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SIGNIFICANT EFFECTS AND MECHANISM OF ACTION OF TWO DIFFERENT PLANT SPECIES OF FAMILY CUCURBITACEAE - *MOMORDICA CHARANTHIA* AND *CITRULLUS COLOCYNTHIS* IN TREATMENT OF TYPE II DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is one of the common and most concerning endocrine disease world-wide. Multiple natural products are beneficial for treating Type II Diabetes Mellitus (T2DM). Among many well-known plant families, Cucurbitaceae has different species having reported anti-hyperglycaemic activity. *Momordica charantia* is a common plant in Asian subcontinents, Africa and other tropical regions. The fruits of *M. charantia* are consumed as vegetable. These fruits have multiple biological activities like anti-helminthic, stomachic and laxative. The phytoconstituents responsible for anti-hyperglycemic activity includes momordicin – a triterpenoid saponin, charantin – a non-steroidal glycoside, and galactose-binding lectin. Apart from inhibiting glucose uptake from gut, the fruit juice also increases uptake of glucose in skeletal muscle, thereby reducing the blood glucose level. *M. charantia* demonstrated regeneration of insulin secreting pancreatic beta cells. Another important plant of this same family is *Citrullus colocynthis* or bitter apple. It has laxative, anti-helminthic and anti-inflammatory activities. The phytoconstituents responsible for its anti-hyperglycemic effect is postulated to include isoorientin, cucurbitacin B, cucurbitacin E, and cucurbitacin I. The main mechanism of *C. colocynthis* includes increased insulin secretion from pancreas and reduced absorption of glucose from gut. The fruits of both the species significantly reduce the blood

sugar level of Streptozotacin treated rat significantly. The anti-hyperglycemic activities is due to the presence of saponins and glycosidic components.

Keywords: Cucurbitaceae, *Momordica charantia*, Charanthin, anti-hyperglycemic, momordicin, *Citrullus colocynthis*

INTRODUCTION

Plants are the major source of lead compounds for modern medicine. Statistically modern medicine derived from plants are nearly about 25%. Only about 5-15% of terrestrial plants have been screened for their pharmacological actions **[1]**. Phytoconstituents obtained from different plants have shown to have multiple pharmacological effects, including antidiabetic (*Aloe vera, Anemarrhena asphodeloides, Eugenia jambolana, Momordica charantia, Pterocarpus marsupium*, etc.) **[2]**; anticancer (Taxol from *Taxus brevifolia*, vincristine and vinblastine from *Catharanthus roseus*, podophyllotoxin from *Podophyllum peltatum*, etc) **[3]**; antihyperlipidemic (Plant families like Amaranthus, Malvaceae, Myrtaceae, Fabaceae and Apiaceae) **[4]**, antihypertensive (Dicentrine from *Lindera megaphylla* and *Actinodaphne sesquipedalis*, Laurotetanine from *Luureliu sempervirens*, Dehydroevodiamine from *Evodia rutaecarpa*, etc.) **[5]** and in treatment of multiple other diseases.

Diabetes can be classified broadly in two categories, insulin dependent and insulin independent diabetes. Type I or insulin dependent DM occurs mainly because of insufficiency in number of insulin secreting pancreatic beta cells. Type II or insulin independent DM (T2DM) occurs because of impaired secretory response of insulin. The insulin sensitivity of cells reduces in T2DM **[6]**. It is a major threat to public health, which have already affected more than 400 Million person world wide **[7]**.

The family Cucurbitaceae is the largest family of summer vegetables, that contain over 125 genera [8]. Cucurbit family of Cucurbitaceae has two sub-families namely, Zanonioideae (19 genera) and Cucurbitoideae (111 genera) **[8]**. Both plants, *Momordica charantia* and *Citrullus colocynthis* belongs to the subfamily Cucurbitoideae. *Momordica charantia* is found in tropical regions. It is widely spread in different parts of Asia, and Africa. It belongs to family Cucurbitaceae. It is a green climber. Synonyms includes bitter gourd in English. In Indian vernacular, it is called 'Karela' **[9]**. The term *'Momordica'* a Latin derived word. It means 'to bite'. This is because of its leaves which have serrated edges that seems to be half bitten **[8]**. The fruits of the plants were consumed cooked or raw **[9]**.

Citrullus colocynthis is another species belonging to the sub-family Cucurbitoideae. It is a wild, harsh, perennial, non-tough plant which thrive in arid region **[10]**. It is often called as Bitter apple or Bitter cucumber **[11]**. The seeds and fruits were often consumed as food.

PHYTOCONSTITUENTS OF *M. charantia*

Various research and analytical studies over the years have proved presence of multiple chemical compounds as constituents of extract of *Momordica charantia* **[12]**. The different phytoconstituents presents, are categorized based on their chemical classes. Multiple sterols, triterpenoids, alkaloids, phytosterols, amino acids, flavonoids, vitamins, fatty acids were found from its extracts **[13]**.

M. charantia, contains primary metabolites including heteropolysaccharides, fibres, proteins. The heteropolysaccharides includes several sugar molecules like glucose, fructose, mannose, rhamnose **[14]**. The phytosterols are compounds which have upto 30 carbons and are found in quite low concentrations in plant **[13]**. Medicinally, these phytosterols play very important role **[13]**. The phytosterols present is responsible for its anti-hyperlipidaemic activity **[15]** – Stigmasterol, Diosgenin **[16]**. Various researches conducted by different scientists, proves the presence of various other phytosterols in extract. Phytosterols like β-sitosterol, Daucosterol **[14]**, Δ5–avenasterol, 25,26-dihydroelasterol, clerosterol **[14]** are present in *M. charantia*. Apart from hypolipidemic properties, these phytosterols also possesses immunomodulatory and skin protection properties.

Among the secondary metabolites present in the plant extract, triterpenoids are most abundant **[15]**. There are several curcurbitane type saponins present but only two olenane type of triterpenoid present **[13]**. The antiviral properties are due to the Cucurbitane-type saponin compounds **[15]** - Goyaglycosides A to H. **[17]**. These triterpenoids are present in form of triterpenoid saponins. These contribute to the anti-hyperglycaemic properties of extract of *Momordica charantia*. Charantagenins D and charantagenins are triterpenoids that are mostly used as anti-diabetic compounds **[18]**. Momordicin and charantin **[19]**, act as insulin mimetic and has structural similarity with multiple marketed anti-diabetic drugs.

Different polyphenolic compounds have also been isolated from *M. charantia*. These polyphenolic compounds occurs mostly in form of flavonoids **[13]**. Apart from gallic acid, caffeic acid, catechin, quercetin, the other different polyphenolic compounds isolated are kaempferol, chlorogenic, rutin, are most significant **[20]**. Polyphenoilic

flavonoids shows different properties like anti-oxidant and anti-cancer activites **[13]**.

M. charantia has reported anti-inflammatory, anti-cancer and antioxidant activites as well.

The most abundant phytoconstituents in the plant includes cucurbitanes. These are tetracyclic triterpenoids and their glyosidic derivatives **[17]**. triterpenoids are composed of six isoprene units. A total of about 98 Triterpenoids of *M. charantia* are classified as follows: **[23]** Cucurbitane type (96 compounds): 5, 19-hemiacetal cucurbitane (28 compounds); Normal cucurbitane (51 compounds); Nor cucurbitane (17 compounds) and Olenane type (2 compounds). Triterpenoids saponins are chemically glycosides where dehydration of hydroxy group, connects the aglycone to the sugar moiety. The triterpenoid saponins, can also be divided to cucurbitane type and olenane type **[23]**. Different triterpenoid saponins are responsible to elicit anti-diabetic activity. 5β,19-epoxy-3β,25-dihydroxy-cucurbita-6,23(E)-diene **[24]**, a type triterpene belonging to 5, 19-hemiacetal cucurbitane along with 5β,19-epoxy-25-methoxy-cucurbita-6,23-diene-3β,19-diol **[25]**; Arantagenins A and C **[23]** and 3β,7β,25-trihydroxycucurbita-5,23(E)-dien-19-al **[25]**. Momordicine I, VI, VII, VIII **[26]** are Normal-cucurbitane type saponins **[23]**; Momordicines II, III, IV are Nor – cucurbitane type saponins **[23]** and Charantin is considered to be an important anti-diabetic agents **[23]**.

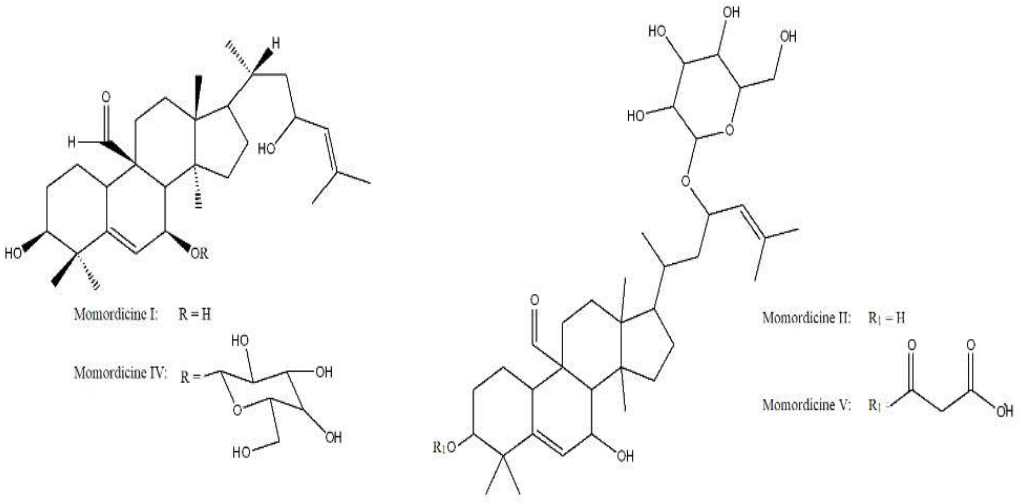

Figure 1: Momordicines obtained from *M. charantia*

MECHANISM OF ANTI-HYPERGLYCAEMIC ACTIVITY OF *Momordica charantia*

In animal models and cell based assays, the extract of bitter gourd leaves and fruits were effective to induce anti-hyperglycemic effects **[25]**.

Studies involving Streptozotocin induced T2 Diabetes induced high fat diet rats where extract of *Momordica charantia* was

administered demonstrated marked decrease in the blood glucose level. It also demonstrated reduction in total cholesterol and triglyceride level. The insulin resistance index was also reduced **[27, 28, 29]**.

The different mechanism of actions of *M. charantia* is proposed to be:

Inhibit fat accumulation and promoting lipolysis

Increase in abdominal and intra-abdominal fat content along with increased triglyceride content (both intrahepatic and intramuscular) lead to insulin resistance and destruction of pancreatic β −cell **[30]**. Extracts of *Momordica charantia* showed to reduce the expression of SBP-1 via mdt-15. It also increased the expression of age-1 via daf-2. The combined effects significantly reduced expression of fat-5, 6, and 7. This in turn reduces the total fat accumulation and thereby reduces T2DM **[30]**. It is found that *M. charantia* improves fatty acid transportation, and also increases acyl-CoA dehydrogenase enzymes system and mitochondrial carnitine palmitoyltransferase (CPT). This increases oxidation of fatty acid **[31]**. It results in reduced insulin resistance due to overexpression of CPT and JNK (C-Jun N-terminal kinase) **[32]**. PPARs are targets of lipid metabolism. Extracts of *M. charantia* show to activate proliferator-activated receptor – gamma in adipose tissue (PPARγ) and upregulates its expression, which thereby leads to metabolism of lipids **[19]**. The phytoconstituent which act as an activator of PPARγ gene is 9c,11t,13trans conjugated linoleic acid **[33]**.

Effect in metabolism and uptake of glucose

One of the major reasons of T2DM is reduced permeability of the blood glucose to the body cells. This is caused by reduced sensitivity of cells to the insulin. The leaf extract in alcohol reduces concentration of glucose 6-phosphatase. It reduces fructose 1,6-diphosphatase and inhibits gluconeogenesis **[17]**. Formation of glucose molecules from non-hexose precursors in the liver is called gluconeogenesis. The reaction of fructose-1,6-bisphosphate is the rate limiting step in gluconeogenesis. Reduction in fructose-1,6-bisphosphate, reduces glucose formation by gluconeogenesis **[13] [Figure 2A]**.

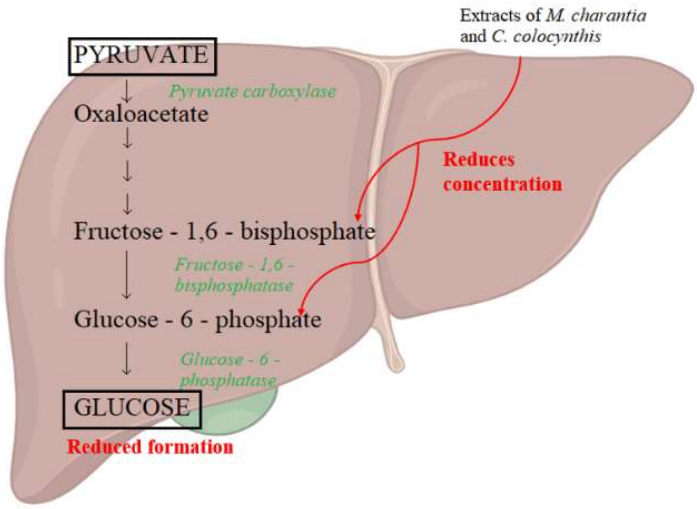

Figure 2: Two main substrates of Gluconeogenesis, are inhibited by extract of *M. charantia*

M. charantia extract enhances enzymes like glucose 6-phosphatase dehydrogenase and increases glycolysis **[17]**. Extracts of *M. charantia* induces glucose transporter-4 (GLUT4) expression, which results in increased uptake of glucose in cells **[19]**. Charantin is a phytoconstituent of *M. charantia*. It shows competitive inhibition of α-glucosidase and thus reduces blood glucose level **[34]**. The extract decreases the amount of glucose absorbed from the intestine. In jejunum brush border cells, it reduces Na-K dependent glucose absorption **[35]**.

Extracts of *M. charantia* increases glycogen synthesis in liver and decrease hepatic gluconeogenesis. It improves glucose oxidation, that occurs in RBC and lipocytes **[36]**. Absorption of disaccharides is mostly prevented **[15]**.

Structural mimicry of insulin molecule by the phytoconstituents

Charantin or momocharin **[Figure 1C]**, has structural similarity to insulin. It is the polypeptide p. It is found in seed extracts of *M. charantia* along with a two steroidal glycosides **[36]**. The chemical structure of momordicin are almost similar to insulin structure [38]. Momordicin has structural similarity to some marketed anti-diabetic drugs like glibenclamide, gliclazide **[Figure 3] [37]**. These molecules are insulin mimetics and act as anti-diabetic agents.

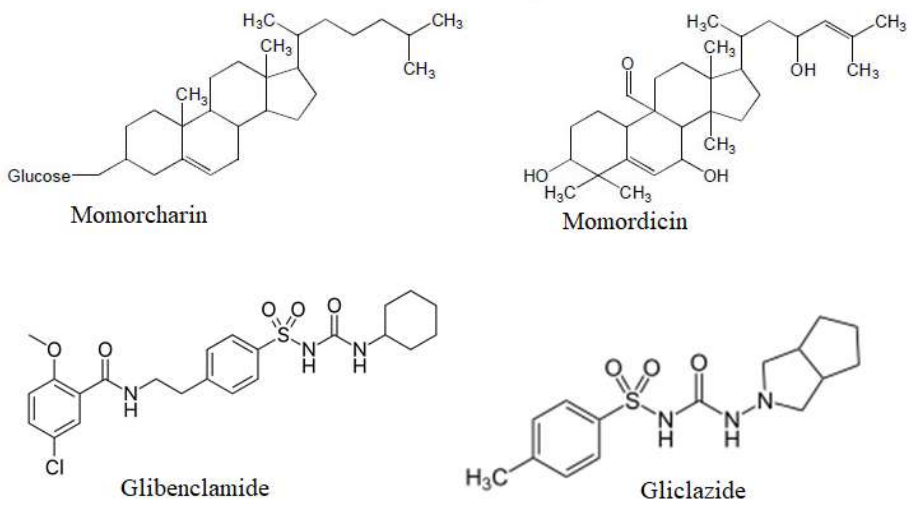

Figure 3: Structure of Momorcharin, Momordicine, Glibenclamide and Gliclazide

Affecting pancreatic Beta cell and induce insulin secretion

Insulin promotes the absorption of plasma glucose by body skeletal muscle cells. *M. charantia* affects the insulin secretion from beta cells. It increases number of insulin producing cells **[38]**.

Extracts of *M. charantia* increases the glucose uptake in hepatic cells and increase hexose kinase and glycogen synthase, which occurs only in presence of increased insulin level **[38]**. The secretagogue activity of insulin is enhanced by extract of *M. charantia* **[39]**. *M. charantia* increases intracellular Ca^{2+} concentration. Thus, it depolarizes L-cell, causing release of GLP, and regenerates β-cell **[19]**.

Inhibiting inflammation

Development of inflammation is linked to progression of T2DM **[19]**. To hinder the progression of T2DM, inflammation should be controlled. Fruit juice of *M. charantia* suppresses proinflammatory Th1 and shift to favourable Th2 in rats. This reduces hyperglycaemia **[40]**.

It mediates TLR-4 (Toll like receptor), which reduces inflammation in rats and prevent lipid accumulation. Thus, it inhibits glucose tolerance **[41]**.

Increase action of AMPK

AMP-activated protein kinase α (AMPK) [13] oxidizes fatty acids in liver and uptakes glucose **[42]**. It inhibits gluconeogenesis and synthesis of cholesterol **[42]**. The active metabolites of *M. charantia* possesses action similar to AMPK **[13]**. This reduces the expression of CREB-regulated transcription co-activator 2 (CRTC2), responsible for gluconeogenesis **[43]**. Constituents of *M. charantia* activates AMPK in the muscle tissue **[13]**. This activated AMPK leads to increased uptake of glucose by skeletal muscle cells and

reduced gluconeogenesis, causing anti-diabetic activity **[17, 42] [Figure 4]**.

Role of peptides isolated from *M. charantia*

Two different peptides were obtained from *M. charantia* which showed anti-hyperglycemic property of the extract. The first peptide is P-insulin **[13]**. Extracts of *M. charantia* contains P-insulin **[35]**. It is a polypeptide hypoglycemic agent. This P-insulin obtained from bitter melon works as insulin sensitizers and promotes uptake of blood glucose by cells **[44]**.

Polypeptide P, which is present in *M. charantia*, shows anti-hyperglycemic **[13]**. Two different types of Polypeptide P were isolated from the extract, with molecular weights 11kD and 3.4kD **[13]**. The role played by polypeptide P is cell recognition and adhesion **[44]**.

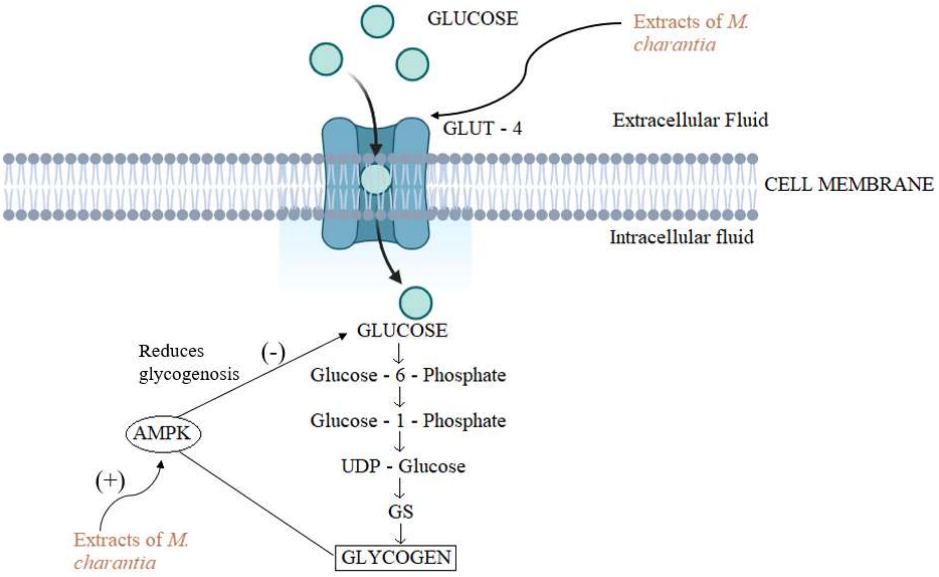

Figure 4: Extract of extracts of *M. charantia* results in increased uptake of glucose in cells

PHYTOCONSTITUENTS OF *Citrullus colocynthis*

Extracts of *C. colocynthis* are still under investigation by various researchers to determine the phytoconstituents present in it. The chemicals components isolated from the extract are categorized based on their chemical classes **[46]**. The chemical compounds isolated includes cucurbitacins, alkaloids, fatty acids and flavonoids **[46, 47]**.

Cucurbitacin and its glycosides are the primarily most important class of chemical compounds present in *C. colocynthis* **[48]**. These are highly oxygenated tetracyclic molecules and have triterpene skeleton (six repetition of isoprene units) **[46]**. The basic skeleton is called cucurbitane skeleton. It can be represented as 19-(10-9β)-abeo-10α-

lanost-5-en. The -CH_3 group present in Carbon 9 of steroidal moiety has shifted to Carbon 10. This makes it a non-steroidal moiety **[46]**. Cucurbitacin A - D, I, J and K are found in extract of *C. colocynthis* **[49, 50] [Figure 5]**.

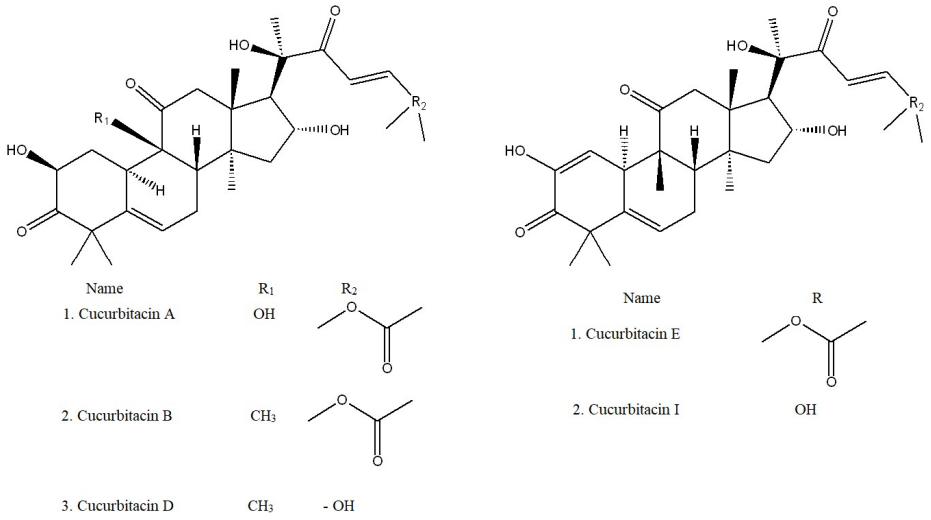

Figure 5: Different types of Cucurbitacin and its glycoside found in *C. colocynthis*

Cucurbitacin E is most abundantly found **[51]**. These glycosides of Cucurbitacin have immense role in anti-diabetic properties of *C. colocynthis*. The glycosides derived from the extracts of the plant, includes flavonoid glycosides like isoorientin 30 -O-methyl ether **[52]**. Two other important flavonoids are isovitexin and isosaponarin **[52]**.

Few alkaloids were found from the plant extract **[53]**. It includes quinoline and its structural analogues including isoquinoline, 2/4/6/8-hydroxyquinoline, and 2/4/6/8-methylquinoline **[53]**.

Different tocopherols including $\alpha, \beta, \gamma, \delta$ tocopherols were isolated from the plant extract **[48]**.

The phytoconstituents which leads to anti-hyperglycaemic property of extracts of *C. colocynthis* includes Cucurbitacin A, B, E, I and flavonoid glycoside isoorentin.

MECHANISM OF ANTI-HYPERGLYCAEMIC ACTIVITY OF *Citrullus colocynthis*

Dose of 300mg/kg of aqueous seed extract of *C. colocynthis* showed antidiabetic properties in rats, which were treated with Streptozotocin to induce T2DM (Jayaraman *et al*. 2009), (Sebbagh *et al*. 2009) **[47, 54]**. The different mechanism of actions of *C. colocynthis* are:

Reduction in plasma level of aspartate aminotransferase

Extract of *C. colocynthis* when administered orally, decreased the level of AST (aspartate aminotransferase) **[48]**. The transfer of amino group from aspartate to glutamate is

catalysed by AST **[56]**. AST is transfers amino groups in the biological gluconeogenesis process in liver **[57, 58]**. Thus, reduction in level of plasma AST reduces gluconeogenesis in liver, and decreases the blood glucose level.

Improved glucose transportation

Blood glucose enters the cells of skeletal muscle through GLUT-4 transporter. Extracts of *C. colocynthis* increases insulin induced uptake of glucose by GLUT-4 transporter by skeletal muscle **[Figure 6]**. This reduces the blood glucose level [59]. It shows anti-diabetic activity.

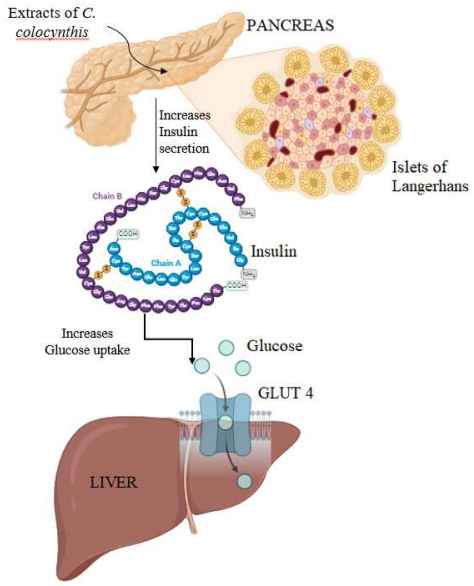

Figure 6: Extracts of *C. colocynthis* increases insulin secretion from pancreatic beta cell

Alteration in enzyme activity

The formation of fructose 6-phosphate is a rate-limiting step in the process of gluconeogenesis. Extract of *C. colocynthis* significantly decreases the level of Fructose-1,6-bisphosphate **[60]**, thereby hampering gluconeogenesis process. Reduction in gluconeogenesis, reduces blood glucose level. *C. colocynthis* extracts, increases the level of liver hexose kinase **[60]**. Increase in hexose kinase increases the rate of glycolysis in cytoplasm of skeletal muscle cell and causes reduction in level of blood glucose **[60]**.

Effect on insulin secretion and insulin resistance

Extract of *C. colocynthis* elevates the of secretion of insulin by the pancreatic beta cells **[59]**. Fruit extracts on rats showed increased insulinotropic actions. It increases the number of insulin producing beta cell mass **[54]**. *C. colocynthis* extract involves regeneration of pancreatic beta cells. Streptozotocin induced rats showed lower insulin resistance after two-month treatment with extracts of *C. colocynthis* **[54]** as shown in **Figure 6**.

DISCUSSION

Both the plants belong to the family Cucurbitaceae **[8]**. The main phytoconstituents responsible for anti-hyperglycaemic activities of *Momordica charantia* are mainly triterpenoid glycosides. Thus includes Arantagenins A and C **[23]**, 3β,7β,25-trihydroxycucurbita-5,23(E)-dien-19-al **[25]**, Momordicine I, VI, VII, VIII **[26]**, Momordicines II, III, IV **[23]** and Charantin **[23]**. Investigations to analyse and determine the phytoconstituents present in *Citrullus colocynthis* are yet continuing. Cucurbitacin, a triterpenoids but non-steroidal, play important role in eliciting anti-diabetic response of *Citrullus colocynthis*. Both *M. charantia* and *C. colocynthis* showed antidiabetic properties in Streptozotocin induced diabetic rats (Mahmoud *et al*., 2017); (Rajasekhar *et al*., 2009) **[27, 47, 54]**. Treatment of *M. charantia* showed reduced blood glucose. It reduced insulin index, cholesterol and triglyceride levels in rats **[27]**. Administering extract of *M. charantia* in rats delayed cataract formation **[13]**. *C. colocynthis*, reduced blood glucose level, insulin resistance, HbA1c level on Streptozotocin induced diabetic rats.

The anti-diabetic mechanisms of *M. charantia* is much more diverse than that of *C. colocynthis.* Extracts of both the plants reduce gluconeogenesis by reducing concentration of Fructose-1,6-bisphosphate **[17, 60]**. The extracts increase the level of Hexose kinase enzyme in liver and increase the rate of glycolysis **[38, 60]**. Increase in insulin secretion were found in both cases. Increased GLUT-4 mediated glucose transportation and regeneration of β-cells **[19, 59]**.

CONCLUSION

The comparison shows both *M. charantia* and *C. colocynthis* are effective natural sources of anti-hyperglycaemic agents. The extracts of both the plants shows antidiabetic effect in Streptozotocin treated diabetic rats. The number of adjuvant beneficial effects, obtained by treatment of *M. charantia* were found to be more. The different mechanisms of anti-hyperglycaemic activity were claimed is not yet proven. There are scopes of further research to prove the different mechanisms of anti-hyperglycaemic activity of these plants.

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