Karela: A promising antidiabetic vegetable therapy

Ashok K. Tiwari

Karela (Momordica charantia Linn.) is described in ayurveda as beneficial in diabetic disorders and other disease conditions. Modern scientific analyses of its antidiabetic properties reveal that it has the capacity to regulate vitiated carbohydrate digestion, glucose metabolism and utilization, possesses insulin mimetic and secretagogue activities, and corrects the impaired antioxidant defence in diabetes. Therefore, Karela has the potential to attenuate development of diabetes and its complications. This article presents a fusion of ancient ayurvedic knowledge with modern scientific evidences on its multifaceted antidiabetic properties.

Keywords: Antidiabetic properties, karela, Momordica charantia, vegetable therapy.

Food items are now being recognized not just as a source of chemical energy, but they also possess ingredients that help reduce the risk of chronic lifestyle-related diseases like diabetes, heart disease, atherosclerosis, hypertension, arthritis, cancer, allergies and related abnormal modalities. Our increased scientific understanding of the health benefits of key components of food items has fuelled this renaissance. This global renaissance is nothing but the resurgence of the ancient Chinese dogma 'Medicine and food are isogenic' and the doctrine of Hippocrates (460–377 BC), 'Let food be thy medicine and medicine be thy food'. These statements of belief still continue in the form of traditional system of medicine, particularly in developing countries. Ayurveda, a traditional Indian system of medicine and an integral part of Indian culture, still continues to provide health care to a large percentage of our people.

Modern scientific analysis of food items described in classical texts of ayurveda is being renovated to justify the claims made in age-old classics. In ayurveda, karela (Momordica charantia Linn.) Karavellan (Sanskrit), bitter gourd or bitter melon (English), is grouped under vegetable class (शूकर वर्ग) of medicine and claimed to possess several therapeutic properties. The compendia of Indian medicinal plants called Nighantas were written between 7th to 17th centuries AD. The Kalyadeva Nighantu and Bhava Prakash Nighanta date between AD 1500 and 1600 and compilation of these Nighantas known as Nighanta Ratnakar was made in 1867. These classical texts describe karela to possess the following therapeutic properties:

Accordingly, these verses mention that Karela is bitter in taste, regulates the digestion and metabolism, softens and clears the motion, and improves digestion of sweet substances (स्वाद उच्च). It also cures fever (उत्तान), harmonizes enzymatic (पिद) and related metabolic (क्रम) vitiations, is beneficial in anaemia (पाण्डु), and diabetes/polyurea (गृह), and also relieves worms (कृश). Furthermore, verses from Nighanta Ratnakar and Kaiyadeva Nighantu disclose that:

The above verses indicate that Karela possesses properties to destroy the lack of taste for food (अर्धे), unwanted metabolites (क्रम), oxidative disorders (धर्म), problems related to blood (रक्त दशौ), fever (उत्तान), worms (कृश), enzymatic disturbances (पिद), anaemia (पाण्डु), skin disorders (कृश), diabetic symptoms (प्रमेयं, मैंह), jaundice (कांपनं), and respiratory disorders (श्वास-कर्स). However, Karela’s primary therapeutic benefits in diabetes (प्रमेयं) and polyurea (मैंह) have drawn considerable scientific attention. Ever since its first scientific evidence of hypoglycaemic property published in 1960, volumes of literature have now surfaced testifying its versatile beneficial effects in the management of diabetes mellitus. This article presents a fusion of ancient ayurvedic

Ashok K. Tiwari is in the Pharmacology Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India.
e-mail: astiwari@yahoo.com

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knowledge with modern scientific evidences on the multifaceted antidiabetic properties of karela.

**Mitigating diabetes development**

Animal experiments reveal that 10% edible portion of karela in the diet checked about 30% appearance of primary symptoms of diabetes development like increased water consumption, urine volume and urine sugar in streptozotocin (STZ)-induced diabetic rats. Furthermore, it also prevented renal hypertrophy (38%) and reduced glomerular filtration rate by 27% in some animals. Fasting blood glucose level was observed less (30%) in animals consuming karela-added diet than the control diabetic animals. This study demonstrates that regular consumption of karela in the diet may tone-down diabetes in primary developmental stages. In ayurveda also, similar symptoms of diabetes (प्रमेर) development are described as: प्रमेर वार्त वर्त वा मेरति पुत्र चार्यम कृति वसिनु सेवे स प्रमेर. Evidences of mitigating diabetes development in experimental animals therefore, approve the antidiabetic (प्रमेर नाशक) property of karela as described in ayurveda.

**Influence on disturbed carbohydrate digestion during diabetes**

Accelerated digestion of carbohydrates and increased absorption of glucose in the intestine due to alterations in activities of brush border disaccharidases are noticed in diabetes. A recent study observed that a diet supplemented with 10% seedless bitter-gourd powder ameliorated increased activities of maltase and lactase during diabetes. Potential intestinal α-glucosidase inhibitory activity of karela has also been reported. Karela juice is further reported to reduce transport of glucose from the alimentary canal into the blood by reduction of Na⁺ and K⁺-dependent transport of glucose from the intestinal tract into the blood.

Postprandial hyperglycaemia precedes elevation in fasting blood glucose levels by 4 to 7 years, providing an early marker for impending diabetes. Diabetic complications begin to develop during the period when postprandial hyperglycaemia is present and fasting glucose level remains in the normal range. An association has been observed between nonfasting hyperglycaemia and coronary heart disease, myocardial infarction, death from myocardial infarction, stroke, retinopathy, and increased foetal weight and size (Zimmerman and references cited therein). Slow dietary carbohydrate digestion by karela due to its inhibitory activities on carbohydrate hydrolases and reduced glucose transport into the blood may explain in part, the reduction of postprandial hyperglycaemia in moderate non-insulin-dependent diabetic (NIDDM) patients. Karela has also been reported to depress the activities of key gluconeogenic enzymes, glucose-6-phosphatase and fructose-1,6-bisphosphatase. These enzymes play an important role in elevation of fasting blood glucose level in diabetics. This gluconeogenic enzyme regulatory activity of karela may be responsible for the lowering of fasting serum glucose level in some patients. According to ayurvedic descriptions, उपध्रातिरिक्ता (विद्रोह जानातिपातू सप्तभीजवयाम) vitiation in enzymatic (रित) and related metabolites (के) leads to the development of diabetes mellitus (मयमय). Therefore, experimental evidences of harmonization of vitiated enzymatic process in diabetic conditions by karela appear to be important facets that may reduce development of diabetes mellitus.

**Insulinomimetic, secretagogue and glucose uptake activities**

Diabetes mellitus is associated with reduction in body weight, the number of insulin-positive cells per islets in pancreatic β-cells, and plasma insulin along with increased blood osmolarity and systolic blood pressure. These destructive organic and physiological changes lead to hypertension and insulin resistance. Khanna et al. for the first time isolated active protein fraction from *Momordica charantia* (MC), which is also called p-insulin, and showed hypoglycaemic activity in gerbils, langurs, and diabetic patients. Sirinton et al. have recently isolated zinc-free, slow-acting protein extract from fruit pulp of MC. Subcutaneous injection of this protein extract markedly decreased plasma glucose levels in both normal and STZ-induced diabetic rats. In perfused rat pancreas, this protein fraction increased insulin secretion and enhanced glucose uptake into C2C12 myocytes and 3T3-L1 adipocytes. This study approves the presence of insulin secretagogue and insulin mimetic principles in protein fraction, as reported earlier by Khanna et al.

Insulin resistance hampers physiological uptake of glucose in muscle. MC juice or extract has been reported to increase glucose uptake by augmenting phosphatidyl inositol-3-kinase pathway, which suggests that MC possesses insulin-like activity responsible for augmentation of glucose as well as amino acid uptake into skeletal muscle cells. An investigation on KK-Ay mice with water extract of MC juice revealed significant reduction in blood glucose as well as serum insulin level. This study further observed increased muscle content of facilitative glucose transporter isofrom-4 (GLUT-4) protein in the plasma membrane fraction from muscle by oral MC treatment that may be held responsible for amelioration of insulin resistance in diabetes. The verse स्वतंत्रा महापरायणो ताणात्मा भविष्यत इतिविवरणिताणि मूल्यायतः मनुष्य्याणां तत्वं स्वरूपायति in the ayurvedic classic *Madhavanidan* mentions that when diabetes (प्रमेर) turns into diabetes mellitus (मयमय), it becomes incurable. Interestingly, however, disclosure of the presence of insulinomimetic, insulin secretagogue and muscle glucose-uptake increases.
ing activities in MC by modern scientific research raises the hope of management of diabetes mellitus by this simple vegetable.

**Regulation of oxidative stress in diabetes**

Increasing evidences, both in experimental and clinical studies, suggest that oxidative stress plays a major role in pathogenesis of type I and type II diabetes as well as development of diabetic complications\(^3\). Aqueous extract of the seeds of MC is reported to restore decreased antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-peroxidase and glutathione (GT) in STZ-induced diabetic rat liver and kidney\(^2\). Treatment with the seed extract for a month has been shown to decrease thiobarbituric acid reactive substance (TBARS), and hydroperoxides in plasma, liver and kidney with improvement in circulatory antioxidants, α-tocopherol and ascorbic acid levels\(^2\). Treatment with aqueous extract of MC was also observed to improve the reduced GT in the pancreas of diabetic rats\(^2\).

These observations suggest protective effect of MC juice against free radical-mediated oxidative damage to biomolecules and membranes, and normalization potential for vitiated antioxidant defence in oxidative stress during diabetes. Ayurvedic descriptions also highlight aggrivated वाणि (free radical and oxidative stress conditions) in diabetes mellitus (मधुमेह)…कृतित वाणि मधुमेह्रसम्बन्धी:\(^1\). These experimental evidences of potentiation of antioxidant defence and free-radical scavenging properties of karela approve the वाणि-नाशक (free-radical scavenging/antioxidative stress) capacity as described in the ayurvedic classics.

**Regulation of vitiated lipid profiles in diabetes**

Oxidative stress is one of the principle mechanisms that mediates premature atherosclerosis in diabetes. It has been proposed that free radical-mediated loss of glycosaminoglycan leads to the reduction in capillary endothelium-bound lipoprotein lipase action that accounts for increase in plasma triglycerides and reduced high-density lipoprotein (HDL) levels in diabetes\(^3\). Significant increase in serum total lipids, triglycerides and total cholesterol in alloxanized diabetic rats are observed\(^3\). Furthermore, increase in activities of lipogenic enzymes in kidney was also noticed. Treatment of alloxanized diabetic rats with MC fruit extract prevented these alterations and maintained all these parameters near normal values\(^3\). Treatment of diabetic rats with methanol extract of MC fruit for 30 days has been shown to significantly reduce serum triglycerides, and low-density lipoprotein with significant increase in HDL level\(^3\). Feeding of MC fruit extract for over ten weeks to STZ-induced type-I diabetic rats leads to normalization of increased plasma non-esterified cholesterol, triglycerides and phospholipids, and restoration of HDL cholesterol\(^3\). These observations provide evidence of antidiyslipidemic property of karela that may be beneficial in arresting development of cardiovascular complications in diabetics.

**Clinical studies**

Glucose tolerance test (GTT) with aqueous homogenized suspension of MC vegetable pulp in 100 moderate cases of NIDDM showed significant reduction in both fasting and postprandial serum glucose levels\(^5\). In maturity onset diabetic patients, fruit juice of MC has been reported to improve GTT in significant population of the patients studied\(^9\,10\). CCL4 + C6H6 MC soft extract at a dose of 200 mg twice daily in NIDDM patients has shown hypoglycaemic effect\(^9\). Interestingly, pronounced hypoglycaemia was noticed when the extract was used with half the dose of known hypoglycaemic drugs, metformin or glimepiride\(^6\). Baldwa et al.\(^7\) reported decrease in fasting blood glucose levels in six type-1 and three type-2 diabetic patients by subcutaneous injection of V-insulin extract from MC.

None of these studies reported any adverse effect or any kind of hypersensitivity reaction. However, in the absence of randomized controlled trials, the US Preventive Services Task Force, American Diabetic Association guidelines has categorized these studies as Level-III C\(^18\). A recent review on efficacy and safety of MC suggests that bitter melon may have additive effects when taken with other glucose-lowering agents\(^9\). It further warrants that bitter melon may have hypoglycaemic effect, but clinical data are not sufficient to recommend its use in the absence of careful medical supervision and monitoring\(^9\).

**Adverse effects**

In a study utilizing aqueous extract powder of fresh, unripe whole fruits of MC, no signs of nephrotoxicity and hepatoxicity were observed in rats\(^8\). Feeding of diets containing either bitter melon or various fractions isolated by organic solvents could neither affect food intake nor growth in rats\(^8\). Supplementation of freeze-dried powder to rat food could not show any adverse effect on growth parameters and relative liver weight\(^11\). On the other hand, adverse effects of bitter melon, like hypoglycaemic coma and convulsion in children, reduced fertility in mice, a favismsyndrome, increase in gamma-glutamyltransferase and alkaline phosphatase levels in animals and headaches are also observed\(^9\).

**Future prospects**

India and China are predicted to show the largest increases in terms of diabetes prevalence\(^12\). ‘Diseases of affluence’
like diabetes, obesity and cardiovascular disorders, are a threat to the future generations and pose heavy burden on economic development even at individual level. For diabetic individuals in India, it is estimated that 15–25% of household income is required to cover treatment cost[4]. However, in USA, according to a local pharmacy estimate, the annual costs of common oral hypoglycaemic drugs such as rosiglitazone (8 mg, twice a day), metformin (1000 mg, twice a day) and acarbose (100 mg, three times a day) become approximately US $4408, $624 and $1192 respectively[4].

The concept of “functional food”[2] has propagated quickly around the world after its birth in 1980. The current trend of reconsidering traditional foods and their key components as the first line of defence against lifestyle-related diseases has grown from the increased scientific understanding of their health benefits. Globally, 80% of the indigenous population in developing countries relies upon traditional medicine and medicinal plants as primary healthcare[5]. The ancient lineage and modern scientific scrutiny of multiple beneficial effects of karola in diabetes discussed here therefore, provides enough opportunity for this vegetable to become a promising anti-diabetic therapeutic. However, in view of some adverse effects adequately powered, randomized, placebo-controlled trials are needed to properly assess safety and efficacy before it can be routinely recommended as therapy.


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