obesity and dyslipidemia are major comorbid factors contributing to the development of diabetes. In the onset of diabetes, insulin bioactivity is affected, which leads to a reduction in fatty acid transport. Plasma has less triglyceride (TG) removed, so fat synthesis is inhibited, simultaneity lack of insulin causes a large amount of adipose tissue to decompose, leading to disorder of lipid metabolism .[50] Therefore, blood lipid control can improve the status of diabetes. Rats fed a high-fructose diet during gestation and lactation were supplemented bitter melon juice powder, which could ameliorate fructose-induced dyslipidemia and hepatic oxidative stress in male offspring .[63] For streptozotocin-(STZ) and nicotinamide-(NA) induced diabetic rats, giving fresh BMJ directly can lower blood glucose level (56%) and improve lipid profile .[20] These results indicate that the raw bitter melon is capable of hyperglycemia management by regulating blood lipids.

The raw bitter melon can also improve blood glucose levels through other mechanisms. For example, adding β-cyclodextrin (β-CD) to bitter melon juice, the bitterness of BMJ can be reduced while increasing its antioxidant capacity and total phenolic content, so the addition of β-CD may result in increased bioavailability of BM .[34] Direct administration of BMJ can improve pancreatic tissue lesions in diabetic rats, and also increase glucose uptake by diaphragms of the rats .[35] BMP could improve the pancreas function by repairing damaged pancreatic cells and protecting liver tissue .[36] Another research has also found that the total phenolic content (TPC) in freeze-dried BM samples were obviously excessive than fresh samples, at the same time, TPC was inversely related to α-amylase inhibition activity. So the fresh BM sample mostly showed relatively better antioxidant and antidiabetic activities compared with the freeze-dried BM .[33]

Aqueous extract of bitter melon (AEBM) and its hypoglycemic mechanisms

Glucagon-like peptide (GLP-1) is an important hormone which could stimulate the secretion of glucose-dependent insulin from islet β-cells and is an important physiological regulator of metabolic control .[37] According to those reports, the continuous treatment of T2DM with GLP-1 agonist can improve β-cell function, restore first-phase insulin secretion and normalize blood glucose .[64] Therefore, GLP-1 agonist has been developed as a new generation of anti-diabetes drugs, which can effective control and treat T2DM .[65] AEBM was found to increase tissue glycogen, serum insulin and GLP-1, meanwhile decrease in FBG and glycosylated haemoglobin in diabetic Wistar rats .[37] The study revealed that the AEBM could depolarize the L-cell through augment of intracellular Ca^{2+} concentration and which in turn releases GLP-1, then the GLP-1 can increase β-cell proliferation and insulin secretion .[37] In vitro, AEBM stimulated the secretion of GLP-1 in STC-1 (a mouse intestinal endocrine cell line) in a dose-dependent manner .[66] Therefore, the AEBM may contain a GLP-1 receptor agonist.

Circulating concentrations of branched-chain amino acids (BCAAs) can influence carbohydrate metabolism in skeletal muscle, which may also transform insulin sensitivity. BCAAs concentrations are elevated in response to over-nutrition, which is positively correlated with insulin resistance. Metabolic changes of it may play a role in the early pathogenesis of T2DM .[67] In obese mice, the upward trends of BCAAs were suppressed by AEBM treatment, including the rising trend of free fatty acids and eicosanoids. The result indicated that bitter melon can enhance sensitization to insulin by reducing BCAAs concentration in the body .[38]

Methanolic extract of BM and its hypoglycemic mechanisms

Studies have found that tissue secretion of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) can lead to inflammation and insulin resistance .[68] Therein, TNF-α has been recognized as an important factor in the physiological development of insulin resistance, as TNF-α expression is increased in adipose tissue in most patients with T2DM .[58] The inflammatory response leads to an increase in the incidence of T2DM by triggering insulin resistance, thereby increasing and promoting long-term diabetic complications in the presence of hyperglycemia .[69] Therefore, inhibiting the expression of inflammatory cytokines can reduce insulin resistance and blood glucose. Study has shown that TNF-α can induce insulin resistance in FL83B cells, while methanol extracts from bitter melon fruits, seeds or stems all contained compounds that effectively improve this phenomenon. Hence, methanolic extract of BM could prevent cellular insulin resistance through enhancing glucose uptake and phosphorylation of insulin resistant substrate-1 .[70]

In addition, different varieties of bitter melon were studied, then measured and found that the methanolic extract of the inner tissue (pulp and seed) of Indian bitter melon has highest total phenolic level (57.28 ± 1.02 mgCE/g of FD), which was also associated with the highest DPPH radical scavenging activity .[39] The free radical scavenging activity of the methanol extract of bitter melon fruit largely corresponds to its anti-diabetic properties. The methanol extract of BM could stimulate the release of insulin from residual pancreatic beta cells and improve the antioxidant activity of diabetic rats to enhance their anti-diabetic ability .[40,41] At the same time, the methanol extract of bitter melon also can lower levels of triglyceride (TG) and low-density lipoprotein (LDL), and raise levels of high-density lipoprotein (HDL) to maintain the normal glucose levels in normal rats and diabetic rats .[40,41]

Ethanolic extract of BM and its hypoglycemic mechanisms

Inflammatory responses in adipose tissue have been proved to be the main mechanism for inducing insulin resistance in surrounding tissues .[71] The inflammatory signals TNF-α and IL-6 can also activate inhibitory molecules for insulin-signaling pathway such as the suppressor of cytokine signaling-3 (SOCS-3) and c-Jun N-terminal kinase (JNK), which could suppress insulin-signaling pathway and cause insulin resistance .[71] Ma Chunyu et al. found that bitter melon ethanol extracts can regulate mRNA and protein levels of SOCS-3 and JNK to improve insulin resistance in T2DM rats .[43] So, the

BM could regulate the mRNA and protein levels of SOCS-3 and JNK, which could ameliorate the insulin resistance.

Compared with other solvent extracts, the ethanol extract of bitter melon may have better hypoglycemic activity. In the alloxan-induced diabetic rabbit model, parallel treatment with methanolic and ethanolic extracts of bitter melon for two weeks. The experimental results revealed that the ethanol extract of bitter melon can significantly reduce the hyperglycemia of diabetic rabbits, but methanol extract has no significant effect .[72] Another study also proved this conclusion, which indicated that the ethanolic extract of BM showed the highest inhibition activity of α-glucosidase in a concentration dependent manner compared with other solvent extracts .[42] In addition, this type of extract could enhance the body's antioxidant capacity, thereby resisting the oxidative stress induced by diabetes .[44] The ethanol extract of bitter melon could also synergize with glibenclamide to improve the body's blood lipids and up-regulate the expression of liver PPAR-α, thus showing better anti-diabetic effect than glibenclamide alone .[45]

Other solvent extracts of BM and their hypoglycemic mechanisms

Intestinal cells can secrete α-glucosidase, which further catalyzes the breakdown of oligosaccharides such as maltose and sucrose into simple carbohydrates. Then the monosaccharides are absorbed by intestinal epithelial cells. Salivary glands and pancreas can secrete α-amylase, which hydrolyzes the glycoside bonds within the starch, and the hydrolysate is oligosaccharide .[39] The action sites are shown in the Fig. 2. Thus, inhibiting the activity of these enzymes can reduce the absorption of carbohydrates, thereby lowering blood glucose levels in diabetics .[39] Thereinto inhibition of α-glucosidase enzyme could be a key strategy in the control of DM .[73] When the plant materials were sequentially extracted using hexane, chloroform and acetone, then measured and found that the acetone extract of BM can reduce blood glucose level most effective by inhibiting α-amylase activity. The chloroform extract and hexane extract can inhibit α-glucosidase to different degrees, thus reducing blood glucose .[39] The ethyl-acetate extract of bitter melon also can inhibit significantly α-glucosidase activity, and the IC_{50} comparable to the drug 1-deoxynojirimycin .[74] In addition, the EtOAc-soluble fraction of BM could also stimulate insulin secretion and enhance the body's insulin sensitivity .[46]

11-Hydroxysteroid dehydrogenase type 1 (11-HSD1) is a metabolic enzyme for glucocorticoids, which is responsible for converting active glucocorticoids to their inactive precursors and regulating local glucocorticoid concentrations .[75] Some studies suggest an aetiological role for 11-HSD1 in obesity and type 2 diabetes. 11-HSD1-deficient mice show improved lipid and lipoprotein profile, attenuated gluconeogenesis, enhanced glucose tolerance, and improved hepatic insulin resistance .[76] The reliable evidence that increased activity of fat 11-HSD1 is likely to lead to obesity and type 2 diabetes, so inhibition of 11-HSD1 activity has become a possible anti-diabetic strategy. Meanwhile, a study has shown that bitter melon capsules can selectively inhibit the activity of 11-HSD1, demonstrating that the extract of BM contains at least one active ingredient that could inhibit 11-HSD1 .[77] This finding provides a novel explanation for the hypoglycemic effect and anti-diabetic potential of BM.

Phyto-metabolites of BM and their hypoglycemic mechanisms

Bitter melon contains a variety of secondary metabolites, such as polysaccharides, saponins, triterpenoids, protein, alkaloids, flavonoids, quinine, amino acids, fatty acids, amino acids, and trace elements .[1] Most of these metabolites have the effect of lowering hyperglycemia, with relatively more research on polysaccharides, saponins, triterpenes and phenolics (Table 2).

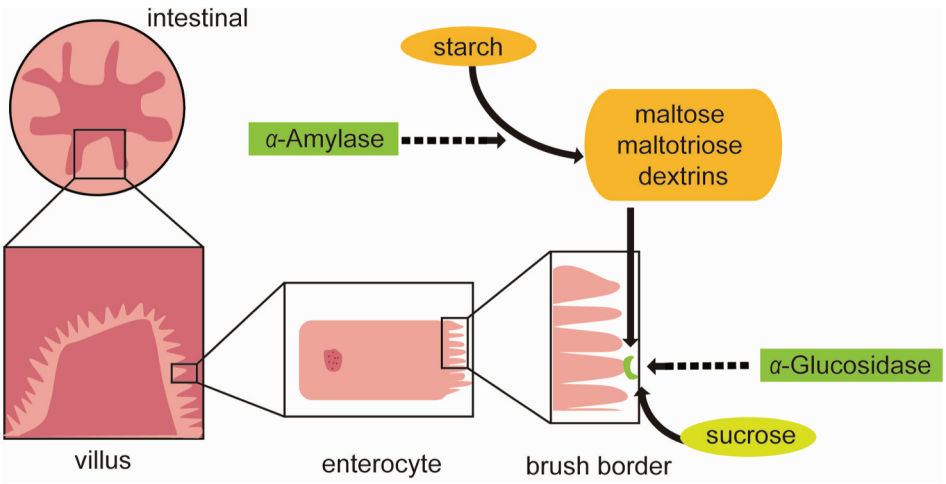

Figure 2. Simplified schematic diagram of carbohydrate hydrolysis by *α*-amylase and *α*-glucosidases at the intestinal brush border.

Polysaccharides of BM and their hypoglycemic mechanisms

M. charantia polysaccharides (MCP) is one of the main components with hypoglycemic effect of BM, which is mainly composed of glucose, galactose, and galacturonic acid .[78] Due to the complexity of the structure, the relationship between its structural characteristics, solution behavior and biological activity is unclear .[47] However, the scavenging effect on free radical of polysaccharides from *M. charantia* (MCPs: BP1, BP2, BP3, PS, MCPS1, MCPS2, MCPS3, MCPS4, MCPS5, MCPB) have been widely studied in vitro previously, which also showed considerable antioxidant activity .[78–82] The reason for their good activity is that hydroxyl groups in polysaccharides act as the hydrogen donator to remove DPPH free radicals and neutralize the role of oxidative stress .[83]

Islet *β*-cells are a sort of crucial endocrine cells that normally secrete insulin to regulate blood glucose levels. Diabetes can be caused when the function of islet *β*-cells is impaired, and cannot secrete enough insulin .[84] Therefore, restoring damaged islet *β*-cells can increase insulin secretion and improve blood glucose level. MCPIIa is an allogeneic polysaccharide consisting mainly of arabinose and galactose with low molecular weight, which could protect the pancreatic *β*-cells, thus showing hypoglycemic activity .[47] Studies found that oral administration of MCP also could markedly increase the antioxidant capacity of the diabetic mice by increasing the level of superoxide dismutase (SOD) and decreasing the level of malondialdehyde (MDA). Meanwhile the histopathology analysis of pancreas indicated that the MCP can alleviate the STZ-induced pancreas injury. Hence the hypoglycemic mechanism of MCP might be repairing damaged islet-*β* cells and increasing antioxidant capacity .[48,50]

Chromium is an important trace element for human beings and is indispensable in regulating blood glucose levels .[85] Numerous studies have shown that trivalent chromium ion can facilitate insulin secretion and improve insulin sensitivity, however, chromium ion has low bioavailability and needs to be combined with ligands .[86,87] Polysaccharides from natural products are considered to be the best ligands for chromium complexes. The MCP reacts with chromium ion to form *M. charantia* polysaccharide-chromium (III) complex (MCPIIaC), which could improve carbohydrate metabolism by enhancing insulin levels and sensitivity and promoting glycogen synthesis in the liver. The effective dose of MCPIIaC is ten times lower than the MCPIIa .[4]

Furthermore, studies have shown that the content of galactose and glucose in polysaccharides are linearly related to anti-hyperglycemia activity .[88] *M. charantia* bioactive polysaccharide contains high amounts of galactose and glucose, so it exhibits excellent *α*-amylase inhibitory activity (better than

acarbose) in a dose-dependent manner .[78] Another study found that fermentation could alternate the monosaccharide composition, viscosity and molecular weight of MCP, so the intake of fermented polysaccharides (FP) is beneficial to ameliorate the Intestinal flora, and increase the production of SCFAs of diabetic rats, thereby enhance the anti-diabetes effects of MCP .[49]

Saponins of BM and their hypoglycemic mechanisms

It is generally acknowledged that the adenosine monophosphate-activated protein kinase (AMPK) is a key factor in regulating energy metabolism, AMPK phosphorylation can decrease tissue lipid storage, enhance insulin sensitivity and lower blood glucose levels .[89] The liver is a primary metabolic organ of human body, which is mainly responsible for gluconeogenesis and glycogen decomposition .[90] Liver AMPK maintains glucose homeostasis through inhibiting gluconeogenesis and promoting glycogen synthesis. Meantime, activated AMPK could regulate diabetic complications by reducing the activity of nuclear factor κB (NF-κB) (a transcription factor of the inflammatory response) .[50,91] Therefore, activation of AMPK in liver is a reliable way to improve T2DM .[92] *M. charantia* saponins (MCS) are the one biologically active substances of bitter melon having antihyperglycemic activity. And the saponins of bitter melon have a better effect of reducing insulin resistance than the polysaccharides of bitter melon .[50] For STZ-induced T2DM mice, oral administration of MCS can regulate TC, TG, LDL-C, and HDL-C levels to achieve the effect of anti-hyperlipidemia. In the meantime, hepatic AMPK phosphorylation at MCS group, was markedly increased compared with diabetic control group, which lead to a decrease in NF-κB levels. So the hypoglycemic mechanism of MCS may involvement in the AMPK/NF-κB signaling pathway by activating AMPK phosphorylation and regulating energy metabolism in the body .[50]

MCS can also achieve the effect of lowering blood glucose through other mechanisms. The saponin-rich fraction from bitter melon could stimulate insulin secretion in MIN6 pancreatic-cells in a concentration-dependent manner while at the same time, it does not damage pancreatic-cells .[52] In addition, MCS can fight diabetes by improving the lipid metabolism disorder, regulating the insulin signaling pathway, and antioxidation .[51] Another study has shown that the higher the content of saponins from bitter melon extracts, the stronger the antioxidant capacity, therefore, it also has higher hypoglycemic activity .[93]

Triterpenoids of BM and their hypoglycemic mechanisms

The triterpenoids in bitter melon are mainly cucurbitane-type molecules, which are regularly found in *Cucurbitaceae* plants, they are featured by the tetracyclic cucurbitane nucleus skeleton (9β-methyl-19-norlanosta-5-ene) (Fig. 3) .[94] Triterpenoids are the key research objects of hypoglycemia in bitter gourd, which exert hypoglycemic effects in a variety of ways. The main mechanisms are showed in the Fig. 4.

Firstly, insulin triggers signaling through binding to the insulin receptor, including insulin receptor substrate (IRS), phosphoinositide 3-kinase (PI3-K), phosphatidylinositol (3,4,5)-trisphosphate (PIP_3), phosphoinositide-dependent protein kinase-1 (PDK-1), protein kinase B (Akt), glycogen synthase kinase 3 (GSK-3), extracellular signal-regulated kinase 1/2 (Erk1/2), atypical protein kinase C (aPKC) and glucose transporter 4 (GLUT4) translocation, which mediates the absorption of glucose into insulin-sensitive tissues (liver, muscle and adipose tissue) .[95] Triterpenoids isolated from the bitter melon can significantly increase the activation of insulin signaling pathway, lead to glucose transporter 4 translocation, and then enhance glucose uptake. Therefore, the triterpenoids have the potential to prevent and improve diabetes by regulating the insulin signaling pathway and controlling glucose homeostasis .[96] A cucurbitane-type triterpenoid, (19 R,23E)-5β,19-epoxy-19-methoxy-cucurbita -6,23,25-trien-3β-ol (**1**), was isolated from BM, can affect genes and proteins involved in insulin metabolism signaling to attenuate the metabolic symptoms of diabetes in ALX-induced diabetic mice .[53]

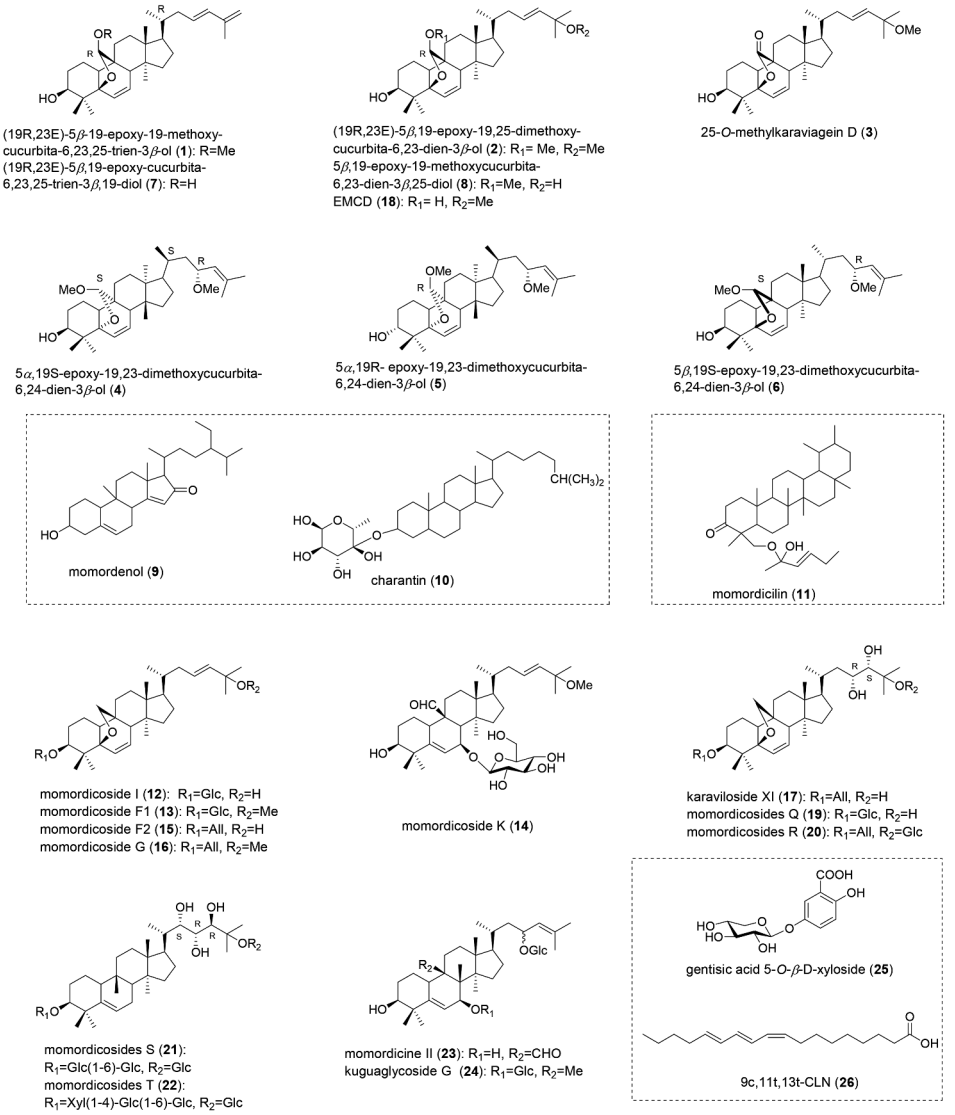

Figure 3. Compounds with hypoglycemic activity from bitter melon. Tetracyclic triterpenoids (**1–8, 12–24**), steroids (**9–10**), pentacyclic triterpene (**11**), phenolic acids (**25–26**).

Secondly, protein tyrosine phosphatases (PTPs) are enzymes that catalyze the dephosphorylation of protein tyrosine .[97] Protein tyrosine phosphatase 1B (PTP1B) dephosphorylates the tyrosine residue on essential proteins in insulin signaling, thus PTP1B is considered to be a negative regulator of insulin receptor signaling .[98] And the inhibitors of PTP1B are supposed to enhance the sensitivity of insulin .[99] Cucurbitane triterpenoids (19 R,23E)-5β,19-epoxy-19,25-dimethoxycucurbita-6,23-dien-3β-ol (**2**) and 25-*O*-methylkaraviagein D (**3**), showed higher PTP1B inhibition activities than Na_3VO_4 (a known PTP1B inhibitor), and then reduced insulin resistance and lowered blood glucose .[54] Another study also suggested that cucurbitane triterpenoids 5α,19S-epoxy-19,23-dimethoxycucurbita-6,24-dien-3β-ol (**4**), 19 R-epoxy-19,23-dimethoxycucurbita-6,24-dien-3β-ol (**5**), 5β,19S-epoxy-19,23-dimethoxycucurbita-6,24-dien-3β-ol (**6**), (19 R,23E)-5β,19-epoxy-19-methoxy-cucurbita-6,23,25-trien-3β-ol (**1**), and (19 R,23E)-5β,19-epoxy-cucurbita -6,23,25-trien-3β,19-diol (**7**) exhibited better inhibition activity against the PTP1B .[55] Structural

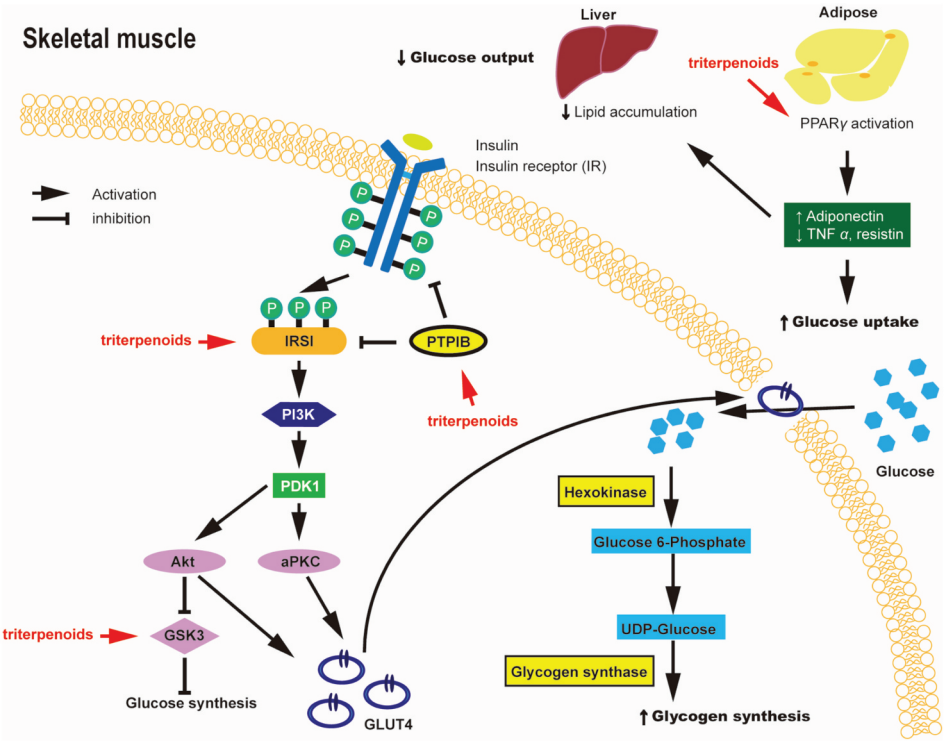

Figure 4. The main hypoglycemic mechanisms of triterpenoids from bitter melon. Triterpenoids are involved in the regulation of insulin signaling pathway, and then enhance glucose uptake in insulin-sensitive tissues. They can also act as inhibitors of PTP1B and GSK-3 to reduce insulin resistance in the tissues. In addition, triterpenoids can be used as PPARγ activator to reduce glucose output in liver and increase glucose intake in skeletal muscle.

activity relationship analysis showed that the inhibition activity of PTP1B was related to the presence and quantity of -OH groups .[55] Therefore, the cucurbitane triterpenes can be used as PTP1B inhibitors to lower blood glucose.

Thirdly, peroxisome proliferator-activated receptors (PPARs, -*α*, -*β*, -*γ*), ligand-inducible nuclear receptors, control many intracellular metabolic processes .[100] Thereinto, PPAR-*γ* is mainly expressed in adipose tissue and immune system, and is closely related to insulin resistance. Meanwhile, it is a target molecule of insulin sensitizer (thiazolidinedione) and has become a research hotspot in recent years .[2] 5*β*,19-epoxy-19-methoxycucurbita-6,23-dien-3*β*,25-diol (**8**), a triterpenoid isolated from BM, was identified as a PPAR-*γ* activator with an IC_{50} of 10 μM in breast cancer MCF-7 cells .[56]

Fourthly, glycogen synthase kinase 3 (GSK-3) is a serine/threonine protein kinase that regulates glycogen metabolism. It is one of the rate-limiting enzymes in glycogen synthesis and can phosphorylate and inactivate glycogen synthase .[101] GSK-3 levels and activity are increased in skeletal muscle of patients with T2DM suggesting that there was a positive correlation between the level of GSK-3 and insulin resistance .[99] Three anti-diabetic compounds namely momordenol (**9**), charantin (**10**), momordicilin (**11**) (one pentacyclic triterpene and two sterols) were taken from bitter melon can block the active site of the GSK-3 protein, and improve insulin resistance, wherein momordicilin (**11**) is a potent inhibitor of GSK-3 and can be used as the major anti-diabetic compound form bitter melon .[59]

Triterpenoids of BM also play a hypoglycemic role through other mechanisms. Shivanagoudra et al. isolated six monoglycoside cucurbitane-type triterpenes compounds from BM, momordicoside I (**12**), momordicoside F_1 (**13**), momordicoside K (**14**), momordicoside F_2 (**15**), momordicoside G (**16**), karaviloside XI (**17**), which showed significant inhibitory effect on *α*-amylase and moderate inhibitory

activity on α-glucosidase .[57] 5β,19-epoxy-25-methoxy-cucurbita-6,23-diene-3β,19-diol (EMCD, **18**), it inhibited the activation of the IkB kinase (IKK) complex and the NF-κB pathway, could attenuate TNF-α-induced inflammation, which is a potential drug for treating complications of diabetes .[58] Five cucurbitane glycosides, momordicosides Q (**19**), momordicosides R (**20**), momordicosides S (**21**), momordicosides T (**22**), and karaviloside XI (**17**) were isolated from the vegetable BM, they can increase activity of AMPK and stimulate GLUT4 translocation to the cell membrane in L6 myotubes and 3T3-L1 adipocytes .[60] Moreover, cucurbitane triterpenoids momordicine II (**23**) and kuguaglycoside G (**24**) can significantly stimulate insulin secretion in MIN6 β-cells, which further proved that bitter melon has hypoglycemic properties .[52]

Phenols of BM and their hypoglycemic mechanisms

Free radicals are generated during normal physiological processes like mitochondrial and microsomal electron transport, immune response, platelet activity, and autooxidation of biomolecules .[102] During unfavorable environmental conditions, tissues in the body encounter oxidative bursts that lead to oxidative stress and formation of free radicals, and oxidative stress causes depletion of antioxidants in the body and contributes to diabetes .[103] Mental stress increases the levels of cortisol and catecholamines, and high levels of cortisol are reported to deplete reduced glutathione and reduce superoxide dismutase activity, leading to elevated blood glucose levels .[104] Antidiabetic drugs with antioxidant activity can improve glucose tolerance in patients with diabetes by delaying glucose absorption or stimulating insulin secretion, and can also alleviate oxidative environment by counteracting free radicals produced by hypoglycemia, so they may provide better therapeutic effects .[105] Phenolic substances can scavenge free radicals, thus achieving antioxidant effect. Studies illustrated that phenolic compounds, such as quinic acid, catechin, caffeic acid, protocatechic acid, syringic acid, and 4-coumaric acid in BM have the ability to remove DPPH free radicals and the antioxidant capacity of reduced iron .[106] Meanwhile the positive correlation between total phenolic levels and DPPH free radical scavenging activity .[39,107]

One phenolic derivative, gentisic acid 5-*O*-β-D-xyloside (**25**) (Fig. 2), was isolated and identified from BM, which exhibited inhibition of α-amylase and α-glucosidase activities, and it could significantly suppress the expression of pro-inflammatory markers COX-2 and IL-6 to have an anti-inflammatory effect that reduces insulin resistance .[57] Phenolic compounds in bitter melon may play an important role in the inhibition of α-glucosidase, so the sequential extraction of hexane, chloroform and ethyl acetate was considered to be the most appropriate method for the extraction of α-glucosidase inhibitors from bitter melon .[105] Furthermore, the fatty acid, cis-9, trans-11, trans-13 conjugated linolenic acid (9 c,11 t,13 t-CLN) (**26**) (Fig. 2), was isolated from BM, which could stimulate adipocytokine production, improve insulin sensitivity and lower blood lipid content as an activator of PPARα .[108]

Other phyto-metabolites of BM and their hypoglycemic mechanisms

The protein extract from both *M. charantia var. charantia* (MCC) and *M. charantia var. muricata* (MCM) inhibited the activity of α-amylase and α-glucosidase through competitive inhibition, which activity were on par with Acarbose .[61] What's more, two sterols compounds namely momordenol (**9**), charantin (**10**) were taken from bitter melon. These can block the active site of the GSK-3 protein, and improve insulin resistance .[59]

Concluding remarks

In recent years, people are increasingly interested in traditional medicinal vegetables/fruits. As a functional food, bitter melon has great prospects. Animal models provide convincing evidence that bitter melon contains a variety of effective hypoglycemic components (such as polysaccharides,

saponins, triterpenes and phenols), and different chemical components exert hypoglycemic effects through different mechanisms of action. However, supportive evidence from clinical studies is lacking, which makes the hypoglycemic claims of bitter melon unconvincing. Therefore, controlled randomized clinical trials should be further designed to explore the active ingredients in bitter melon, the structural characteristics of the bioactive substances, and the relationship between structure and activities. Of course, to lucubrate the hypoglycemic mechanism of bitter melon is indispensable, and it can help increase the theoretical basis for the use of bitter melon and expand the treatment strategy of diabetes.

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