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The protective effect of Momordicacharantia L

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ABSTRACT: Diabetes mellitus is the most common disorder in developed and developing countries, and the disease is increasing rapidly in most parts of the world. It has been estimated that up to one-third of patients with diabetes mellitus use some form of complementary and alternative medicine. Diabetes mellitus is a chronic disorder of the carbohydrate, lipid and protein metabolism that contributes to several kinds of complications including male defective reproductive capacity. In fact, uncontrolled diabetes mellitus is frequently linked with sexual and reproductive dysfunctions in male humans and experimental animals in the form of sterility, erectile dysfunction, reduced libido, semen alterations due to decreased serum androgen levels and impairment of spermatogenesis.

One plant that has received the most attention for its anti-diabetic properties is the bitter melon, Momordicacharantia (M. charantia), commonly referred to as bitter gourd, karela and balsam pear. Its fruit is also used for the treatment of diabetes and related conditions amongst the indigenous populations of Asia, South America, India and East Africa. Abundant pre-clinical studies have documented in the Anti-diabetic and hypoglycemic effects of M. charantia through various postulated mechanisms. However, clinical trial data with human subjects are limited and flawed by poor study design and low statistical power.

Keywords:hypoglycemic-sterility-a chronic-mellitus-alternative medicine

I. MATERIALS & METHODS:

Male adult rats of Sprague-Dawley strain were assigned to four groups, eight rats in each; control group, STZ-induced diabetic group (in which, diabetes mellitus was induced by an intraperitoneal injection of a single dose of streptozotocin (STZ) (60 mg/Kg body weight) after 18 hours fasting), bitter melon treated group (given 50 mg/kg Bwt /day of bitter melon fruit extract by gavage), STZ-induced diabeticandbitter melons treated group (given TCDD at the dose of 100 ng/kg Bwt /day and 50 mg/kg Bwt /day of ginger root extract by gavages). After four weeks of treatment, the rats were weighed and sacrificed where testis were removed and weighted, and the relative testis weights were calculated. The testes were processed for routine paraffin embedding and staining. Tissue sections were examined for different morphometric and histopathological changes of the testis.

2-The Aim:

This study was designed to evaluate the potential protective/ameliorative effect of bitter melon extract administration on testicular damage induced by experimental diabetes in rats.

3- Introduction

Diabetes mellitus is considered as one of the five leading causes of death in the world**(Joseph and Jini,2011a)**. DM is caused by a deficiency in the secretion of insulin and the inability of tissues to efficiently respond to insulin, causing chronic hyperglycemia affecting all organs.The main types of DM are insulin-dependent (or type I) that characterized by a total lack of insulin and insulin-independent (or type II), for which obesity is a risk factor **(Kazuya et al., 2002; ADA, 2005)**.

Diabetes mellitus is a major global health concerning with a projected rise in prevalence from 171 million in 2000 to 366 million in 2030**(Shaw et al.,2010)**. It is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia)**(Patel et al.,2012)**. Being a major degenerative disease, diabetes is found in all parts of the world, and it is becoming the third most lethal disease of mankind and increasing rapidly**(Ogbonnia et al.,2008)**. It is the most common endocrine disorder, affecting 16 million individuals in the United States and as many as 200 million individuals worldwide**(Sharma et al.,2012)**.

DM is a chronic disorder of the carbohydrate, lipid and protein metabolism that contributes to several kinds of complications including male defective productive capacity **(Schneider, 2004)**. In fact, uncontrolled DM is frequently linked with sexual and reproductive dysfunctions in male humans and experimental animals in the form of sterility, erectile dysfunction, reduced libido, semen alterations due to decreased serum androgen levels and impairment of spermatogenesis **(Steger and Rabe, 1997; Baccettiet al., 2002; Betancourt-Albrecht and Cunningham, 2003; Ballester et al., 2004; Scarano et al., 2006; Agbaje et al., 2007; Cameron and Cotter,2007)**.

4-Medicinal plants

Medicinal plants and its products continue to be an important therapeutic aid for alleviating the ailments of humankind**(Joseph and Raj,2010b; Joseph et al.,2012; Singh et al.,2012)**. Herbs for Diabetes treatment are not new. Since ancient times, plants and plant extracts were used to combat diabetes. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter. The World Health Organization (WHO) has listed 21 000 plants, which are used for medicinal purposes around the world. Among them, 150 species are used commercially on a fairly large scale**(Joseph and Jini,2011a; Zohary and Hopf, 2000)**.

Momordicacharantia (M. charantia), also known as bitter melon, karela, balsam pear, or bitter gourd, is a popular plant used for the treating of diabetes-related conditions amongst the indigenous populations of Asia, South America, India, the Caribbean and East Africa**(Cefalu et al., 2008; Cousens, 2008)**. Its fruit has a distinguishing bitter taste, which is more pronounced as it ripens, hence the name bitter melon or bitter gourd. Biochemical and animal model experiments have produced abundant data and hypotheses accounting for the anti-diabetic effects of M. charantia. In comparison, clinical studies with human subjects are sparse and low quality in design.

Momordicacharantia is a member of Cucurbitaceae family known as bitter melon. It is grown in tropical and subtropical countries **(Raja et al., 2012)**. This plant has traditionally been used as herbal medicine **(Bano et al., 2011)**. The fruit contains charantin, momordium, carbohydrates, mineral matters, ascorbic acid, alkaloids, and glucosides. The ethanolic extract of the fruit showed the presence of proteins, alkaloids, tannins, steroids, glycosides and carbohydrates and two classes of saponins known as cleanane and oleanane**(Popovich et al., 2010; Patel et al., 2011)**. Bitter melon has a positive effect on diabetes, blood pressure, immune system, pneumonia, cancer and infection **(Lee-Huang et al.,2000; Basch et al., 2003; IlikciSagkan, 2013)**. The extract of fruits has a protective effect on diabetic kidney disease due to its antioxidant properties **(Teoh et al., 2010)**. Also, it can stimulate insulin secretion and induce glucose uptake in the liver of diabetic rats **(Garau et al., 2003)**.

5-the relationship of Momordicacharantia

Regarding the relationship of Momordicacharantia(bitter melon) to the reproductive system, review of the publications reveals a constant attention on the female rats. The seed has been shown to induce abortion in gestational mice. The roots documented to possess uterine stimulant effect also reputed for its aphrodisiac property **(Koller, 2009)**. The fruit and leaf have exhibited an in-vivo female antifertility effect; even though the fruit was not found to induce miscarriage, safety a margin in pregnancy was yet to be established **(Raintree Nutrition, Tropical Plant Database, 2008)**. On the male reproductive effect of this plant; there exists a lack of literature while almost none on the cytometric quantification (counting and measuring of cells). However, in one study various extracts (ether, benzene, and alcohol) of MC seeds were administered orally and intraperitoneally to male rats for 35 days. All three extracts demonstrated prevailing antispermatogenic activity, the most potent being ethanol extract. Again the effects on the male rats were assessed by measuring the testicular weights and biochemical assay

6-**Plant-based anti-diabetic medicine**

Plant-based medicine has been used cost-effectively worldwide to treat diabetes. In fact, in many parts of the world, especially poor countries, this may be the only form of therapy available to treat diabetic patients. There are several reviews by different authors about anti-diabetic herbal plants**(Malviya et al.,2010; Ayodhya et al.,2010; Joseph and Jini,2011a; Joseph and Jini,2011b; Patel et al.,2012)**. Ayurveda and other traditional medicinal systems for the treatment of diabetes describe some plants used as herbal drugs. Hence, they play an important role as alternative medicine due to fewer side effects and low cost. The active principles present in medicinal plants have been reported to possess pancreatic β cells regenerating, insulin-releasing and fighting the problem of insulin resistance**(Kavishankar et al.,2011)**. Hyperglycemia is involved in the etiology of the development of diabetic complications. Hypoglycemic herbs increase insulin secretion, enhance glucose uptake by adipose or muscle tissues and inhibit glucose absorption from intestine and glucose production from liver**(Hui et al.,2009)**. Insulin and oral hypoglycemic agents like sulphonylureas and biguanides are still the major players in the management, but there is quest for the development of more effective anti-diabetic agents.

7- **Plant description**

MomordicacharantiaorM. Charantia (bitter melon or bitter gourd) (Figure 1) is a flowering vine in the family Cucurbitaceae. It is a tropical plant that is widely cultivated in Asia, India, East Africa, and South America for its intensely bitter fruits that are commonly used in cooking and as a natural remedy for treating diabetes**(Abascal and Yarnell,** 2005**)**. It is a climbing perennial that usually grows up to 5 m, and bears elongated fruits with a knobbly surface. It is a useful medicinal and vegetable plant for human health and one of the most promising plants for diabetes**(Lee et al.,2009)**.

Figure 1: M. charantiaplant.

8-Nutrient profile

Bitter melon is a powerful nutrient-dense plant composed of a complex array of beneficial compounds. These include bioactive chemicals, vitamins, minerals and antioxidants which all contribute to its remarkable versatility in treating a wide range of illnesses. The fruits contain high amounts of vitamin C, vitamin A, vitamin E, vitamins B1, B2, and B3, as well as vitamin B9 (folate). The caloric values for leaf, fruit and seed were 213.26, 241.66 and 176.61 Kcal/100 g respectively**(Bakare et al.,2010)**.

The fruit is also rich in minerals including potassium, calcium, zinc, magnesium, phosphorus, and iron, and is a good source of dietary fiber (bitter melon "monograph", 2008). Medicinal value of bitter melon has been attributed to its high antioxidant properties due in part to phenols, flavonoids, isoflavones, terpenes, anthroquinones, and glucosinolates, all of which confer a bitter taste**(Snee et al.,2011)**.

9- Phytochemistry

The main constituents of bitter melon which are responsible for the antidiabetic effects are triterpene, proteid, steroid, alkaloid, inorganic, lipid, and phenolic compounds**(Budrat and Shotipruk, 2008; Saeed et al.,2010)**. Several glycosides have been isolated from the M. charantia stem and fruit and are grouped under the genera of Cucurbitane-type triterpenoids**(Chang et al.,2006; Tan et al.,2008)**. In particular, four triterpenoids have AMP-activated protein kinase activity which is a plausible hypoglycaemic mechanism of M. Charantia**(Tan et al.,2008)**.

M. charantia fruits consist glycosides, saponins, alkaloids, reducing sugars, resins, phenolic constituents, fixed oil and free acids**(Liu J et al.,2009)**. M. charantia consists the following chemical

constituents including alkaloids, charantin, charine, cryptoxanthin, cucurbitins, cucurbitacins, cucurbitanes, cycloartenols, diosgenin, elaeostearic acids, erythrodiol, galacturonic acids, gentisic acid, goyaglycosides, goyasaponins, guanylate cyclase inhibitors, gypsogenin, hydroxytryptamines, karounidiols, lanosterol, lauric acid, linoleic acid, linolenic acid, momorcharasides, momorcharins, momordenol, momordicilin, momordicin, momordicinin, momordicosides, momordin, momordolo, multiflorenol, myristic acid, nerolidol, oleanolic acid, oleic acid, oxalic acid, pentadecans, peptides, petroselinic acid, polypeptides, proteins, ribosome-inactivating proteins, rosmarinic acid, rubixanthin, spinasterol, steroidal glycosides, stigmasta-diols, stigmasterol, taraxerol, trehalose, trypsin inhibitors, uracil, vaccine, v-insulin, verbascoside, vicine, zeatin, zeatin riboside, zeaxanthin, zeinoxanthin amino acids-aspartic acid, serine, glutamic acid, thscinne, alanine, g-amino butyric acid and pipecolic acid, ascorbigen, b-sitosterol-d-glucoside, citrulline, celastrol, flavochrome, lutein, lycopene, pipecolic acid. The fruit pulp has soluble pectin but no free pectic acid. Research has found that the leaves are nutritious sources of calcium, magnesium, potassium, phosphorus and iron; both the edible fruit and the leaves are great sources of the B vitamins**(Kumar et al.,2010)**.

10-Bioactive compounds

Based on the multitude of medical conditions that bitter melon can treat, scientists are more and more interested in studying its bioactive compounds and their actions on the body. However, as many studies report, there has been substantial emphasis on the anti-diabetic compounds and their hypoglycemic properties**(Islam et al.,2011; Hazarika et al.**, **2012)**. A number of reported clinical studies have shown that bitter melon extract from the fruit, seeds, and leaves contain several bioactive compounds that have hypoglycemic activity in both diabetic animals and humans**(Fuangchana et al.**, **2011; Wehash et al.**, **2012)**.

11- **Charantin**

Charantin is a typical cucurbitane-type triterpenoid in M. charantia and is a potential substance with antidiabetic properties**(Krawinkel and Keding et al.**, **2006; Patel et al.**, **2010)**. Pitiphanponget al. demonstrated that charantin could be used to treat diabetes and can potentially replace treatment**(Pitiphanpong et al.**, **2007)**. It is a mixture of two compounds, namely, sitosteryl glucoside and stigmasterylglucoside**(Pitiphanpong et al.**, **2007)**. Chen et al. isolated 14 cucurbitane triterpenoids, kuguacins, including two pentanorcucurbitacins, one octanorcucurbitacin, and two trinorcucurbitacins, along with six known analogues from the vines and leaves of M. charantia**(Chen et al.**, **2009)**. The charantin from bitter melon fruit was extracted and estimated by high-performance thin layer chromatographic method**(Thomas et al.**, **2012)**.

Studies have reported that the compound is more effective than the oral hypoglycemic agent tolbutamide**(Cousens, 2008)**. In a study, two aglycones of charantin were isolated and identified as sitosterol and stigmastadienol glycosides, however, when tested separately for their hypoglycemic effects in vivo, these two constituents did not produce any notable changes in blood glucose levels**(Harinantenaina et al.**, **2006)**. This is an indication that charantin may contain other specific components, yet to be identified, that are responsible for the hypoglycemic activity observed in diabetics.

12- Polypeptide-p

Bitter melon is one of the most commonly used vegetable that contains polypeptide-p and is used to control diabetes naturally**(HellolifePlypeptide-P (plant insulin)-2008)**. Polypeptide-p or p-insulin is an insulin-like hypoglycemic protein, shown to lower blood glucose levels in gerbils, langurs, and humans when injected subcutaneously**(Tayyab et al.**, **2012)**. The p-insulin works by mimicking the action of human insulin in the body and thus may be used as plant-based insulin replacement in patients with type-1 diabetes**(Paul and Raychaudhuri 2010)**. Recently, Wang et al. have cloned and expressed the 498 bp gene sequence coding for the M. charantia polypeptide p gene and have also proved the hypoglycemic effect of the recombinant polypeptide in alloxan induced diabetic mice**(Wang et al.,2011)**. The oral intake of the extract from bitter melon seeds does produce hypoglycemic effects in streptozotocin (STZ) induced type-1 diabetic rats**(Wehash et al.**, **2012)**. This indicates that compounds in bitter melon seeds other than p-insulin may also be effective in the treatment of type-1 diabetes.

- 13- **Other components**

Many other bitter melon constituents have been identified and isolated by various extraction techniques. The first study to show the in a vivo hypoglycemic activity of the major compounds of bitter melon was done by a group of Japanese scientists. They isolated 11 compounds by fractionation of a methanol extract from dried bitter melon fruits. The structure of three cucurbitane triterpenoids was determined, as well as two other major compounds that were tested and shown to significantly lower blood glucose levels in diabetic mice**(Lee et al., 2009)**. Four compounds that may be responsible for the bitter taste of the plant were isolated

and identified as momordicosides K and L, and momordicinesI and II. The last two compounds isolated were identified as sitosterol and stigmastadienol, the aglycones of charantin**(Harinantenaina et al., 2006)**.

14-Medicinal propertiesofM. charantia

Bitter melon is traditionally known for its medicinal properties such as antidiabetic, anticancer, anti-inflammation, antivirus, and cholesterol lowering effects. It contains many phenolic compounds that may have the potential as antioxidant and antimutagen**(Budrat and Shotipruk,2008; John et al., 2010)**. The fruit, stems, leaves and roots of bitter melon have all been used in traditional medicine to help treat ailments such as hyperlipidemia, digestive disorders, microbial infections and menstrual problems**(Yibchok-Anun et al., 2006)**. Bitter melon has been shown to possess powerful antiviral properties that can stimulate the immune system and activate the body's natural killer cells to help fight off viruses such as white spot syndrome virus and human immunodeficiency virus**(Bot and Ekpoma, 2004; Grover and Yadav, 2004; Balasubramanianet al.,2007)**. Studies have also shown that bitter melon has anti-carcinogenic properties and can be used as a cytotoxic agent against many types of cancer**(Haqueet al.,2011)**. Ray et al. showed that the extract of bitter melon modulates signal transduction pathways for inhibition of breast cancer cell growth and can be used as a dietary supplement for prevention of breast cancer**(Ray et al.,2010)**.

The bitter melon extract can also be used as a broad-spectrum antibacterial agent to fight off infections caused by Escherichia coli, Salmonella, Staphylococcus aureus, Staphylococcus, Pseudomonas, and Streptobacillus(**Saeed and Tariq,2005**). Also, the plant possesses antihelmintic properties, which are effective in the treatment of malaria. Traditionally, bitter melon has also been used as an abortifacient agent used to induce abortions. Therefore, pregnant women are advised to avoid consumption of the plant**(Grover and Yadav, 2004)**. The extract of the seed also has antispermatogeniceffect**(PatilandPatil, 2011)**.

II. RESULTS

2-1Body and testis weights:

As shown in **Table 1**, it was observed that diabetes caused a highly significant reduction in the body and testis weights when compared to both control and diabetes&bitter melon extract treated groups. The combined administration of bitter melon extract along with diabetes caused an improvement in such parameters towards the control values with no significant differences. Because the body and testicular weights decreased together, the relative testis weight did not much change from the control groups. Nonetheless, the lowest relative testis weight was seen in diabetic group when compared to both, control value and diabetic&bitter melon extract treated groups. Combined administration of bitter melon extract along with diabetes showed that the mean values of the above parameters were not significantly different from those in control groups.

Testicular size, diameter of seminiferous tubule and germinal epithelial height (Table 2):

As shown in **Table 2**, following diabetes alone, there was a decrease in all parameters, which was highly significant when compared with those of both control group and diabetic&bitter melon extract treated groups. After combined administration of bitter melon extract along with diabetes, there was an improvement in such parameters towards the control values with differences which were not significant. Moreover, combined administration of bitter melon extract along with diabetes revealed that the mean values of the above parameters were not significantly different from those in the control groups.

2-2Testosterone assay:

The level of serum testosterone showed a significant decrease in the group of rats with diabetes (0.40 ± 0.007) when compared with the rats of the control groups (0.49 ± 0.01and 0.50 ± 0.012). Moreover, combined administration of bitter melon extract along with diabetes showed that the serum testosterone rose nearly to the control value (0.47 ± 0.009) **(Table 2)**.

Table 1: showing body weight, testis weight, and relative boy/testis weight.

Groups	Initial Body weight (g)	Final Body weight (g)	Body weight gain (g)	Testis weight (g)	Relative testisweight (%)
Control	269.2 ± 8.9	320.9 ± 12.4	51.7 ± 3.5	1.58 ± 0.05	0.49 ± 0.01
Bitter melon extract	268.9 ± 8.4	322.4 ± 12.6	53.5 ± 4.2	1.61 ± 0.06	0.50 ± 0.012
Diabetes	270.0 ± 9.5[a,c]	308.7 ± 10.1	38.7 ± 4.6	1.25 ± 0.03[a,c]	0.40 ± 0.007[b,d]
Diabetes + bitter melon extract	271.2 ± 9.1	318.6 ± 11.7	47.4 ± 3.6	1.49 ± 0.04	0.47 ± 0.009

a- $P < 0.001$ compared to control.

b- $P < 0.01$ compared to control.

c- P< 0.01 compared to diabtic&bitter melon extract treated group.
d- P< 0.05 compared to diabtic&bitter melon extract treated group.

Table 2: showing length and width of the testis, diameter and germinal epithelial height of the seminiferous tubules, and Testosterone serum level.

Groups	Length of testis (cm)	Width of testis (cm)	Seminiferous tubule diameter (um)	Germinal epithelial height (um)	Serum Testosterone (ng/ml)
Control	2.22 ± 0.15	1.27 ± 0.09	257.44 ± 12.68	87.72 ± 7.1	2.81 ± 0.42
Bitter melon extract	2.25 ± 0.17	1.29 ± 0.1	260.1 ± 12.95	89.31 ± 7.4	2.92 ± 0.44
Diabetes	1.94 ± 0.12[b,d]	1.02 ± 0.06[b,d]	205. 74 ± 11.84[a,c]	67.29 ± 8.6[a,c]	1.7 ± 0.32
Diabetes + bitter melon extract	2.18 ± 0.13	1.24 ± 0.08	248.21 ± 12.75	80.76 ± 7.9	2.45 ± 0.39

a- P < 0.001 compared to control.
b- P < 0.01 compared to control.
c- P< 0.01 compared to diabtic&bitter melon extract treated group.
d- P< 0.05 compared to diabtic&bitter melon extract treated group.

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