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Article *in* Journal of Cellular Biochemistry · February 2019

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Received: 6 October 2018 | Revised: 9 December 2018 | Accepted: 13 December 2018

DOI: 10.1002/jcb.28483

PROSPECTS

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Possible molecular mechanisms of glucose-lowering activities of *Momordica charantia* (karela) in diabetes

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Abstract

Diabetes mellitus is a highly prevalent metabolic disorder which is characterized by impaired glucose tolerance, with a relative or absolute insulin deficiency and profound changes in the metabolism of macronutrients. Traditional and complementary medicine is therapeutic strategies that have both been applied to improving glycemic control. *Momordica charantia* is one of the plant-based, folk medicines that used for improving glycemic control. We aimed to review, the effects of *M. charantia* on blood glucose with a clarification of the molecular pathways involved. Of the compounds derived from the plants, the insulin-like peptide, charantin, and the alkaloid vicine, have been reported to have hypoglycemic effects. Different mechanisms contribute to the antidiabetic activities of *M. charantia*, these include increasing pancreatic insulin secretion, decreasing insulin resistance and increasing peripheral and skeletal muscle cell glucose utilization, inhibition of intestinal glucose absorption and suppressing of key enzymes in the gluconeogenic pathways.

KEYWORDS

diabetes, glycemic indices, molecular mechanisms, *Momordica charantia*

1 | INTRODUCTION

Diabetes mellitus is a metabolic disorder which is characterized by hyperglycemia, and abnormal metabolism of carbohydrates, fats, and proteins, and is the result of a relative or absolute insulin deficiency (beta cell dysfunction) or insulin resistance, and is classified into two major categories, type 1 and type 2. Type 2 diabetes mellitus (T2D) is the cause of 90% of all types of diabetes.[1,2]

Type 2 diabetes mellitus is one of the most common chronic diseases worldwide and it has a prevalence of approximately 8.3% among adults globally.[3,4] The global

Naseh Pahlavan and Fatemeh Roudi are co-first authors.

prevalence of diabetes was 382 million in 2013 and is expected to reach 592 million by 2035.[5] In one study, the prevalence of type 2 diabetes in Iran was 5.4%.[6] The cost of health care for diabetes is high and it imposes a great economic and health burden on patients and national health costs.[7] The major complications of type 2 diabetes are microvascular and macrovascular pathologies, including cardiovascular disease, neuropathy, peripheral gangrene, nephropathy, and retinopathy, and causes 17.5 million deaths annually in the world.[8] Obesity, low physical inactivity, race, and unhealthy diets are among the most important risk factors for type 2 diabetes.[9] Hyperglycemia and oxidative stress are the main causes of microvascular and macrovascular complications in type 2 diabetes.[10] One important approach to preventing the complications of type 2 diabetes is the careful control of blood pressure, hyperglycemia, and dyslipidemia.[11,12]

Treatment options for type 2 diabetes include diet therapy, increased physical activity, complementary medicine, and traditional medication.[13] Complementary and alternative medicine refers to a wide range of treatments that are outside mainstream medical treatments.[14] Herbs and dietary supplements are used in the field of complementary medicine.[14] More than 400 plants have been shown to have antidiabetic effects (in vitro and/or in vivo and randomized controlled trials).[15] The potential mechanisms by which plant constituents have their effects in the treatment and control of diabetes include: affecting insulin resistance, the incretin pathways, glucose reabsorption, and improvement of pancreatic beta cell functions.[15] Bitter cucumber or bitter melon is the fruit of the *Momordica charantia* plant and has been used to treat diabetes in Ayurveda and complementary medicine.[16] *M. charantia* also has antibacterial and antiviral effects.[17] *M. charantia* is commonly referred to as the balsam pear, bitter gourd, and karela, and has been used to improve glucose tolerance.[16] The aim of this review was to summarize the effects of *M. charantia* on blood glucose and the molecular pathways through which it may do these effects.

2 | *M. CHARANTIA* FEATURES, STRUCTURE, AND COMPONENTS

M. charantia is widely cultivated in Asia, Africa, and South America and it has been used extensively in folk medicines for the treatment of diabetes mellitus (Figure 1 Mo).[18] *M. charantia* contains a number of chemical compounds including nutritionally important vitamins and minerals, antioxidants, and many other phytochemicals, that include: saponins, phenolic constituents, glycosides, fixed oils, alkaloids, resins, reducing sugars, and free acids. *M. charantia* is a good source of vitamins A and C, iron, phosphorus, protein (440-780 mg/kg), carbohydrates, zinc, calcium, and magnesium.[19,20] The pulp around the seeds of the mature *M. charantia* is one of the best sources of the carotenoid lycopene.[20] The caloric value of *M. charantia* varies from 176/61 kcal/100 g (leaf) to 241/66 kcal/100 g (seeds).[21] Although its active components are not fully identified, its antidiabetic components include polypeptides, glycosides, sterols, and alkaloids (vicine).[22] The active components of *M. charantia* can be divided into several groups: flavonoid, and phenolic compounds, cucurbitane type triterpenoids, oleanane-type triterpene, cucurbitane-type triterpene glycoside, insulin-like peptides, and saponins.[23] The phenolic compounds include caffeic acid, coumaric acid, ferulic acid, and gallic acid.[23] Some important triterpenoid components of *M. charantia* include: charantin, kuguacin A, momordicin I, and karavilagenin A; their structures are shown in Figure 2. The major components that have hypoglycemic effects include charantin, polypeptide p and vicine (a glycol alkaloid, a pyrimidine nucleoside).[16]

FIGURE 1 MO *Mordica charantia* plant: fruits, leaf, and flowers

To the best of our knowledge, there have been no studies on the effect of *M. charantia* in Persian medicine

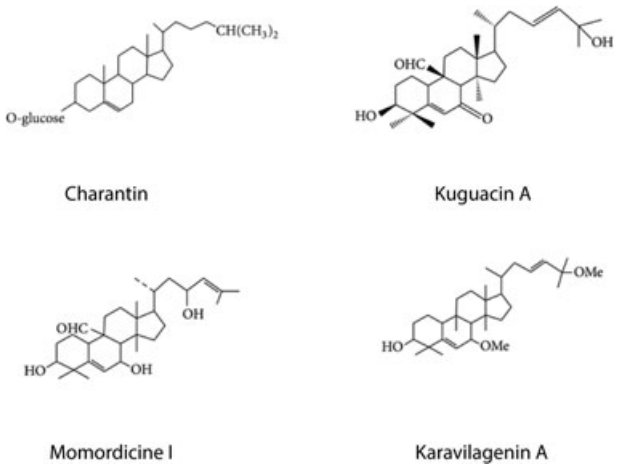

FIGURE 2 Chemical structure of some components derived from *Momordica charantia*

and *M. charantia* consumption is not mentioned in ancient Persian medicine textbooks.[24,25]

In addition to the antidiabetic and hypoglycemic effect of *M. charantia*, some of the other pharmacological properties and medicinal functions of this plant that have been reported, which include antibacterial, immunomodulation, antioxidant, anti-inflammatory, antiviral, antitumor, and hepato-protective properties.[16,21,26-29]

The potential interactions of this plant, include antidiabetes drugs (concomitant use of herbal products with antidiabetic drugs may increase the risk of developing hypoglycemia, and when taking herbal products with antidiabetes medications, patient's blood glucose levels should regularly be monitored) and cholesterol-reducing drugs (it may increase the effect of cholesterol-lowering drugs).[29]

Previous studies have reported a very low frequency of serious adverse effects of *M. charantia*.[30] Although, there have been some case reports, including hypoglycemic coma and convulsions in children[30,31]; hypoglycemic effects of *M. charantia* on blood glucose are very slow and do not cause a sudden induced hypoglycemia in adults.[16,32,33] Oral and subcutaneous administration of *M. charantia* is safe and encapsulated extract dosage ranges from 100 to 200 mg three times daily are recommended, but its intravenous injection is not recommended due to possible toxic effects because its seeds contain momorcharin and show the probability of abortion and infertility in female mice.[34] Administration of *M. charantia* in patients with glucose-6-phosphatase deficiency may be a risk because of the vicine component. Its safety during pregnancy is unproven, and the active compounds of the plant are secreted in milk, so the plant should be consumed by lactating women with caution.[29,30]

2.1 | Hypoglycemic effect of *M. charantia*

Many studies including cell-based assays, animal models and human clinical trials have suggested that *M. charantia* has hypoglycemic effects.[27,28,35,36]

2.2 | A possible mechanism of hypoglycemic effects of *M. charantia*

2.2.1 | Metabolic indices and insulin resistance

Several mechanisms for lowering metabolic indices have been proposed. *M. charantia* facilitates fatty acid transport and fat catabolism in tissues and improvement of the carnitine palmitoyltransferase (CPT) and acyl-CoA dehydrogenase enzymes system in mitochondria that can increase fatty acid oxidation.[37] Overexpression of CPT-1, cytokine signaling-3, c-Jun N-terminal kinase (JNK), and Akt expression at both protein and mRNA levels in liver improves insulin resistance.[38,39] Among the isolated components of *M. charantia*, only insulin-like peptide, charantin, and alkaloid showed hypoglycemic effects.[16] Overweight and deposition of fat in the abdomen is an early sign of obesity that can lead to type 2diabetes, studies in animal models have shown supplementation with *M. charantia* can reduce body weight and fat deposition in these animals.[39] And it has been shown that *M. charantia* reduces leptin and resistin levels in adipose tissue, which can reduce the insulin resistance in animal studies.[40] A recent study also suggests that *M. charantia* may increase adipocyte death via cyclic adenosine monophosphate–activated protein kinase mediated apoptosis in white adipose tissues.[41] In addition, *M. charantia* reduces fat accumulation during the differentiation process (from a preadipocyte to adipocyte), and downregulates peroxisome proliferator activated receptor γ (PPARγ) that is the vital regulator in adipose differentiation.[42,43] *M. charantia* can reduce PPARγ, sterol regulatory element-binding protein, and perilipin mRNA gene expression and these molecular effects can lead to increase lipolysis in human fat tissue.[44] *M. charantia* has been shown to improve the lipid profile and decrease levels of serum glucose by downregulation of PPARγ gene expression.[45] Dyslipidemia is a risk factor for insulin resistance in type 2 diabetes, but furthermore, dyslipidemia in diabetes can result from free fatty acid release in insulin-resistant adipose cells.[46] *M. charantia* has lipid-lowering effects in animal and human studies and can reduce hepatic and serum total cholesterol and triglyceride levels and increase the concentration of high-density lipoprotein-cholesterol in serum.[47-49]

M. charantia supplementation decreases oxidative stress with increases the activity of glutathione peroxidase and superoxide dismutase enzymes, and due to these antioxidant properties, *M. charantia* may be effective in reducing the complications of diabetes.[50,51]

2.3 | Pancreatic insulin secretion

Insulin is a peptide secreted from pancreatic β cells in response to increased plasma glucose level and increases glucose uptake in skeletal muscle and adipose tissues. In addition, insulin increases glycogen synthesis and decreases glycogenolysis and gluconeogenesis in the liver.[52] Previous studies have demonstrated that *M. charantia* stimulates insulin secretion by increasing the number of insulin-producing cells and regulates glucose uptake by different tissues including the liver. Furthermore, it may possess some insulin-like properties like growth and proliferation of cells.[16] *M. charantia* may stimulate an increase in liver hexokinase and glycogen synthase. However, these changes in liver enzymes may result from increased insulin secretion rather than a direct *M. charantia* effect.[26]

Studies have been undertaken to explain the mechanism of the higher rates of insulin secretion after consumption of *M. charantia*.[26] One study have reported an increase in number of β cells in pancreas after 10 ml/ kg administration of bitter ground juice and fruits in diabetic rats without any effect on the number of α and δ pancreatic cells.[53]

These findings are supported by many other studies that reported similar effect of *M. charantia*, ethanolic extracts and isolated components of the plant on insulin level and number of pancreatic β cells in histopathological tests.

M. charantia may also prevent pancreatic β cell necrosis and many studies have demonstrated that this protective effect is related to *M. charantia*'s antioxidative and anti-lipid peroxidation effects; for example: thiobarbituric acid reactive substances, lipid hydroperoxides and glutathione were found to be lower, and apoptosis was reported to be reduced in *M. charantia* treated cells in comparison to the control.[26,55-57]

Huang et al[58] reported increasing expression of GLP-1 (a stimulant mediator for insulin secretion) from intestinal cells cultured in cell culture and high fat diet fed mice.[58]

In other study *M. charantia* extract suppresses the activation of mitogen-activated protein kinases (MAPKs); these include stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK), p38, and p44/42, and necrosis factor-κB (NF-κB).[59] The findings support the claim that *M. charantia* protects pancreatic β cells by downregulation of MAPKs and NF-κB.[16,59]

2.3.1 | Glucose uptake

Previous molecular studies have shown that *M. charantia* aqueous and alcoholic extracts can inhibit enzymes involved in the glycolysis pathways including glucose 6-phosphatase, fructose 1,6-diphosphatase; these plant extracts stimulate glucose 6-phosphatase dehydrogenase.[27,60] The protein extract of *M. charantia* may lead to competitive inhibition of α-amylase and α-glucosidase activities as well.[61]

In addition, *M. charantia* is reported to increase glucose uptake in peripheral cells; several studies have demonstrated that *M. charantia* stimulates *N*-methyl-amino-α-isobutyric acid uptake and inhibits ^{3}H-deoxyglucose uptake by skeletal L6 myotubes and these effects are related to *p*-insulin (polypeptide-p) that is present in *M. charantia*.[16,62] *M. charantia* can also suppress Na and K dependant glucose absorption in the jejunal brush border cells.[16] Another mechanism of hypoglycemic effect of *M. charantia* through peripheral glucose uptake is stimulating glucose transporter 4 translocation to the cell membrane, and this translocation is associated with increased activity of AMP-activated protein kinase (a major cellular regulator of lipid and glucose metabolism).[39] *M. charantia* consumption leads to increased skeletal muscle insulin stimulated IRS-1 tyrosine phosphorylation in high fat fed rats.[63] *M. charantia* increases adipose PPARγ and liver PPARγ mRNA levels also.[32]

Figure 3 shows the mechanisms by which *M. charantia* can affect biochemical indices and improve management or reduce risks of diabetes.

Several mechanisms have been suggested to account for the hypoglycemic effects of *M. charantia*, however, the precise mechanisms responsible for the hypoglycemic effects are not yet well established. Different studies investigated various types, extracts or components of this plant and in different doses; therefore their results are inconsistent and not conclusive. Further investigations especially in vivo studies are necessary to be carried out to clarify antidiabetic mechanisms of actions of this plant. Dose dependency of the hypoglycemic effects of *M. charantia* needs to be investigated at the molecular levels in vitro, in vivo and clinical trials.

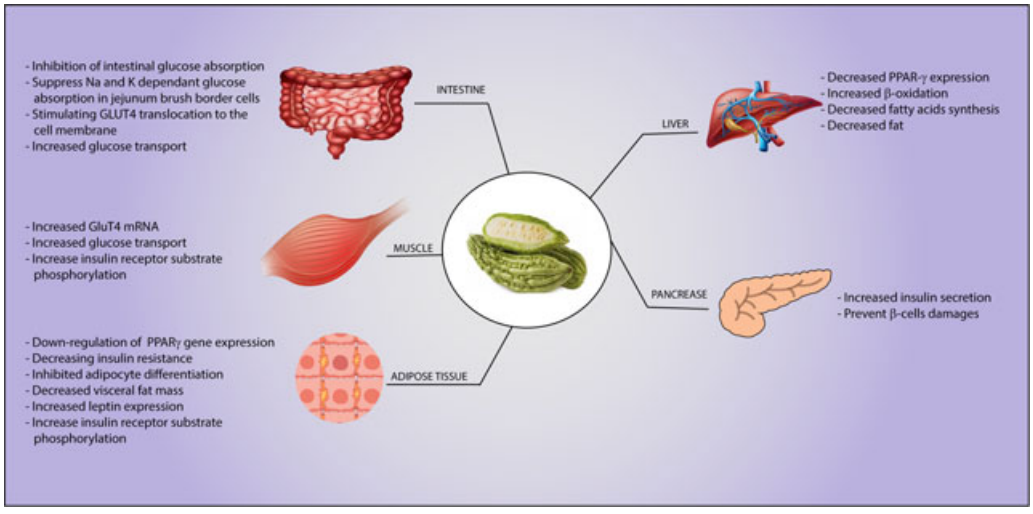

FIGURE 3 Effect of *Momordica charantia* on various organ and the probable molecular targets for improving glycemic indices and diabetes

TABLE 1 Effects of *Momordica charantia* on glycemic indices in clinical trial studies

Country (Reference number)	Study design (Sex)	Participants numbers	Type and dose of M. C administered	Duration (Mean age of subjects)	Outcome measures	Author (year)
India[64]	Parallel RCT (M/F)	50 type 2 diabetes patients	2 tablets thrice daily each tablet: 1 g	4 weeks (52.8 years)	N.S in FBS/PPS N.S in Serum fructosamine level	John et al (2003)
Philippines[65]	Parallel RCT (M/F)	40 type 2 diabetes patients	two capsules of M. charantia three times a day(dose not mentioned...)	3 months (59.2 years)	S.R in HbA1C level M.C group N.S on fasting blood sugar, total cholesterol, and weight or on serum creatinine, ALT, AST, sodium, and potassium	Dans et al (2007)
India[66]	Case series (no referent group) (M/F)	60 noninsulin dependent male diabetics	G1Raw powered mixture (bitter melon fruit, fenugreek seeds, jambu seeds) in the form of capsules (1.5 g/d) G2: salty biscuits	6 weeks AGE (mean years (SD)): No information	S.R in FBS, post prandial glucose and significant decrease needing to oral hypoglycemic drugs	Kochhar et al (2005)
Canada[67]	Cross-over RCT (M)	5 overweight men	G1: no MC (placebo) G2: 50 mg/kg MC G3: 100 mg/kg MC	Single dose oral administration prior to OGTT (34 years)	N.S in Plasma glucose N.S in insulin levels N.S in energy expenditure N.S in carbohydrate and lipid oxidation rates N.S in appetite profile	Kasbia et al (2009)
Thailand[68]	Parallel RCT (M/F)	143 type 2 diabetes patients	G1: 500 mg/day M.C G2: 1,000 mg/day M.C G3: 2,000 mg/day M.C G4: 1,000 mg/day metformin	4 weeks (51.8 years)	S.R in fructosamine level in G3 and G4 S.R in fasting plasma glucose in all groups but S.R in G1,2,3 were less than S.R in G2	Fuangchan et al (2011)
Pakistan[69]	Parallel RCT in three groups (M/F)	90 type 2 diabetes patients	Capsule G1: 2 g/d M.C G2: 4 g/d M. C G3: 5 mg/d glibenclamide	10 weeks (52.1 years)	S.R in HbA1C and FPG in G1, G2 and G3 S.R in 2 hour OGTT in G3 2 hour OGTT in G1 and G2 were N.S	Rahman et al (2015)
United state[70]	Cross-over RCT (M/F)	10 pre-diabetic adults	Beverage containing 1.25–3 g of M.C extract 30 minutes before OGTT	3 days (61.3 years)	S.R in Plasma glucose and AUCglu in 50% of subjects	Boone et al (2017)
Mexico[71]	Paralel RCT in two groups (M/F)	24 type 2 diabetes patients	Capsule G1: 2 g/d M.C G2: 2 g/d placebo	12 weeks (48.3 years)	S.R in HbA1C and FPG in M.C group. Increase in insulin secretion significantly in M.C group	Cortez-Navarrete et al (2018)
Tanzania[72]	Cross-over RCT (M/F)	52 pre-diabetic adults	Juice containing 2.5 g M.C extract	8 weeks (47.5 years)	S.R in FPG, N.S in insulin levels and lipid profile	Krawinkel MB et al (2018)

Abbreviations: AUCglu, area under curve glucose; F, female; FBS, fasting blood sugar; FPG, fasting plasma glucose; G, group; M, male; M.C, *Momordica charantia*; N.S, not significant difference; OGTT, oral glucose tolerance test; PPS, postprandial sugar; RCT, randomized clinical trial; S.R, significant reduction.

3 | HYPOGLYCEMIC EFFECTS OF *M. CHARANTIA* IN CLINICAL TRIAL STUDIES

The effects of *M. charantia* on glycemic indices in randomized clinical trial studies as the most important and decision making studies are summarized in Table 1.

As shown in Table 1, despite some studies in diabetes mellitus have shown that *M. charantia* extracts possess glucose lowering properties and also reduce some of the complications of diabetes[20]; there are some randomized clinical trials that have shown no significant effect of *M. charantia* supplementation on glycemic indices.[64,73] For example, in one study that was conducted in 2015 in Pakistan, *M. charantia* could decrease fasting plasma glucose and HbA1C in type 2 diabetes patients, however, this effects on 2 hours oral glucose tolerance test was not significant.[74] In another study that was undertaken in 2018 in Mexico, supplementation with 2 g/d *M. charantia* for 12 weeks significantly reduced HbA1C, fasting plasma glucose and increased insulin sensitivity.[75] These effects are probably due to the presence of insulin-like peptide and other antioxidants in *M. charantia*. Conversely, administration of 4 g/d of *M. charantia* for 4 weeks had no significant effect on levels of fasting blood sugar and postprandial sugar in type 2 diabetes patients.[64] Although experimental studies suggested that *M. charantia* has hypoglycemic effects; there are only a limited number of human studies investigating the hypoglycemic effects of *M. charantia* and they are inconclusive.[30]

Most of them investigate the effect of *M. charantia*, its various extracts, and components on fasting and postprandial plasma glucose and other glycemic factors like HbA1C and insulin levels; many of them had selection bias; previous clinical trials often lacked a population-based control group, were not properly blinded, the duration of treatment was too short and methodologically errors were common in previous studies, for example, statistical methodology and study protocol details were not described as adequate as to allow a validity assessment.[30,31,52]

Further strong randomized clinical trial studies with a large number of participants will be necessary to find out the exact effects of *M. charantia* on controlling blood glucose, other glycemic indices, and diabetes complications.

4 | CONCLUSION

Different physiological, pharmacological, and biochemical mechanisms are assumed for antidiabetic activities of *M. charantia,* its extracts, and isolated components; these include increasing pancreatic insulin secretion, decreasing insulin resistance and increasing peripheral and skeletal muscle cell glucose utilization, inhibition of intestinal glucose absorption, and suppressing of key enzymes in gluconeogenic pathways.

Although supplementation with *M. charantia* potentially can improve some glycemic indices such as fasting blood glucose, HbA1c and insulin secretion, but the previous human clinical evidence is inconclusive. This inconsistency may result from the difference in the type of administered plant, dose, and duration of supplementation.

Despite a large number of articles published in this area, the conclusions about the definitive effects of this plant on glycemic indices are inconsistent. Further in vitro, in vivo, and clinical trial studies will be necessary to find out the exact molecular mechanisms of *M. charantia* in controlling blood glucose and other glycemic indices.

ACKNOWLEDGMENTS

We are very thankful to numerous colleagues with whom we have shared our research on *Momordica charantia* and its cellular and molecular mechanisms in diabetes and who have helped us with valuable comments.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

The authors' responsibilities were as follows. NP, FR, HR, and MGM: designed the research; NP, FR, AM, and MZ: conducted the library search and wrote the manuscript; JGN designed table and figures; and HR and GAF participated in the drafting and editing of the manuscript. All of the authors read and approved the final manuscript.

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How to cite this article: Pahlavani N, Roudi F, Zakerian M, et al. Possible molecular mechanisms of glucose-lowering activities of *Momordica charantia* (karela) in diabetes. *J Cell Biochem*. 2019;120: 10921-10929. https://doi.org/10.1002/jcb.28483