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MOMORDICA CHARANTIA AND POLYPEPTIDE-P: A MINI REVIEW ON THEIR MEDICINAL POTENTIAL IN DIABETES CARE

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Abstract:
Diabetes militias represents a significant global health concern, with an increase in its prevalence from 171 million in 2000 to an estimated 366 million by 2030. In current era there is a trend of shifting towards alternative and complementary medicine among the diabetic individual. The functional and health endorsing perspectives of those foods are attributed to the bioactive components in them. Among such natural plant based sources *Momordica charantia* holds a prominent place in traditional medicine for its therapeutic properties especially for treatment diabetes mellitus, cancer, inflammation, and related complications. Ample pre- clinical studies have shown the effect of *Momordica charantia* usage in controlling ailments like diabetes and cholesterol lowering effects. It is abundant in active components that have a potency for management of diabetes. Among those are p-insulin that is called as plant based insulin. P-Insulin has the ability to enhanced insulin sensitivity, inhibition of glucose absorption, and regenerate the pancreatic beta cells.

Key words: Polypeptide-P, P-insulin, Diabetes Care, mechanism of polypeptide-P

Introduction

Diabetes is one of the top five leading causes of the death worldwide. Diabetes mellitus is one of the major health concerns. Almost with an expected rise in incidence from 171 million in the year 2000 to 366 million in the year 2030. (Shaw et al., 2010). Diabetes Mellitus is a chronic disease that is associated with elevated blood glucose levels also termed as hyperglycemia. It is the result of insufficient production of the hormone 'insulin' in the body that may be because of damaged beta cells present in pancreas, or may be the body become insulin resistant and unable to use up insulin properly. Insulin is extremely important for balancing glucose mechanism in the body as it not only assist in glucose uptake but also transport glucose to all the cells in the body. There are several types of diabetes but the most significant types are type-I, type-II, gestational and pre-diabetes (DeFronzo, *et al.*, 2009). Diabetes mellitus a syndrome of metabolic disorder, usually due to the presence of both hereditary causes and environmental causes, it has resulted in abnormally high blood glucose levels termed as hyperglycaemia (Patel et al., 2012). Symptoms associated with High blood glucose include increased in thirst and hunger, leading to subsequently increased in urination. A prolonged state of hyperglycemia can lead to numerous critical health problems such as hypertension, cardiovascular

diseases, renal diseases, cognitive problems, and nerve damage. The risk factors for diabetes mellitus include genetics, obesity, high carbohydrate diet, sedentary lifestyle, hypertension, age and race, therefore a lifestyle designed to reduce such conditions also falls in the prevention and management of high blood glucose (Knowler *et al.*, 2006).

Management of diabetes often involves lifestyle modifications, pharmacotherapy, and insulin therapy. In recent years, there has been growing interest in exploring natural compounds for their potential therapeutic effects in diabetes management (World Health Organization, 2016). The management of diabetes mellitus using drugs are effective but significant challenge are associated with those allopathic drugs. Consequently, shifting the research interest from drugs to traditional medicine. Numerous researches have uncover the role of plants and plant based diet in curing diabetes mellitus and associated complications. (Babish et al., 2012; Butt and Sultan, 2012). Bitter gourd is a vine native to tropical and subtropical regions, cultivated in Asia especially in Pakistan, China, Taiwan, India, Brazil, Guyana, Nepal and Philippines as a source of vegetable and medicine. In plain areas it is sown annually as a summer season crop from January to June but in areas with mild or frost free winter it is grown as perennial crop. *Momordica charantia* (MC) locally known as bitter gourd or kerela is one such example that provides health benefits against various ailments by improving the quality of the life. It is nutrient dense plant containing versatility of bioactive compounds (Ali et al., 2011).

It is herbaceous plant grows around five meter and bears simple serrated leaves of 4-12 cm long and 1-3 inch wide with three to seven separate lobes. Its fruit is characterized by different shapes like rectangular, ovoid, spindle, or oblong cylindrical, and about two to ten inches long in length, and possessing a hollow cross-section. Fruit is consist of a fleshy soft outer pod that contain a central cavity filled with seed and pith. The color changes in whole fruit parts are indication of the different maturity stages. Like at unripe stage both seeds and pith are white, while the fully ripened stage they turned orange and red from green, resulting in increased bitterness (Sharma *et al.*, 2011).

Bioactive components of plants are non-nutritive but health promoting compounds that naturally occur in plants. These not only gave appropriate sensory attribute but also have potential implications for in suppressing the disease causing agents and blocking those carcinogens resulting in interfering with their degeneration processes (Biesalski et al., 2009). Thus, herbal medicines are becoming popular not only in developed countries but also in developing countries (Potawale et al., 2008). Among the phytonutrients dense plants, bitter gourd or momordica cherentia holds a potential to be used as theraputic against different diseases.

The fruit has a distinct bitter flavor that grows stronger as it develops, causing it to be named as bitter melon. M. charantia has considerable antidiabetic and hypolipidemic property, allowing it to be used as supplement to allopathic medicines for treating DM, prevent disease progression and the prevention of late complications. In this review, we have enlightened the antidiabetic activity of M. charantia, as well as the therapeutic potency that causes hypoglycemic activity in the body. (Dasgupta, Mukherjee & Mitra, 2012).

The current review provide a deep insight about the antidiabetic potential of MC p-insulin by assembling the chemistry, way of action and clinical studies, of p-insulin. Thus providing a brief implication for diabetes management.

Chemical Composition of Momordica charantia

Momordica charantia contains 91.8% water, 0.20% fat, 4.2% carbohydrates and 1.4% fiber. Notably, the proteins found in bitter melon seeds meet the essential amino acid requirements set by (FAO/WHO/UNU) for preschool children. These proteins fractions contain albumin, globulin, and glutelin, with proportions of about 49.3%, 29.3%, and 3.1%, respectively with molecular weights ranging from 45 to 55 kDa (Horax et al., 2010).

Additionally, bitter melon seeds contain approximately 35 to 40% oil, with a fatty acid profile revealing 36.71% saturated fatty acids (SFA), 3.33% monounsaturated fatty acids (MUFA), and a predominant presence of polyunsaturated fatty acids (PUFA) at 59.96%. Amongst PUFA, α-eleostearic acid (54.26%) is a conjugated linolenic acid and is of significance importance (Grossmann et al., 2009; Liu et al., 2010). The mineral profile reveals that it exhibit distinguished amount of

potassium, magnesium, calcium, sodium, and phosphorous and mostly present in fruit and leaves (Ayoola et al., 2010). Furthermore, bitter melon seeds emerge as excellent sources of chromium and zinc, containing 5.65 and 45.45 mg/100 grams, respectively, highlighting their nutritional significance (Liu et al., 2010; Bangash et al., 2011).*Momordica charantia* boasts an impressive nutritional profile, with 91.8% water, 0.20% fat, 4.2% carbohydrates, and 1.4% fiber.

Bitter melon contains a variety of potentially bioactive compounds.it is rich in saponins, a diverse group of naturally occurring glycosides known for their diverse pharmacological activities. It contains two types of saponins known as cucurbitane and oleanane-type triterpenoids (Popovich et al., 2010). *Momordica charantia* also contains cucurbitane-type triterpenoids, including momordicoside U, momordicine I and II, and related glycosides. These triterpenoids have demonstrated various biological activities, including antidiabetic and antitumor effects by enhancing adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) activity (Ma et al., 2010). Twenty five different compounds are present in bitter gourd essential oil. The main identified constituents of essential oils are trans-nerolidol, apiole, cis-dihydrocarveol and germacrene (Mesia et al., 2008). The alpha-eleostearic acid is present in plentiful amount and is beneficial in inhibiting the tumor cell proliferation, lowering blood fat, anti-cancer, anti-inflammatory and preventing cardiovascular diseases (Liu et al., 2010). Gallic acid is present as major phenolic acid in bitter gourd. The other phenolic constituents present in its extracts are catechin, gallic acid, gentisic acid, chlorogenic acid, and epicatechin (Horax et al., 2010; Ibrahim et al., 2010). Principle components of bitter melon are charantin, momordicine and p-insulin which are steroidal saponin, alkaloid and polypeptides in nature, respectively (Paul and Raychaudhuri, 2010). Charantin and momordicine are primarily responsible for the bitterness of fruit and health-promoting effects. Charantin, polypeptide-p, and vicine are three big bitter melon compounds that have been described as hypoglycemic agents. These compounds like Charantin, momordicilin and momordenol, are comparable in their structures and functional characteristic similar to insulin (Kumar et al., 2011). Similarly, momordicine II and kuguaglycoside G are helpful in recovering the insulin production in body. They are helpful in balancing glucose in our body by preventing lipid synthesis, fatty acid oxidation and improve glucose level. Charantin is further classified into sitosteryl glucoside and stigmasteryl glucoside. These compounds belong to the class of glucosides, which are molecules consisting of a sugar moiety (glucose) attached to another chemical group (Chen et al., 2009). Vicine is a chemical compound found in certain plants, including fava beans (Vicia faba). It belongs to the class of glycosides and is specifically categorized as a cyanogenic glycoside. Vicine is known for its potential toxicity due to its ability to release hydrogen cyanide when hydrolyzed by enzymes (Fasoyiro, & Oyedele, 2012).

Momordica charantia contains a compound known as polypeptide-p also known as p-insulin. That is similar to natural insulin existed in human body. It is isolated from bitter gourd seeds and fruits and exhibit water-soluble properties with a complex chemical composition. Several studies have characterized the chemical structure of polypeptide P using various analytical techniques, including chromatography, mass spectrometry, and nuclear magnetic resonance (NMR) spectroscopy. Studies have suggested that P-insulin exhibits insulin-like effects, making it a potential candidate for the management of diabetes. Research into the mechanisms of action of P-insulin has revealed several potential pathways through which it may exert its antidiabetic effects (Tayyab et al., 2012).

Structural composition of p-insulin

The amino acid composition of polypeptide-P or p-insulin has been extensively investigated. This polypeptide, consisting of 17 amino acids and comprising 166 residues, showed no cross-reactivity in an immunoassay for bovine insulin. Polypeptide-p demonstrated insulinomimetic properties with a minimum molecular weight of approximately 11,000 (Chaubey, 2019).

Studies have reported that it is rich in amino acids such as leucine, isoleucine, valine, and glycine, which are known to play crucial roles in regulating glucose metabolism and insulin secretion. Additionally, polypeptide P contains essential and non-essential amino acids, contributing to its biological activity.

The analysis revealed that polypeptide k contained 9 out of 11 essential amino acids, among a total of 18 types of amino acids. Glutamic acid, aspartic acid, arginine, and glycine are the most abundant (17.08%, 9.71%, 9.50%, and 8.90% of total amino acids, respectively). Polypeptide also have potent inhibition of α-glucosidase enzyme 79.18% and α-Amylase inhibition by 35.58% (Ahmad et al., 2012).

Mode of action of chemical compounds in curing diabetes

Numerous treatments are available for diabetes but because of the adverse effect of pharmacological drugs upon prolong usage shifting consumer alternative traditional medicines given the association between insulin resistance and aging, strategies to mitigate this resistance bitter gourd hold potential for enhancing the lifespan of individuals with diabetes mellitus. (Preuss *et al.*, 2011).

Momordica charantia demonstrates hypoglycemic and hyperglycemic impact that is comparable to the conventional antidiabetic drugs. Bitterness of MC is believed to be effective in prevention of diabetes mellitus and alleviate associated complications. The hypoglycemic properties of this plant come from various physiological, biochemical, and pharmacological mechanisms. These include the repairing of damaged β-cells, increase in insulin levels & its sensitivity by the islets of Langerhans, regulation of glycogen storage in the liver, inhibition of glucose absorption by suppressing glucosidase activity, and reduction of serum and hepatic triglycerides.

Similarly, it stimulates the synthesis and release of thyroid hormones& adiponectin by increasing the β-cell production and activity of AMP-activated protein kinase (AMPK) (Pandeya *et al.*, 2013).

It has the ability to enhance glucose homeostasis and uptake is mediated through the regulation of glucose transporter-4 (GLUT-4), peroxisome proliferator-activated receptors γ (PPAR-γ), and phosphatidylinositol-3 kinase (PI3K). The consumption of MC in appropriate amount increase tyrosine phophorylation and stimulated insulin receptors substrate-1 occurs (IRS1) (Nerukar et al., 2008; Sridhar et al., 2008). Furthermore, bitter gourd components such as charantin, p-insulin, and momordicine exhibit potent antidiabetic effects. Lectin found in bitter melon, also holds insulin-like activity, and reduces blood glucose amount by reacting on peripheral tissues and reducing the appetite in similar pattern of insulin's effects in the brain (Gadang et al., 2011).

Studies indicated that both powder and chloroform extracts of *Momordica charantia* are comparable to insulin in their effects on glucose and amino acid transport in cell membranes. Similarly these solvent extracts in 5-10µg/mL are sufficient to inhibit the 3H-deoxyglucose and 14C–Me AIB (N-methyl-amino-α-isobutyric acid) uptakes by L6 myotubes of skeletal muscles (Ahmed et al., 2004; Cumming et al., 2004). Oral administration of bitter melon seeds and extracts significantly reduces blood glucose levels and oxidative stress markers in diabetic animals, while also attenuating hypercholesterolemia and lipid peroxidation (Sathishsekar and Subramanian, 2005a). Bitter melon extract capsules contain ingredients with selective inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), a key factor in obesity-linked diabetes (Blum et al., 2012). Furthermore, bitter melon extract activates peroxisome proliferator-activated receptor-α (PPARα) and PPARγ signaling pathways, resulting in improved lipid metabolism and reduced liver triglyceride levels (Chao et al., 2011; Gadang et al., 2011).

Polypeptide-P

Polypeptide P exhibits various biological activities, with its most notable function being its hypoglycemic effects. It functions by mimicking the action of insulin or enhancing insulin sensitivity in target tissues, thereby promoting glucose uptake and utilization. Additionally, polypeptide P may exert antioxidant, anti-inflammatory, and immunomodulatory effects, contributing to its overall therapeutic potential in diabetes management.

A previous study extracted water-soluble peptide MC2-1-5 from *Momordica charantia* and purified it by ultrafiltration, gel filtration chromatography and reverse-phase high performance liquid chromatography (RP-HPLC). Researcher study their impact on hyperglycemia. In alloxan-induced diabetic mice, oral administration of MC2-1-5 at a dose of 2 mg/kg resulted in a reduction of blood glucose levels by 61.70% and 69.18% at 2 and 4 hours, respectively. Furthermore, the oral glucose tolerance test (OGTT) demonstrated that MC2-1-5 led to reductions of 25.50%, 39.62%, and 41.74% in blood glucose levels after 1, 2, and 3 hours, respectively, compared to diabetic control mice (Yuan, Gu, & Tang, 2008). It was proposed that the mechanism of action may involve the interaction of these peptides with alpha-adrenergic or corticotrophin receptors (Chaubey, 2019).

α-Amylase and α-glucosidase enzymes are responsible for increase in postprandial glucose levels in diabetic individuals. So it is mandatory to suppress the activity of these enzymes. A previous research evaluated the impact of protein extracted from MC on α-amylase and α-glucosidase inhibitory activities in vitro, as well as their glucose-lowering effects after oral administration in vivo. The results indicated that the protein extracted inhibited the activity of α-amylase and α-glucosidase through competitive inhibition, demonstrating inhibition percentages ranging from 66 to 69% and IC50 values between 0.26 to 0.29 mg/ml. These inhibitory effects were comparable to those of Acarbose, a known antidiabetic medication. Furthermore, protein extract significantly reduced high blood glucose levels and the area under the curve in Streptozotocin-induced diabetic rats, which were orally challenged with starch and sucrose (Poovitha & Parani, 2016). Another research also support this finding that Polypeptide also have potent inhibition of α-glucosidase enzyme 79.18% and α-Amylase inhibition by 35.58% (Ahmad et al., 2012).

One more study, investigated the antidiabetic potential of aqueous extract of MC through transcriptomic analysis. Also the protein ingredients that was responsible for hypoglycemic mechanism were identified using proteomic, docking, and receptor-binding assays. Findings revealed that MC seed extract at a dose of 1 g/kg significantly reduced blood glucose levels in control and experimental mice. While transcriptomic analysis revealed that seed extract initially regulate the insulin signaling pathway in body by targeting the insulin receptor (IR), and resulting in stimulating the downstream pathways and exhibiting hypoglycemic activity in experimental subjects. They research also investigated that a trypsin inhibitor (TI) from MC directly interacted with IR and dose-dependently activated its kinase activity. This novel finding suggests that TI acts as an IR-binding protein in MC, thereby triggering the insulin signaling pathway (Figure 1) (Lo et al., 2013). Later these scientist identified a novel 68-residue polypeptide named M. charantia insulin receptor (IR)-binding protein (mcIRBP), which activates IR signaling pathways, enhances glucose uptake in cells, and improves glucose clearance in mice. These proteins are typically broken down into peptides with fewer than 20 amino acid residues by gastrointestinal digestive enzymes. Researcher identified through in vitro digestion, a range of peptides varying from 5 to 28 amino acid residues in length that were released from mcIRBP. Subsequently, a series of synthesized peptides derived from mcIRBP were analyzed for their IR-binding abilities using various assays including IR-binding assay, IR kinase activity assay, and kinetic analysis. The findings revealed that mcIRBP-19, spanning residues 50–68 of mcIRBP, emerged as the key IR-binding and blood glucose-lowering peptide motif. It exhibited comparable IR-binding capacity and glucose uptake ability to mcIRBP (Lo et al., 2016).

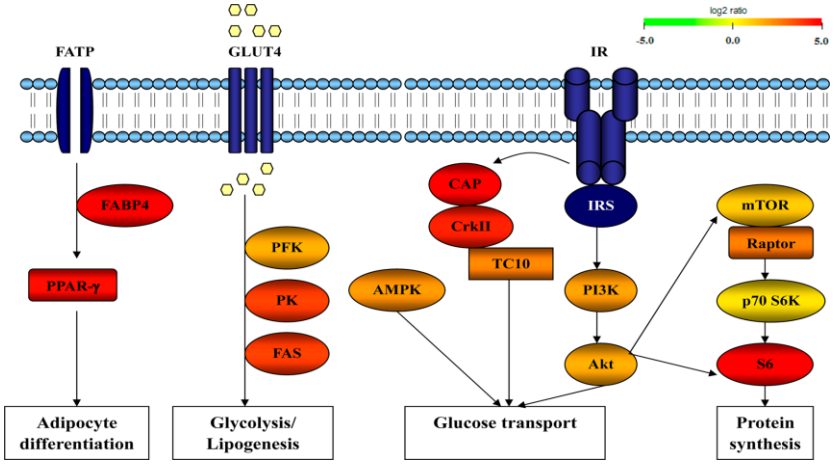

Figure 1: Signal transduction pathways contributing to the modulatory effect of MCSE on glucose metabolism in diabetic mice. Normalized log2 expression levels are color-coded according to the legend at the top. Increased levels are colored red and decreased levels, green. AMPK, AMPactivated protein kinase; CAP, Cb1 adaptor protein; FABP4, fatty acid binding protein 4; FAS, fatty acid synthase; FATP, fatty acid transport; GLUT4, glucose transporter 4; IR, insulin receptor; IRS, insulin receptor substrate; mTOR, mammalian target of rapamycin; p70 S6K, p70 S6 kinase; PFK, phosphofructokinase; PI3K, phosphoinositide 3-kinase; PK, pyruvate kinase; PPAR, peroxisome proliferator-activated receptor; Raptor, regulatory associated protein of mTOR; S6, S6 ribosomal protein (Lo et al., 2013).

Diabetic nephropathy (DN) is a significant complication of diabetes characterized by chronic inflammation and immune dysfunctioning. A study was conducted a long-term experiment to assess the therapeutic effects and underlying mechanisms of mcIRBP-9 on DN. Type 2 diabetic mice were administered mcIRBP-9 orally for 12 weeks, and various parameters such as renal function indexes, vascular leakage, and pathological lesions were evaluated to assess DN progression. Results revealed that mcIRBP-9 could enter systemic circulation after oral administration in rats. Long-term administration of mcIRBP-9 led to significant reductions in blood glucose and HbA1c levels, along with improved survival rates in diabetic mice compared to control groups. Moreover, these protein demonstrated renoprotective effects by reducing renal vascular leakage and histopathological changes associated with DN (Liao et al., 2022).

In conclusion, bitter gourd and its bioactive compounds offer a promising avenue for the development of alternative therapies for diabetes and its complications. Further research into the mechanisms of action, safety profiles, and clinical efficacy of these compounds is warranted to harness their full therapeutic potential in the management of diabetes mellitus and its associated complications.

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