Karela: A promising antidiabetic vegetable therapy

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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[1]. This global renaissance is nothing but the resurgence of the ancient Chinese dogma 'Medicine and food are isogenic'[2] and the doctrine of Hippocrates (460–377 BC), 'Let food be thy medicine and medicine be thy food'[3]. These statements of belief still continue in the form of traditional system of medicine, particularly in developing countries. Ayurveda, a traditional Indian systems of medicine and an integral part of Indian culture[4], still continues to provide health care to a large percentage of our people[5].

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 (*शाक वर्ग*) of medicine and claimed to possess several therapeutic properties. The compendia of Indian medicinal plants called *Nighantus* were written between 7th to 17th centuries AD[6]. The *Kaiyadeva Nighantu*[7] and *Bhava Prakash Nighantu*[8] date between AD 1500 and 1600 and compilation of these *Nighantus* known as *Nighantu Ratnakar*[9] was made in 1867. These classical texts describe karela to possess the following therapeutic properties:

कारवेल्लं चातितिक्तमग्निदीप्तिकरं लघु,
उष्णं शीतं भेदकं च स्वादु पथ्यं समीरितम्[9].
कारवेल्लं हिमं भेदि लघु तिक्तमवातलम्,
ज्वरपित्तकफास्नघ्नं पाण्डुमेहकृमीन् हरेत्[8].

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 (स्वादु पथ्यं). It also cures fever (ज्वर), harmonizes enzymatic (पित्त) and related metabolic (कफ) vitiations, is beneficial in anaemia (पाण्डु), and diabetes/polyurea (मेह), and also relieves worms (कृमि). Furthermore, verses from *Nighantu Ratnakar*[9] and *Kaiyadeva Nighantu*[7] disclose that:

अरुचिं च कफं वातं रक्तदोषं ज्वरं कमीन्, पित्तं पाण्डुं च कुष्ठं च नाशयेदिति
कीर्तितम्, कोठं कुष्ठं ज्वरं चैव प्रमेहाध्माननाशनम्, कामलां नाशयत्येव गुणास्त्वन्ये तु पुर्ववत्[9].
श्वासकासप्रमेहास्नकोठकुष्ठज्वरानपि, क्षुद्राक्षं कारवेल्लं तु लघूष्णं कृमिवातजित्[7].

The above verses indicate that Karela possesses properties to destroy the lack of taste for food (अरुचि), unwanted metabolites (कफ), oxidative disorders (वात), problems related to blood (रक्त दोष), fever (ज्वर), worms (कृमि), enzymatic disturbances (पित्त), anaemia (पाण्डु), skin disorders (कुष्ठ), diabetic symptoms (प्रमेह, मेह), jaundice (कामला), and respiratory disorders (श्वास्–कास).

However, Karela's primary therapeutic benefits in diabetes (प्रमेह) and polyurea (मेह) have drawn considerable scientific attention. Ever since its first scientific evidence[10] 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

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knowledge with modern scientific evidences on the multi-faceted 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[11]. 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[11]. 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 (प्रमेह) development are described as: प्रचुरम् वारं वारं वा मेहति मूत्र त्यागं करोति यस्मिन् रोगे स प्रमेह[12]. Evidences of mitigating diabetes development in experimental animals therefore, approve the antidiabetic (प्रमेह 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[13]. Potential intestinal α-glucosidase inhibitory activity of karela has also been reported[14]. Karela juice is further reported to reduce transport of glucose from the alimentary canal into the blood[15] by reduction of Na^+ and K^+-dependent transport of glucose from the intestinal tract into the blood[16].

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[17]. 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[17] and references cited therein). Slow dietary carbohydrate digestion by karela due to its inhibitory activities on carbohydrate hydrolases[13,14] and reduced glucose transport into the blood[15,16] may explain in part, the reduction of postprandial hyperglycaemia in moderate non-insulin-dependent diabetic (NIDDM) patients[18]. Karela has also been reported to depress the activities of key gluconeogenic enzymes, glucose-6-phosphatase and fructose-1,6-biphosphatase[19–21]. 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[18]. According to ayurvedic descriptions, उपेक्षयाहि पित्तकफजानामपिमधुमेहप्रदर्शयितुमाह[12], vitiation in enzymatic (पित्त) and related metabolites (कफ) leads to the development of diabetes mellitus (मधुमेह). 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[16]. These destructive organic and physiological changes lead to hypertension and insulin resistance. Khanna *et al.*[22] 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.*[23] 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[23]. In perfused rat pancreas, this protein fraction increased insulin secretion and enhanced glucose uptake into C2C12 myocytes and 3T3-L1 adipocytes. This study[23] approves the presence of insulin secretagogue and insulin mimetic principles in protein fraction, as reported earlier by Khanna *et al.*[22].

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[16,24], which suggests that MC possesses insulin-like activity responsible for augmentation of glucose as well as amino acid uptake into skeletal muscle cells[16,24]. An investigation on KK-Ay mice with water extract of MC juice revealed significant reduction in blood glucose as well as serum insulin level[25]. This study further observed increased muscle content of facilitative glucose transporter isoform-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 सर्वएवप्रमेहास्तु कालेनाप्रतिकारिणः, मधुमेहत्वमायान्ति तदाऽसाध्या भवन्ति हि mentioned in the ayurvedic classic *Madhavanidan*[12], mentions that when diabetes (प्रमेह) turns into diabetes mellitus (मधुमेह), it becomes incurable. Interestingly, however, disclosure of the presence of insulinomimetic, insulin secretagogue and muscle glucose-uptake increas-

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[26,27]. 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[28,29]. 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[28,29]. Treatment with aqueous extract of MC was also observed to improve the reduced GT in the pancreas of diabetic rats[28].

These observations suggest protective potential 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 aggravated वात (free radical and oxidative stress conditions) in diabetes mellitus (मधुमेह)... कुपित वातेन मधुमेहसम्भवाः[12]. These experimental evidences of potentiation of antioxidant defence and free-radical scavenging properties of karela approve the वात–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[30]. Significant increase in serum total lipids, triglycerides and total cholesterol in alloxanized diabetic rats are observed[31]. Furthermore, increase in activities of lipogenic enzymes in kidney was also noticed. Treatment of alloxonized diabetic rats with MC fruit extract prevented these alterations and maintained all these parameters near normal values[31]. 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[32]. 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[33]. These observations provide evidence of antidyslipidemic 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[18]. In maturity onset diabetic patients, fruit juice of MC has been reported to improve GTT in significant population of the patients studied[34,35]. CCL4 + C6H6 MC soft extract at a dose of 200 mg twice daily in NIDDM patients has shown hypoglycaemic effect[36]. Interestingly, pronounced hypoglycaemia was noticed when the extract was used with half the dose of known hypoglycaemic drugs, metformin or glibenclamide[36]. Baldwa *et al.*[37] 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[38]. A recent review on efficacy and safety of MC suggests that bitter melon may have additive effects when taken with other glucose-lowering agents[39]. 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[39].

Adverse effects

In a study utilizing aqueous extract powder of fresh, unripe whole fruits of MC, no signs of nephrotoxicity and hepatotoxicity were observed in rats[40]. Feeding of diets containing either bitter melon or various fractions isolated by organic solvents could neither affect food intake nor growth in rats[32]. Supplementation of freeze-dried powder to rat food could not show any adverse effect on growth parameters and relative liver weight[41]. On the other hand, adverse effects of bitter melon, like hypoglycaemic coma and convulsion in children, reduced fertility in mice, a favism-like syndrome, increase in gamma-glutamyltransferase and alkaline phosphatase levels in animals and headaches are also observed [39].

Future prospects

India and China are predicted to show the largest increases in terms of diabetes prevalence[42]. '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[43]. 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[44].

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[45]. The ancient lineage and modern scientific scrutiny of multiple beneficial effects of karela in diabetes discussed here therefore, provides enough opportunity for this vegetable to become a promising antidiabetic 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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