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Review

Potential Health Benefits of *Cucurbita ficifolia*: An Updated Review

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Summary. Plant-based medicines are widely used in the treatment of type 2 diabetes and its complications. Among them, pumpkin is one of the popular edible plants which are consumed as vegetables. Recent data suggested that pumpkin has significant medicinal properties that can be utilized in the therapy of diabetes and to lower down associated morbidity. The presence of unique natural edible substances in the pumpkin which includes phytochemicals and antioxidants. Several potential medical benefits such as hepatoprotective, anticancerous, antimicrobial, anti-inflammatory and antiulcer activities are also documented. The purpose of the present article is to discourse the antidiabetic potentials and lipid-lowering properties of pumpkin which may convey further research and a clinical trial with this plant for the betterment of mankind. Additionally, the review insight a short description on distribution, botanical and physical characteristics, ecology and nutritional values.

Key words: *Cucurbita ficifolia*, antidiabetic properties, anti-inflammatory properties, hypolipidemic activity

Introduction

Plants are an important source in the Indian system of medicine and other prehistoric systems in the world. There are many antidiabetic plants or herbs, which may contribute useful foundation in the development of drugs, for the therapy of diabetes mellitus. While numerous herbal remedies have been proposed for the treatment of diabetes mellitus only a few have been scientifically established (1, 2). There were various plant preparations which have been stated in Ayurveda and other aboriginal systems of medicine practicing in India, which are demanded and useful in diabetes mellitus and its complications (3). The use of medicinal plants was recorded in an ancient era over 5000 years ago (4). Still, there has been extensively used in modern medicine and approximately one-fourth of prescribed medicines around the world derived from plants (5). Herbal products are not only used in the dietary purpose but it has a discrete role in the treatment of various disease including liver disorder, an inflammatory disorder, hypertension and other cardiovascular diseases, diabetes mellitus, hyperlipidemia etc (6-10). Diabetes mellitus and its complications are now possess a huge increment in numbers around every country and its prevention and treatments are the priority to reduce the burden of disease. Various plants can be used to treat diabetes and its complications. Among them *Cucurbita ficifolia* (Cucurbitaceae), popularly known as pumpkin is widely used to lower the blood glucose levels still there has not been extensive information about this plant and therefore in this review, we highlighted and updated the useful properties of *Cucurbita ficifolia* such as its antidiabetic potential, anti-inflammatory, and anti-lipidemic effects.

Cucurbita ficifolia and its distribution

Cucurbita ficifolia is a perennial climber cultivated for its edible seeds, fruit, and greens. In India, it is known as "Kumra", while in English it is also called chilacayote, chiverre, fig-leaved gourd, malabar gourd, Malabar squash, pie melon, or shark fin melon. The singularity of the plant doesn't allow it to mate with the other members of its genus. It belongs to the family Cucurbitaceae and it consisted of nearly 100 genera and over 750 species (11). There is marvelous genetic diversity within the family, and the variety of versions for cucurbit species comprises tropical and subtropical regions, temperate locations and arid deserts. Cucurbita consisted of a wide source of secondary metabolites. The cucurbitacins, tetracyclic triterpenoids which possess a bitter flavor in many cucurbits, are thoroughly explored as attractants of beetles such as *Diabrotica speciosa* (12)

In recent years, the biochemical isolation techniques become more sophisticated and advanced, and therefore novel compounds of interest are being confined. Mukherjee et al. (1986) isolated amarinin from Luffa amara that inhibits the growth of cultured plant cells and even gibberellin cannot overcome its action (13). The discovery of *Cucurbita ficifolia* leaves a possibility that its ancestral species might still be prevalent in the eastern Andes. The growth of *Cucurbita ficifolia* is done from northern Mexico to Argentina and Chile. It's also widespread in Europe (France and Portugal) and Asia (India)

Botanical description

It is unaffected with low temperatures nonetheless not to severe frosts. It has five vigorous, considerably angular stems and leaves with 5 to 25 cm petioles which are ovate-cordate to suborbicular-cordale, may or may not white spots on the superficial, and presence of three to five curved or obtuse, apiculate lobules, along with the central one greater than the lateral.

The male flowers are long and pediculate with a campanulate calyx which is 5 to 10 mm long and wide of 5 to 15 x 1 to 2mm linear sepals and a tubular campanulate corolla. The main plant consisted of three stamens. The female flowers have strong peduncles, 3 to 5 cm long, which is ovoid to elliptical, with multilocular ovary: sepals are sporadically foliaceous and a corolla which is bigger than male flowers. The flowers are of a thickened style and with three lobate stigmas.

Physical characteristics, ecology, and nutritional values

Basically, it is flowering from July to September, and the seeds mature from August to October. The flowers are monoecious that means both sexes may present on the same plant and pollinated by insects. The plant is self-fertile and it prefers light, medium and clay soils. *Cucurbita ficifolia* prefers acid, neutral and basic (alkaline) soils to grow and necessitates moist or wet soil.

The plants of *Cucurbita ficifolia* are cultivated in virtually all the mountains of Latin America covering large grounds of about 1000 to 3000 meters. The constraint of growth to elevated grounds with differentiates *Cucurbita ficifolia* from other members of its genus through field observations it has been discovered that average-sized fruits enclose 500 or more seeds while the plant produces beyond 50 fruits. The different parts of *Cucurbita ficifolia* plants are put to numerous food uses and the unripe fruit is consumed boiled as a vegetable, whereas the flesh of the ripe fruit is used for preparing sweets and soft alcoholic drinks. Study research in Chile has revealed that some proteolytic enzymes from the flesh of *Cucurbita ficifolia* can be utilized to treat wastewater from the industrial processing of foods.

Antidiabetic properties of *Cucurbita ficifolia*

Hyperglycemia, the main symptom of diabetes, has its deleterious effect on antioxidant levels in the body (14). This was due to the elevated production of oxygen free radicals and a reduction of antioxidant enzymes (15). Thus, oxidative stress has been reported to play a deleterious role in diabetes mellitus, related to micro & macrovascular complications (16). Therefore a compound with both hyperglycemic and antioxidant properties would be a useful anti-diabetic agent.

Numerous plants and natural products have been studied for anti-diabetic activity in different laboratories. Despite the presence of known antidiabetic medicines in the pharmaceutical market, remedies from medicinal plants are used with success to treat this disease. In modern science, no satisfactory effective drugs are available to cure diabetes (17). Marketed drugs such as sulfonylurea and biguanides used for the treatment of diabetes are extremely expensive or have adverse side effects or contradictions (18, 19). Biguanides (metformin) displays gastrointestinal effects, anorexia, vomiting, B12 malabsorption (20). Therefore, there is a necessity to identify natural resources and explore their potential on several identified targets so that it could help in developing new therapeutics. Several traditional plant therapy for diabetes are used across the world. In recent years, there has seen an increasing interest in traditional plant treatments for diabetes. Herbal drugs and herbal formulations are considered as low toxicity and side effects (21, 22).

Many studies have been carried out previously on *Cucurbita ficifolia* regarding its anti-diabetic potentials, based on that the oral administration of *Cucurbita ficifolia* in humans revealed a significant reduction in blood glucose level (23, 24). Not much work is available on human subjects; however many animal studies potentiate the *Cucurbita ficifolia* fruit extract mediated blood glucose-lowering effect in streptozotocin (STZ) induced rats, along with maintaining glycosylated hemoglobin level, plasma insulin level and hemoglobin level (25). The available literature suggested that the different therapeutic properties are specific for different fruit parts, these fruit parts contain several phytonutrients as evident from the work carried out by (26) Glew et al. reported the *Cucurbita spp* seeds and nuts of *Cyperus esculentus* and analyzed them for their content of essential amino acids, minerals, and trace elements, and fatty acids. Additionally, the study also provided detailed percentages of minerals such as potassium, magnesium, manganese, zinc, selenium, copper, chromium, and molybdenum.

The probable mechanism behind its hypoglycemic effect of cucurbita is the availability of certain gluconeogenic enzyme i.e. glucose-6-phosphatase. Moreover, pectin consumption through oral route has shown a significant effect in glycogen synthetase activity (27). Also, it was reported that the administration of pectin, results in a reduction of phosphorylase activity(28). Basically, three main components of *Cucurbita ficifolia* include polysaccharides, oils and proteins from fruit flesh, ungerminated seeds and germinated seeds respectively (29, 30). These chemicals are concentrated in fruit, this fruit extract was reported to have pronounced hypoglycemic/ anti-hyperglycemic activity.

A compound -D-chiro-inositol was isolated and identified in *Cucurbita ficifolia* and functions as an insulin mediator (31). When alloxan-induced diabetic rats were administered with pumpkin powder there was a significant reduction in serum glucose, cholesterol as well as triglyceride level, C-reactive protein (32). Moreover, the histological examination revealed a prominent increase in the area and number of langerhans islets in the pumpkin treated group. As compared to glibenclamide, polysaccharides component present in the aqueous extract of Cucurbita is known to have a potential hypoglycemic effect in alloxan-induced diabetic rats(33). Polysaccharides extracted from food plants for example from the Cucurbitaceae family it was shown that polysaccharides isolated from pumpkin prevent the formation of advanced glycation end-products and aldose reductase which are involved in the diabetic complications (34). In yet another trial the polysaccharide granules of the plant and its polysaccharide liquid have been administered in the human diabetic subject and the study reported a reduction in both postprandial and fasting glucose levels (35). Moreover, one another group showed, pumpkin methanolic extract alleviates the glucose levels and surge the level of insulin in diabetic rats (36). Table 1 revealed the summary of studies in diabetic human and mice after consuming the pumpkin as an alternative therapy

Clinical studies at a large pace are needed to enhance plant extract's marketability. In developing countries, the fruit is consumed in its entirety, which decreases treatment costs and ensures effective healing. Although pumpkin should be given to diabetic subjects to maintain the glycemic index, the specific type of pumpkin prescribed should be carefully considered.

Table 1. Studies in diabetic models after pumpkin therapy

Authors	Duration of study	Dose intake	Study models	Biological activity	Major results
Azade Bayat et al (37)	8 weeks	Green *Cucurbita ficifolia* (100 g)	20 type 2 diabetes mellitus	Anti-diabetic, anti-lipidemic and anti-inflammatory activity	Beneficial effects on triglyceride, high-density lipoprotein, total cholesterol, fasting glucose, glycosylated hemoglobin, systolic and diastolic blood pressure, and c-reactive protein
Díaz-Flores M et al (38)	One month	*Cucurbita ficifolia* aqueous extract at 200 mg/kg	N= 10, diabetic mice	Anti-diabetic, and anti-oxidant properties	Improve GSH redox state, increasing glutathione pool, GSH, GSH/GSSG ratio. Reduction in glycemia, polydipsia, hyperphagia and plasma lipid peroxidation
Roman-Ramos R et al (39)	33 days treatment	3.31 mg of D-*chiro*-inositol/g of *Cucurbita ficifolia* fruit	Streptozotocin-induced diabetes mice	Antioxidant and anti-inflammatory potential	Increased glutathione and decreased malondialdehyde in the liver. Reduction in the TNF-α and increased IL-6 and IFN-γ in serum. Moreover, increased IL-10, an anti-inflammatory cytokine.
Garcia Gonzalez Jessica et al (40)	Aqueous extract (30 days)	*Cucurbita ficifolia* extract of 200 mg/kg	Alloxan-induced diabetic mice	Hypoglycemic effect, induces, glycogen accumulation	Swows hypoglycemic and liver-protective effects, while also possessing antioxidant and anti-inflammatory properties
Alarcon-Aguilar et al (41)	2 weeks	Freeze-dried juice of *Cucurbita ficifolia* (1000 mg/kg body weight/day)	Five diabetic mice received freeze-dried juice (500 mg/kg)	Hypoglycemic effect	Orally and intraperitoneally, produced acute hypoglycemic effects in mice.
Fortis-Barrera Á et al (42)	30 days	Aqueous extract of *Cucurbita ficifolia* 200 mg/kg/day	Male obese mice (N=10)	*Cucurbita ficifolia* extract modulates systemic chronic inflammation	*Cucurbita ficifolia* extract decreased body weight, mRNA expression and protein levels of TNFR2 and IL-6. Elevated protein levels of IL-10 and IFN-γ
Jiang et al. (43)	4 weeks	50 mg/kg body weight daily	Streptozotocin- and high-fat diet-induced diabetic mice (N=10)	Robust blood glucose-lowering activity	Glyceroglycolipids obtained from pumpkin bodyweight were unaffected, with no potential cytotoxicity.
Yoshinari et al (44)	43 days	Diet composition= high sucrose diet + 1% of pumpkin in total diet	Male Wister rat (N=5)	Hypoglycemic effect and anti-lipidemic activity	Improving glucose tolerance, Insulin level increase, Improve insulin resistance, Suppression of triglyceride accumulation in serum and liver

Reduced (GSH) and oxidized (GSSG) glutathione, tumor necrosis factor receptor 2 (TNFR2), interferon-gamma (IFN-γ), interleukin 6 (IL-6)

Effect of *Cucurbita ficifolia* on the inflammatory marker in type 2 diabetes

An impairment of inflammatory signaling has been commonly associated with various conditions such as insulin resistance and obesity, type 2 diabetes, hypertension, heart disease, and other chronic conditions. The inflammatory hypothesis suggests that the production of proinflammatory cytokines i.e. TNF-α, IL-6 etc. are higher and there has been a reduction in the level of anti-inflammatory cytokines i.e. IL-10, adiponectin, etc. partly because of the reason of these disorders and various related complications (45). Hence, the production of TNFα can lead to the development of insulin resistance and diabetes (46). Insulin receptor phosphorylation and insulin receptor substrate (IRS) phosphorylation by TNFα is the well-defined mechanism of suppressing the insulin-stimulated tyrosine phosphorylation of IRS-1 (47). This whole mechanism leads to alterations in insulin binding to the receptor, along with alteration in signaling, resulting in insulin resistance development (48). Therefore, it is important to ameliorate insulin resistance by supplementation of herb or plant which has known medicinal properties. In a study reported by Acosta-Patino et al on type 2 diabetic patients concerning to the hypoglycemic action of, noted a lowering of blood glucose from 217.2 mg/dl to 150.8 mg/dl after 5 h of *cucurbita ficifolia* extract administration (24). Indeed, in *in vitro* systems, some antioxidants i.e. flavonoids have shown an association with increased interferon production. Thus it could be considered that *Cucurbita ficifolia* is an alternative therapeutic compound for effective treatment of diabetes mellitus, which also has antioxidant and anti-inflammatory properties (49). Table 1 summarizes the therapeutic studies of *Cucurbita ficifolia* which may suggest that pumpkin consumption have a protective effect on antioxidants level and inflammatory response.

Effect of *Cucurbita ficifolia* on lipid profile

As far as treatment of type 1 or insulin-dependent diabetes is concerned, STZ induced rats are known to be an established model. Diabetes is known to be one of the most significant risk factors of coronary heart disease, because of variations in the level of plasma lipid as well as lipoprotein profile (50). There are several drug therapies along with few dietary supplements which result in declining the level of serum lipid, which ultimately reduces the risk of vascular disease and other associated complications (51). Various herbal formulations have been reported which shows both hypoglycemic as well as hypolipidemic effects. An experiment conducted on STZ-induced diabetic rats showed that fruit extract of *Cucurbita ficifolia* not only mimics the effect of insulin but also they show hypolipidemic effect (52). Reports have shown that STZ-induced diabetic rats have approximate twofold higher plasma triglyceride as well as LDL levels. But when doses of *Cucurbita ficifolia* fruit extract were given to the experimental models, there was a considerable decline in the deleterious plasma lipid parameters from the circulation (53). The mechanism behind this would be lipoproteins hydrolysis followed by their uptake as well as metabolism by means of various tissues/cells. Plant-like *Momordica charantia* is reported to have thyrogenic effect, and the phytoconstituents of *Cucurbita ficifolia* shows very much similarity index with *Momordica charantia*, thus it is believed that *Cucurbita ficifolia* may also have certain thyrogenic effect (54). Ogbonna et al. reported a positive linear relationship between glycosylated hemoglobin and thyroid function in type 2 diabetes which suggested that high blood glucose causing a risk for thyroid dysfunction (55). The effect ultimately results in the retention of blood glucose from circulatory system into the body cells/tissues. The glucose availed by the cells, gets involved in adenosine triphosphate production along with triglyceride mobilization to specific cells/tissues and ultimately reducing the level of deleterious lipid parameters in the blood. High-density lipoprotein cholesterol has a potential role of picking up low density lipoprotein and other triglycerides from the circulation and transferring them to the liver for elimination (56). Gossell-Williams et al reported that pumpkin seed oil improves the lipid profile in female rats (57). Hypertriglyceridemia and hypercholesterolemia are two major factors that are controlled by *Cucurbita ficifolia* fruit extract (37, 44). Active fractionation of *Cucurbita*

ficifolia fruits could be purified to establish standards for providing a therapeutic mechanism, related to hypoglycemic and hypolipidemic effects (58).

The mechanism behind this would be due to the presence of a considerable amount of pectin in *Cucurbita ficifolia*, pectin plays a significant role in promoting excretion of bile salts excretion. Pectin also has lipoprotein lipase activity, which is involved in lowering the serum lipid levels (59). Cholesterol removal by assimilation, followed by their accumulation in cell membranes along with inhibiting hydroxymethylglutarylCoA reductase and deconjugating bile acids could be a possible mechanism for the same (60). Dchiro inositol along with a good amount of dietary fibers could provide good results in lowering the level of *high-sensitivity C-reactive protein*. Pumpkin is known to have a significant effect in increasing glutathione activity, reduction of lipid peroxidation index involving thiobarbituric acid reactive substances and malondialdehyde (25). Reduction in oxidative stress parameters results in decreasing peripheral vascular resistance as well as cardiovascular disorders.

Evidence has been recorded, which showed a significant reduction in blood sugar level as well as the level of glycosylated hemoglobin. *Cucurbita ficifolia* also has some other characteristics which showed that its intake positively influences pancreatic β cell number, distribution, etc. The mechanism behind this would be inhibition of lipid peroxidation, along with antioxidant, antiglycemic and antilipidemic activity, because of the availability of phenols in *Cucurbita ficifolia* (61). When the same amount of doses was administered in diabetic subjects, it was observed that natural extraction of *Cucurbita ficifolia* was more significant as compared to chemically extracted *Cucurbita ficifolia*. The reason for the results obtained would be the availability of natural components/active compounds like flavonoids, alkaloids, polyphenolic components, glutathione peroxidase, and superoxide dismutase in *Cucurbita ficifolia* natural extract (62).

Other medicinal uses

The seeds Pumpkin (*Cucurbita pepo* L.) of this squash serve as an anthelmintic medicine (63). The husked seeds are crushed and made into a fine flour which is then mixed with water to form an emulsion and is then eaten. Subsequently, the administration of a purgative is essential to banish the tapeworms or parasites. Although this therapy is not as much powerful as that of the root of Dryopteris felix-mas, however, it's more protective for expectant mothers, incapacitated patients and kids. Pumpkin seed extracts were evaluated to control the gastrointestinal nematode infections. It is an economical alternative to the current treatment and promising a novel drug candidate (63).

Conclusions

This review highlighted the antidiabetic properties and to some extend lipid-lowering effects of pumpkin on diabetic animal and human model and suggested that pumpkin has positive effects on glycemic control, antioxidant levels, anti-inflammatory properties and lowering lipid profile. Indeed, more studies are needed to explore the mechanistic approach of the active ingredient of pumpkin that can be a potential area of future research.

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