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A Systematic Literature Review on Bitter Melon (*Momordica charantia*) as Alternative Synthetic Medicine for Hyperglycemia Treatment

Faisal Latif*, Abdul Nabeel

**Department of Biochemistry, Riphah International University, Satyana Road, Faisalabad, Punjab, Pakistan, Wellwisherfaisal73@gmail.com*
Department of Biochemistry, Riphah International University, Satyana Road, Faisalabad, Punjab, Pakistan, abdulnabeel777@gmail.com

A B S T R A C T

One of the most widespread diseases in the world is hyperglycemia. Types I and II of diabetes are included. Lack of insulin synthesis by the Islet of Langerhans causes type-I diabetes. In this kind, an autoimmune reaction causes the pancreatic ß-cells to be destroyed. There are three different types of autoantibodies: islet cytoplasmic antibodies, islet cell surface antibodies, and islet cells' particular antigenic targets. The fact that type-1 diabetes mellitus is an autoimmune condition is supported by a number of changes in the immunoregulation of T cells, notably CD4+ T-cells, and the creation of interleukins by the interaction of monokines and TH1 cells. Moreover, malfunctioning pancreatic alpha cells lead to an overproduction of glucagon. Moreover, malfunctioning pancreatic alpha cells lead to an overproduction of glucagon. Sulfonylureas and biguanides, two common oral synthetic medications, are costly and have negative effects. Hyperglycemia is treated using alternative herbal plants. Numerous medicinal plants, including those in the Leguminoseae, Araliaceae, Liliaceae, Asteraceae, Euphorbiacea, Cucurbitaceae, Rosaceae, Moraceae, and Lamiaceae families, are used to treat hyperglycemia. However, bitter melon is a flowering vine that belongs to the Cucurbitaceae plant family, and Momordica charantia shows promising results. Nonetheless, some people may have certain negative consequences.

Keywords:Diabetes Mellitus; Medicinal Plants; Bitter Melon; Charantia, Insulin, Glucagon

1. Introduction

Hyperglycemia is characterized by higher-than-normal blood sugar levels. Often referred to as diabetes mellitus, it is essentially a metabolic condition that is brought on by flaws in either insulin action or production, or both. A rise in diabetes mellitus is observed worldwide. As a result, the World Health Organization (WHO) anticipates a rise in the number of diabetics that might double (from 177 to 370 million) by 2030 (Rowley and Bezold, 2012). According to estimates, 439 million adults will have diabetes by 2030, up from the 285 million adults who had it in 2010. There are two main forms of diabetes mellitus: type I and type II. Diabetes mellitus of type I is brought on by inadequate insulin production. The generation and release of insulin is carried out by pancreatic ß-cells. Type-1 diabetes mellitus results from a rise in blood sugar levels caused by inadequate insulin secretion. Pancreatic ß-cells in his type are destroyed by an autoimmune reaction (Atkinson et al., 2014). The autoimmune destruction of ß-cells reduces the production of insulin. The pancreatic a-cells' ability to operate is likewise hampered by this destruction. Blood glucose levels rise as a result of type 1 diabetes mellitus's increased glucagon release. High blood glucose levels (hyperglycemia) suppress glucagon release because pancreatic a-cells work differently in mice than in normal people.

1.1. Type-I diabetes

Type-1 diabetes accounts for around 10% of all occurrences of diabetes and affects about 20 million individuals throughout the world. While people of all ages can develop type 1 diabetes, the condition is often identified and treated at a younger age. Nowadays, there is a rising tide of people with type-1

* *Corresponding author.* Tel.:+923027159001;
E-mail address: wellwisherfaisal73@gmail.com

diabetes. 3.4% of children in Europe are diagnosed with type 1 diabetes mellitus before they turn 15; the prevalence is rising fastest among those younger than five. Caused by the immune system's mistaken response to the pancreas cells' proteins, type 1 diabetes is a serious condition. Type 1 diabetes mellitus has been linked to Addison's disease and other endocrine autoimmune illnesses. Those with a history of type I diabetes in their families are also at increased risk for developing autoimmune disorders. Three types of autoantibodies have been identified: those that target islet cytoplasm, those that target the surface of islet cells, and those that target particular antigenic targets of islet cells. There are three different kinds of autoantibodies: Antibodies directed against the cytoplasmic proteins of islet cells, thus the name "islet cell cytoplasmic-antibodies," are present in 90% of type-1 diabetic patients and are utilized as a predictor of the disease's progression. Antibodies specific to islet cell surface antigens are called islet cell surface antibodies. Type 2 diabetics are the most likely to have these antibodies (Raju and Raju, 2010).

1.2. Pathogenesis of diabetes mellitus:Type-I

An auto immune condition called type 1 diabetes mellitus is brought on by the death of B-cells. When a disease first appears, ß-cells are in their last stage. Type-1 diabetes mellitus is believed to be an autoimmune disorder based on the association of disease susceptibility with class-II genes of the major histocompatibility complex, presence of specific autoantibodies in islet cells of the pancreas, several alterations in the immunoregulation by T cells, particularly in CD4+ T-cells, and productions of interleukins by the association of monokines and TH1 cells. Because pancreatic lesions are so heterogeneous in character, it is exceedingly challenging to comprehend how type 1 diabetes' ß-cells cause destruction. With the onset of severe hyperglycemia, there may be a collection of pseudoatrophic islets with cells that make somatostatin, glycogen, infiltrating lymphocytes, pancreatic polypeptide, monocytes, normal islets, and islets that contain ß-cells. Insulin production decreases as a result of the destruction of the pancreatic ß-cells, which causes type 1 diabetes. Moreover, malfunctioning pancreatic alpha cells lead to an overproduction of glucagon. In healthy people, high glucose levels do not restrict glucagon production as they do in those with type I diabetes mellitus. Instead, they increase it. If patients are not given insulin, excessive glucagon and decreased insulin production aggravate metabolic abnormalities including ketoacidosis. Uncontrolled lipolysis in people with type 1 diabetes raises the level of free fatty acids in the blood plasma of the patient, which slows down the rate of glucose metabolism in various body tissues, such as skeletal muscle tissues (Raju and Raju, 2010). Patients with type-1 diabetes must express a variety of genes, such as glucokinase in the liver and the GLUT-4 class (glucose-transporters) in adipocytes, in order to respond to insulin decreases appropriately.

If type-1 diabetes mellitus uncontrolled it increase liver glucose output, first of allstored glycogen in liver is mobilized then by gluconeogenesis glucose is produced by hepatic cells. Insufficient secretion of insulin also effects the utilization of glucose by different other tissues particularly adipose tissue and skeletal muscles. So, these tissues do not uptake glucose properly ultimately results in a reduction in glucose metabolism like glucokinase is also regulated by insulin so reduced insulin level means more delivery of glucose in the blood. Ultimately plasma glucose level increase both by excessive production of glucose by hepatocytes and lower consumption of glucose by body tissues due to lower glucose metabolism. Kidney absorbs glucose during reabsorption process up to a capacity, high level of glucose in blood is not effectively absorbed by kidney that leads to glucosuria. Excessive loss of glucose means loss of body water and different other electrolytes that activates thirst mechanism. Body's energy also decreases due to excessive loss of glucose which results in an increase in appetite (Raju and Raju, 2010).

1.3. Diabetes mellitusTreatment

Diabetes mellitus is often treated with oral synthetic medicines, which can be quite expensive and have a number of potential adverse effects (Singh et al., 2009), It is well accepted that the use of large synthetic medications like sulfonylureas and biguanides, which are used to decrease blood glucose level in an oral way, might cause certain negative effects in patients. Finding novel methods of preventing diabetes or anti-hyperglycemic agents for treating it is therefore crucial. Many plant items that have been shown to have an anti-hyperglycemic impact are the subject of several ongoing investigations (Noor et al., 2008). The antihyperglycemic compounds found in many plants can be utilized to treat diabetes at a reasonable price and with minimal risk to the patient (Singh et al., 2009). It has been shown that several plant families, including the Euphorbiaceae, Moraceae, Liliaceae, Asteraceae, Rosaceae, Araliaceae, Cucurbitaceae, Lamiaceae, and Leguminosae, have hypoglycemia potential, although the mechanism of anti-hyperglycemic action is still unclear for many plant species. As these plants contain a wide variety of bioactive compounds, each of which is more effective than synthesized oral medications and widely available, they provide a chance for novel treatments. To name just a few examples, alkaloids, glycopeptides, gum, glycosides, and polysaccharides are all present in this plant. Medicinal plants include several bioactive chemicals, some of which have only recently been identified. They include terpenoids, peptidoglycans, hypo glycans, guanidine, steroids, and galactomannan.

The Cucurbitaceae (cucurbit family), more often known as the cucumber/pumpkin family, is a genus of flowering plants that thrives in warm climates (tropical and subtropical zones) worldwide. The economic importance of this plant family is reflected in the fact that many of its members are cultivated for their edible fruits and vegetables throughout the summer months. This family of plants is regarded mono-phyletic due to its unique morphological and biochemical characteristics, which set it apart from all other plant families. The blood-cleansing, constipation-relieving, digestion-boosting, and energy-giving properties of plants in this family are shared by a number of different species. If you're looking for a family with anti-diabetic properties, this one tops the list. Anti-diabetic activity and relief from diabetes-related problems have been attributed to many members of this family. Citrullus colocynthis, Coccinia indica, and Cucurbita ficifolia are just a few of the species of this family that have been studied for their potential antihyperglycemic activity. Produced by: Cucurbita pepo, Luffa aegyptica, Momordica charantia, Momordica cymbalaria, and Momordica diocia (Singh et al., 2009). Bitter melon, a member of this family, has been the subject of much research due to its possible anti-diabetic effects.

A member of the family Cucurbitaceae, the bitter melon is a climbing vine that produces fruit (a plant family). It has unbranched or two-branched tendrils on its simple alternating leaves, which range in size from 4 to 7 lobes. It may reach a height of 5 meters, and its three-to-seven lobes are widely spaced. The fruit of this plant is warty appearing on the outside, and is either ovoid or spindle shaped. The flesh around the center chamber, which is full of seeds and pith, is quite thin. While unripe, the bitter melon's seeds and pith have a white appearance, but they turn a brilliant scarlet once the fruit is fully mature. Its unripe flesh has a watery texture and a crunch similar to that of a cucumber, yet its ripe orange and mushy flesh is unlike anything else. The Chinese bitter melon is around 20-30cm in length, has a pale green hue, and seems watery; the Indian bitter melon, in contrast, is narrower in form, with pointy ends that have triangular teeth and ridges on the surface. M. charantia can vary in size, shape, and color anywhere between these two extremes. Staminate flowers are characterized by their yellow color, five-lobed calyx, five-petaled corolla, three stamens inserted at the flower's base, cohesive anthers, prominent and wide filaments, ovoid to spindle-shaped hypanthium, smaller perianth, many ovules, and two- to three-lobed stigmas. Generally speaking, the seeds are limited in number yet well sculpted. It may either be an annual or a perennial vine, depending on the climate, and it is grown from April to July, when the weather is warmest. Two or three seeds are planted at a half-meter apart in each hole. Watering seedlings just once or twice each week and keeping only one plant per pit is typical. Flowers appear 30–35 days after seeding, and fruit can be picked after another 15–20 days of flowering. Analysis of its phytochemical composition indicated the presence of phenolics, flavonoids, phytosterols, fatty acids, and saponins. The phytochemicals it contains have physiological effects on the human body, helping to prevent conditions including cholera, diarrhea, bronchitis, dysentery, ulcers, colic, worms, and cancers of the liver and spleen as well as anemia, blood problems, gout, gonorrhea, rheumatism, and diabetes. Juice made from bitter melon leaves has been shown to be useful in the treatment of piles due to the high concentration of blood purifiers it contains (Ahmad et al., 2016). The M. charantia plant has had its stem, leaves, seeds, pericarp, cotyledons, and unripe fruit isolated in laboratories in numerous countries, including the United States, China, Brazil, Pakistan, Australia, Egypt, the Philippines, Taiwan, and Peru, yielding a total of about 228 different medicinal compounds.

2. Reviewof Literature

2.1. Herbal plants

In the last few years, there has been a significant advancement in the study of plant-based medications. Both in developed and emerging nations, herbal treatments are rising in popularity. Natural origins of herbal medications mean that they have fewer adverse effects. Many of the traditional medications that are still used to treat various ailments are mostly plant-based, however some of them also come from minerals or organic materials. In the Indian medical system, medical professionals define and create their own medicinal formulas for various ailments. The World Health Organization has designated 21,000 species as medical plants, and these plants are utilized to create medications all across the world. Nepal is home to a remarkably diverse range of plants and animals. Nepal is home to 2.2% of the world's blooming plants, although covering only 0.1% of the planet's surface. According to recent studies, out of the 7000 species of higher plants that are found in the Nepal repository, 1400 species have medicinal potential (Kunwar et al., 2013). There are 2500 different species of medicinal plants in India, which is also known as the botanical garden of the world. Out of these medicinal species, 150 are used on a very large scale for the production of herbal medicines on a commercial level. India is the largest producer of herbal plants worldwide. Between 60 to 80 percent of people worldwide rely on various herbal medications as their go-to treatment for illnesses. Similar to how many medicinal plants cure other ailments, diabetes mellitus, which is one of the top five killers worldwide, is also treated by these plants. The number of people with diabetes mellitus has significantly grown from 171 million in 2000 (AD) to 366 million in 2030 (AD), and because many of these cases are still misdiagnosed, it is regarded as a serious global health concern. Disordered metabolism is brought on by hereditary and many environmental factors, which raises the blood glucose level. According to its etiology, diabetes mellitus is brought on by ß-cells producing less insulin or by body parts being less sensitive to insulin, or occasionally by both of these factors. More than 1200 plants are used against diabetes mellitus in the common system of medicine, with very few or no negative effects. Due to the existence of several bioactive phytochemical components that have particular bio-medical effects on various human body parts, these plants have a high therapeutic potential (Chhabra and Dixit, 2013).

2.2. Diabetes Herbal Treatments

The use of oral synthetic medications for the treatment of diabetes is quite expensive, and there are several potential side effects. Ayurveda and other herbal medical systems have identified a variety of medicinal plants with anti-hyperglycemic properties that have very few or no adverse effects and are also less expensive (Singh et al., 2009). Different plant families with hypoglycemic effects include Leguminoseae, Araliaceae, Liliaceae, Asteraceae, Euphorbiacea, Cucurbitaceae, Rosaceae, Moraceae, and Lamiaceae. Basic mechanisms underlying the hypoglycemic activity of all these new bioactive components in these plants are also being studied. These plants' bioactive substances are more potent against diabetes mellitus than man-made medications. A broad variety of herbal plants has the potential to create new classes of medications for various illnesses. For numerous bioactive substances, such as glycosides, steroids, terpenoids, alkaloids, hypoglycans, polysaccharides, glycopeptides, and peptidoglycans, guanidine, and galactomannan gum, a wide range of principles are presented in the literature. However many more bio-active substances that are derived from various herbal plants still need to be thoroughly described.

2.3. Adverse Effects and Toxicity

In normal circumstances, bitter melon is a safe plant for people, but it can have negative consequences depending on the amount, the production process, the medications used, and the individual's physical and medical history. It was shown to be a safe medicinal plant in an animal trial, showing no symptoms of hepatotoxicity, nephrotoxicity, or any other negative effects on food intake, organ growth, body weight, or hematological parameters.

Since 1960, reports of other toxicity categories, including acute, chronic, and reproductive toxicity, have also been made. In animal studies, significant toxicity and even death have occasionally been reported following intravenous administration. Compared to other plant components including the stem, roots, seeds, and leaves, the fruits and seeds are more poisonous. The precise dosage that has beneficial effects on the body, such as decreased blood glucose levels and bad cholesterol, yet has no adverse effects is currently being researched. Recent investigations on the Momordica charantia plant demonstrated that people who are lacking in the enzyme glucose-6-phosphate-dehydrogenase like eating its portions (Leung et al., 2009). The following list of Momordica charantia's most significant side effects is provided.

2.3.1. Teratogenic effect

According to Uche-Nwachi et al. (2010), bitter melon is teratogenic in Sprague Dawley rats, hence it is advised that pregnant women take it with caution.

2.3.2. Antifertility

The uterus may be stimulated by certain bitter melon portions, which causes miscarriage in female humans, while sperm production and spermatogenesis are reduced in male animals. Bitter melon consumption once a month stops pregnancies in India. Animals' testicles and related reproductive systems have undergone histological alterations. by using bitter melon ethanolic extract (Patil et al., 2011). Progesterone and estrogen levels in female rats are decreased by the aqueous extract of bitter melon leaves, which causes infertility.

2.3.3. Diarrhea, Headache, and Hypoglycemic coma

Some of the most significant adverse effects of bitter melon have been observed, including hypoglycemic coma, favism, a rise in y-glutamyl transferase and alkaline phosphatase levels in several animals with headaches.

Studies have shown that taking its tea might cause hypoglycemia coma and convulsions in youngsters. Several occurrences of headache and diarrhea have also been documented (Dans et al., 2007).

2.3.4. RBCs Destruction

Many bitter melon alkaloids are thought to cause red blood cells to die (Dutta and Banyal 1981).

2.3.5. Embryo Growth Depression

According to certain research, bitter melon retards not only embryo development but also embryo implementation and adhesion.

2.3.6. Fluctuations in heart rates and respiratory system

After subcutaneous injection of an alcoholic extract of bitter melon, several pathological alterations, including variations in heart and respiration rates, have been noticed(El-Batran et al., 2006).

2.3.7. Decrease hemoglobin concentration

A drop in hemoglobin content has been seen in albino rats following administration of an aqueous extract of bitter melon(Temitope and Lekan, 2014).

2.3.8. Cytotoxic effect

M. charantia lectin showed cytotoxic effect, inhibited DNA and protein synthesis in human lymphocytes (Licastro et al., 1980).

3. Conclusion

Cucurbitaceae family members' bitter melon has a wide range of bioactive substances. According to the phytochemical examination, it includes phenolics, glycosides, alkaloids, saponins, lipids, fixed oils, flavonoids, and phytosterols. However, the form and coat color of bitter melon vary according on the country and its size. They are reasonably priced and easily accessible in many regions. These plants' bioactive substances are more potent against diabetes mellitus than man-made medications. While rare, bitter melon's adverse effects might differ from person to person.

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