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Medicinal and anti-oxidant effects of Bitter Melon (*Momordica charantia*) in the treatment of diabetic cardiomyopathy

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Abstract

Obesity is a major risk factor for diabetes mellitus (DM), which is a major global metabolic health disorder currently affecting over 460 million people and this number is rising rapidly. Heart failure (HF) is the major cause of death among diabetic patients. The disorder is due to elevated blood glucose or hyperglycemia (HG) beyond physiological level, which in turn leads to a number of long-term or end-organ complications over time and over 80% of all diabetics will eventually die from either HF or cardiomyopathy if left untreated. Treatment of DM is very costly and as such, patients turn to non-pharmacological or alternative forms of treatment, including weight loss, diet modifications and plant-based medicines, which are more cost-effective. There are several medicinal plants, which are currently used to treat for DM and they are known to exhibit anti-diabetic properties. One such plant is *Momordica charantia*, or bitter melon, which is used in many tropical countries as a traditional functional food and medicine, especially for the treatment of obesity, DM, hypertension and cancer. This review is related to the anti-oxidant beneficial effect of *Momordica charantia* in the treatment of diabetic cardiomyopathy (DCM). The beneficial effects of *Momordica charantia* in the treatment of obesity, diabetes and cardiovascular diseases (CVDs) have been reported in clinical and experimental animal studies and this review addresses some of these useful effects. However, the cellular and molecular mechanisms underlying its therapeutic antidiabetic effects of *M charantia* via its anti-oxidant activities are not fully known and further research studies need to be done.

Keywords: Diabetes mellitus, cardiomyopathy, heart, hyperglycemia, *Momordica charantia*

Introduction

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Diabetes mellitus (DM) has been recognized as a major cause of morbidity and mortality for decades [1]. Hyperglycemia (HG) plays a significant role in the development of diabetic cardiomyopathy (DCM). The exact mechanisms underlying the disease remain incompletely clear. The burden of chronic diseases, including cardiovascular diseases (CVDs), renal disease, obesity, diabetes and cancers are rapidly increasing worldwide. These non-communicable diseases (NCDs) have become a major health concern to mankind, not just in developed countries but also in developing countries [2]. The increasing global prevalence of obesity and diabetes poses a huge challenge to health services and it reduces the quality of life of the patients primarily due to CVDs, which are inextricably linked to microvascular complications. As declared by the World Health Organization (WHO), along with the International Diabetes Federation IDF), obesity and DM are currently the modern life-style-induced diseases of the 21st century. According to the IDF, the prevalence of diabetes worldwide had already reached 420 million in 2016 and the estimates for 2030 could reach 630 million people [1]. Six of the top 10 countries with the highest prevalence of diabetes (in adults aged 20 to 79 years) are in the Middle East and they are the United Arab Emirates (UAE), Kuwait, Lebanon, Qatar, Saudi Arabia and Bahrain [3]. The UAE is 16th in the global ranking for countries with highest prevalence of diabetes [4]. In 2000, one study conducted at Al Ain City estimated that 25 percent of UAE nationals were diagnosed with the disorder as compared to 19 percent of the non-nationals [5]. This chronic disease and its complications pose a significant financial burden on the global healthcare systems. The average, in terms of medical expenses, in comparison to a person without diabetes, is more than twice as high for a person with diabetes. The average annual cost of diabetes care in UAE was estimated to be $3,995 (USAD) per patient, rising to as high as $6,175 in patients who have developed complications. Globally, it costs the Governments of the world about one trillion USAD$ to diagnose, treat and care for diabetic patients in order to provide them with a better quality of life [4].

Complementary and Alternative Medicines

Herbs and other dietary supplements are used as complementary and alternative medicine either to avoid or to reduce the use of Western orthodox medical treatment. A recent study showed that up to 30% of diabetic patients use complementary and alternative medicines [6]. Since the ancient times, many plants and their extract were used as a treatment for numerous diseases, including diabetes. The 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 [7]. Bitter melon, which is also known as *Momordica charantia (M. charantia),* is a well-known plant used for treating and preventing diabetes amongst the populations of many tropical countries from Asia, South America, India, the Caribbean and East Africa [6]. *M. charantia*, is also rich in minerals, including potassium, calcium, zinc, magnesium, phosphorus and iron, and is a good source of dietary fiber and vitamins [8]. The medicinal value of bitter melon has been attributed to its high antioxidant properties due in part to phenols, flavonoids, isoflavones, terpenes, momordicine, anthroquinones and glucosinolates, all of which confer a bitter taste [9]. Figure 1 illustrates the bitter melon plant and its green fruits.

Figure 1. A photograph showing the bitter melon plant and its green fruits.

It has been found that *M. charantia* has a significant antidiabetic as well as hypo-lipidemic activity so that it can be used as an adjuvant along with allopathic treatment of medicine to treat diabetes as well as to delay the late complications associated with diabetes, including CVDs [6]. Biochemical and animal model experiments have produced abundant data and hypotheses accounting for the anti-diabetic effects of *M. charantia.* This review summarizes the active

components and medicinal properties of *M. charantia*, especially the activities and mechanisms of its anti-diabetic effect with particular reference to heart failure (HF). Moreover, this review will provide an overview regarding the use M. *charantia* and its medicinal potency responsible for the hypoglycemic and hypo-lipidemic activities in animal and human subjects.

M. charantia to Treat Diabetic Mellitus-Induced Complications

Insulin has a vital role in the regulation of various aspects of cardiovascular metabolism and function. In fact, the human heart produces and uses between 3.5 and 5 kg of adenosine triphosphate (ATP) daily to pump blood around the body. The energy generation depends on the cardiac environment, including coronary flow, blood substrate supply, hormones and nutritional status [10-12]. DM is characterized by reduced glucose and lactate metabolism and increased fatty acid (FA) metabolism [13]. In the diabetic heart, the myocardial glucose transport is impaired because of decreased myocardial concentration of glucose transporter type 1 (GLUT1) and type 4 (GLUT4) protein and mRNA level [14]. A second mechanism of reduced glucose oxidation is via the inhibitory effect of FA oxidation on pyruvate dehydrogenase complex due to high circulating free fatty acids (FA) [15]. Insulin induces glucose uptake in cardiomyocytes by binding to insulin receptor (IR). IR undergoes auto-trans-phosphorylation, which initiates a signaling cascade initiated by tyrosine phosphorylation of insulin receptor substrates (IRS), followed by phosphorylation of phosphatidyl-inositol-3 kinase (PI3K), phosphoinositide-dependent kinase 1 (PDK1), Akt, and protein kinase C (PKC). These events lead the glucose transporter type 1 (GLUT1) and type 4 (GLUT4) translocation to the membrane to facilitate glucose uptake into the cell. In the heart, contractile mediated-translocation of GLUT4 represents the major mechanism that regulates glucose entry in the beating heart, with GLUT1 playing a lesser role [16]. Insulin resistance (IR) and hyperinsulinemia are recognized as risk factors for DCM [17]. In hyperinsulinemia and insulin resistance, a disturbance of insulin-mediated glucose metabolism occurs and it can significantly worsen metabolic efficiency of both skeletal and cardiac muscles. Insulin affects the diabetic heart by both systemic metabolism abnormalities and direct effects on insulin signaling pathways that are intrinsic to the cardiac tissue [18]. In the evolution of insulin resistance, the initial change that develops in the hearts of animal models is the impairment in the ability of insulin to increase glucose transport [19]. A recent study revealed that IR is associated with cardiac contractile dysfunction. The authors of the study generated a new insulin resistant animal rat model on high cholesterol fructose (HCF) diet. HCF diet induced IR on both metabolic response tissue and the heart as well. These findings illustrate that IR is associated with metabolic alteration and consequently leading to the development of DCM [19]. Circulating FA and triglyceride (TG) are increased by enhanced lipolysis in adipose tissue and lipoprotein synthesis in liver, resulting in hyperglycemia and insulin resistance. When the FAs exceed the oxidative capacity of the heart, the FAs are converted to lipid like TG or ceramide, which can lead to lipo-toxicity and cell apoptosis [19]. Thus, DM leads to increased rates of FA oxidation and decreased rates of glucose oxidation. Specific knowledge about *M. charantia* may provide insight for strategic consumption and sustainable use of the plant. The alternate medicine system is now gaining strong momentum with the knowledge of active principles identified from plant species. *M. charantia* possesses significant anti-obese, antidiabetic and hypolipidemic activities so that it can be used as an adjuvant, along with allopathic medicine to treat diabetes and other related-disorders as well as delaying the late complications of diabetes. Thus, the use of *M. charantia,* as treatment, is not a first choice in diabetic cardiomyopathy but only an alternative [19, 20].

Chemical Composition of M. charantia and Antidiabetic Effects

M. Charantia is a flowering vine in the family cucurbitaceous [20]. The green fruit of *M. charantia* is rich in fibres, proteins, vitamin C, carotenoid, phenolic content, and anti-oxidant activity, including the presence of caffeic and celuic acids and a number of cations, including sodium, potassium, calcium, magnesium, manganese, copper and zinc. Among the cations, the fruit had significantly more sodium and

calcium compared to the other cations present [20]. *M. charantia* is composed of plant-based proteins, which have a hypoglycemic activity similar to insulin [21]. In diabetes, glucose uptake is impaired and the chemical impact of *M. charantia* leads to the activation of a protein called AMPK, which regulates fuel metabolism and enables glucose uptake. It was found that when *M. charantia* is taken continuously over a long period, it increases the ability to substitute the insulin in the body [22, 23]. According to a study done on streptozotocin-STZ-induced type 1 diabetes (T1DM), oral administration of the *M. charantia* extract significantly lowered the blood glucose level. Also, blood glucose was controlled by stimulating insulin secretion from β cells in pancreatic islets isolated from obese-hyperglycemic mice [7]. Another study demonstrated that an aqueous extract *M. charantia* fruit also has hypoglycemic activity in cyproheptadine-induced diabetic mice [24]. Orally administered *M. charantia* aqueous extracts lowered glucose concentrations independently of intestinal glucose absorption and involved extra-pancreatic effects [25, 26]. In clinical trials, polypeptide-P isolated from the bitter melon was jreported to have hypoglycemic activity [27]. With the chronic administration of the *M. charantia* fruit juice at 20 mg/kg orally, blood glucose tolerance of alloxan-induced rats was ameliorated significantly from day 7 to day 22, and was reduced to normal levels [28]. It was stated that the mechanism of action by which *M. charantia* extracts control blood glucose level is via both intra- and extra-pancreatic mechanisms involving beta cells [29]. Additionally, it was found that *M. charantia* can affect the liver by reducing glycogenesis, enhancing peripheral glucose utilization and increasing serum protein levels [30].

Hyperglycemia, Oxidative Stress and Diabetes Mellitus

HG results in tissue damage by both acute reversible changes in cellular metabolism and irreversible changes in macro-molecules [31]. HG can cause long-term damage to multiple organs, resulting in severe complication [32, 33]. The microvascular system is a key target of HG-induced damage to small blood vessels which in turn can initiate systematic complication [34, 35]. One major contributor to HG-induced diabetic abnormalities is increased oxidative stress (OS) [36]. The possible biochemical mechanism involves increased OS [37] which is characterized by the imbalance between free radicals and antioxidants. This imbalance could be a result of an increased free radical production and/or decreased antioxidants capacity [38]. The imbalance between free radicals and antioxidant systems gives rise to free radical-mediated damage mainly via ROS [39]. ROS can also cause damage to the mitochondria together with poly (ADP-ribose) polymerase-1 (PARP) activation, leading to the inhibition of the cytosolic enzyme glyceraldehyde-3phosphate dehydrogenase (GAPDH). This inhibition initiates a series of cellular processes by activation pathways leading to HG-induced cellular damage [40]. Inhibition of GAPDH diverts glucose from glycolytic pathways to alternative biochemical pathways, including polyol pathway and AGE formation [41]. Under normal physiological conditions, cellular glucose is predominantly phosphorylated into glucose 6-phosphate by hexokinase and it enters the glycolytic pathway. Only trace amounts of non-phosphorylated glucose (about 3%) enter the polyol pathway [42]. However, during HG, there is increased flux through the polyol pathway, accounting for greater than 30% of glucose metabolism [43]. The polyol pathway converts hexose sugars, such as glucose, into sugar alcohols (polyols). For example, glucose can be converted into sorbitol via the action of the enzyme aldose reductase. Aldose reductase is the rate-limiting enzyme for this pathway [44]. Increased aldose reductase activity and accumulation of sorbitol have been found in diabetic animal models. As sorbitol does not easily dissolve across cell membranes, this increases cellular osmolarity, ultimately leading to cell shrinkage and subsequently, damage. Sorbitol may also glycate nitrogen molecules on proteins, such as collagen, producing AGE-related products [44]. Increased polyol flux is associated with reduced levels of intracellular glutathione and an increase in cardiac cell apoptosis [45].

M. charantia has a beneficial effect on most metabolic and physiological processes of the human body. Many bioactive compounds of the *M. charantia* fruit, in addition to cations and vitamins, were studied and classified as carbohydrates, proteins, lipids and others [20]. It has triterpenoids [46], saponins [47],

polypeptides, flavonoids, alkaloids and sterols [46]. Several studies have reported the different bioactive components and their related functions [46]. Other studies have shown that *M. charantia* is a great source of antioxidant under experimental conditions. In fact, it was found to possess an activity against oxidant damage *in vitro* and *in vivo* [48-52]. Both the pulp and extracts of *M. charantia* followed by the seed powder and its ethanol/water extracts exhibited stronger anti-oxygenic activity than other solvent extracts as determined via several *in vitro* models. In diabetic rats, administering supplementation of *M. charantia* (13.33 g/kg) resulted in a significant rise of anti-oxidants (SOD, CAT and GST) activities [53, 54]. Flavonoids are known to be one of the most effective free radical scavengers and antioxidants from *M. charantia*. The antioxidant capacity enhanced gradually with the increase of flavonoid concentration [55]. Steroidal saponins, which are active ingredients of *M. charantia*, can decrease gluconeogenesis, increase glucose metabolism and tolerance by affecting the expression of the peroxisome proliferator-activated receptor alpha and gamma (PPARα and PPARγ), which may mitigate insulin resistance, and a protein extract that exerted insulin-mimetic activities [56, 57].

Other Medical Properties of M. charantia

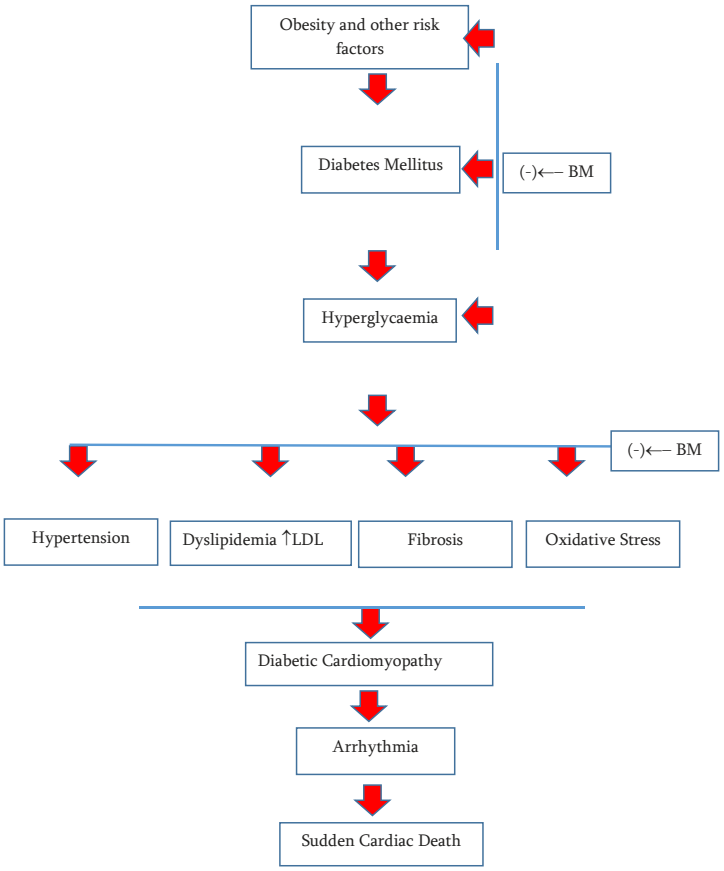
M. charantia is a useful plant for human health and one of the most promising plants for cancer, obesity and diabetes treatment and prevention [46]. *M. charantia* helps in the entire digestion process by stimulating the secretion of gastric juices. It is very helpful in stimulating liver for secretion of bile juices that are very essential for metabolism of fats. It helps in improving the peristaltic movements and hence, it is very helpful in avoiding gastric disturbances [58]. It was reported that *charantin*, which is an active fraction of *M. charantia*, when it is administered to healthy rabbits, it produced a fall in blood sugar level. Another study found that pancreatectomy was reduced, but not abolished by the hypoglycemic effect of *charantin*, indicating a dual mechanism of action [58]. Furthermore, it is known to have anti-lipolytic properties. Recent research reports suggest that its extracts may ameliorate a high fat diet, which induced obesity and hyperlipidemia in animal models. Most findings related to obesity and hyperlipidemia also showed that plant extracts may modulate fat, metabolizing kinases such as AMPKs, genes, and affected adipocyte differentiation [56]. Moreover, it is a good source of all essential vitamins, such as vitamin A, thiamine, riboflavin, and vitamin C, and minerals like iron. Moreover, it is anti-inflammatory, anti-cancer, anti-hypertensive and astringent. It has specific action on bowel movements [22]. As indicated earlier, *M. charantia* is also rich in the anti-oxidants caffeic and celuic acids and minerals, including potassium, calcium, zinc, magnesium, phosphorus and iron, and it is a good source of dietary fiber [22].

Clinical Studies of M. charantia

An earlier study on the development of diabetic cataracts demonstrated that blood sugar level-dependent cataract formation was slowed down by the consumption of bitter gourd fruit extract in association with better glucose homeostasis [59]. Today, processed bitter melon, in the form of capsules or tablets is commonly advertised and sold commercially. The products are marketed under the brand name Glucobetic in Canada, India, the United Kingdom, the United States, and in many Asian countries. Products can also be ordered online [59]. Compared with animal studies, clinical studies regarding the hypoglycemic effects of *M. charantia* have been sparse and sporadic. Lakholia, a physician, was probably the first person to document the therapeutic effect of bitter melon in 1956, using himself as the subject. Table 1 shows other clinical studies which have been done on *M charantia* in diabetic patients [60].

Table 1. Some clinical studies, which employed *M. charantia* to treat diabetes

Study design	Subjects	Form(s) *of M. charantia* administered	Treatment duration	Outcome measured	Statistical significance	Reference
Double-blind randomized controlled trial	40 with T2D (twenty trial and twenty control subjects)	Commercial herbal supplement capsules	3 months	HbA1c	No	[61]
Controlled trial	15 with T2D in 3 groups	Methanol extract of ground whole fruit	1 week	Fasting + postprandial blood glucose	Yes	[62]
Randomized controlled trial	50 with T2D (26 trial and 24 control subjects)	Tablets from dried whole fruit	4 weeks	(1) Fasting postprandial blood Glucose (2) Fructose amine	No	[63]
Controlled trial	Trial subjects: 9 DM Control subjects: 5 DM + 5 normal	Aqueous extract refined to subcutaneous injection (v- insulin)	Single treatment	Blood glucose	Yes	[64]



LDL = low density lipoprotein; (-) reduced insulting effect by BM.

Figure 2. A flow diagram illustrating the beneficial effects of bitter melon (BM) in preventing sudden cardiac death in obesity-induced diabetes mellitus. This study proposes that BM has a direct anti-oxidant effect on obesity, diabetes-induced hyperlipidemia and hyperglycemia and indirectly either delaying or preventing the development of hypertension, dyslipidemia, oxidative stress and fibrosis in the myocardium.

Beneficial Effects of Bitter Melon on the Cardiovascular System

The flow chart in Figure 2 illustrates the beneficial effects of bitter melon in either preventing or delaying sudden cardiac death induced by diabetes. Obesity and other risk factors can induce diabetes, which in turn elicits a cascade of cellular and molecular events, including an elevation in blood glucose and lipids, which induces hypertension, dyslipidemia, oxidative stress, fibrosis, DCM, arrhythmia and SCD. Bitter melon, on the other hand, has a major therapeutic role in delaying and possibly preventing DCM. A number of studies, including unpublished recent data from our laboratory, showed that bitter melon juice or extract can reduce BMI, high blood pressure, elevated blood glucose, total lipids and triglycerides following treatment. Sustained hypertension is well known to be able to elicit heart failure and high levels of cholesterol, especially low-density lipoprotein (LDL) which can be deposited in coronary arteries in the heart to form plaques, thereby increasing the risk of heart diseases and even SCD [65-70].

Conclusion

Both obesity and DM are major global metabolic health disorders, which can lead to damage and subsequent failure to a number of organs in the body, including the heart. *M. charantia* is a useful plant for human health and one of the most promising plants for obesity and diabetes treatment and prevention. Also, it is composed of chemicals, which have anti-oxidant properties and hypoglycemic activity similar to insulin. The cellular and molecular mechanisms underlying the mechanisms related to its anti-diabetic and anti-oxidant properties is not fully clear and further research should be done. However, it is a rich source of potential chemically novel medicinal compounds, vitamins, cations and fibers, which need more attention for screening against new targets in the future. The present review supports the need for better-designed clinical trials with sufficient sample size and statistical power to further indicate the acclaimed efficacy of *M. charantia* as a natural nutritional treatment for DM and related diseases. In particular, *M. charantia* may be a feasible cost–effective option for people who have a high prevalence of obesity, diabetes and CVDs but prefer treatment based on natural products according to their economic status and cultural beliefs.

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