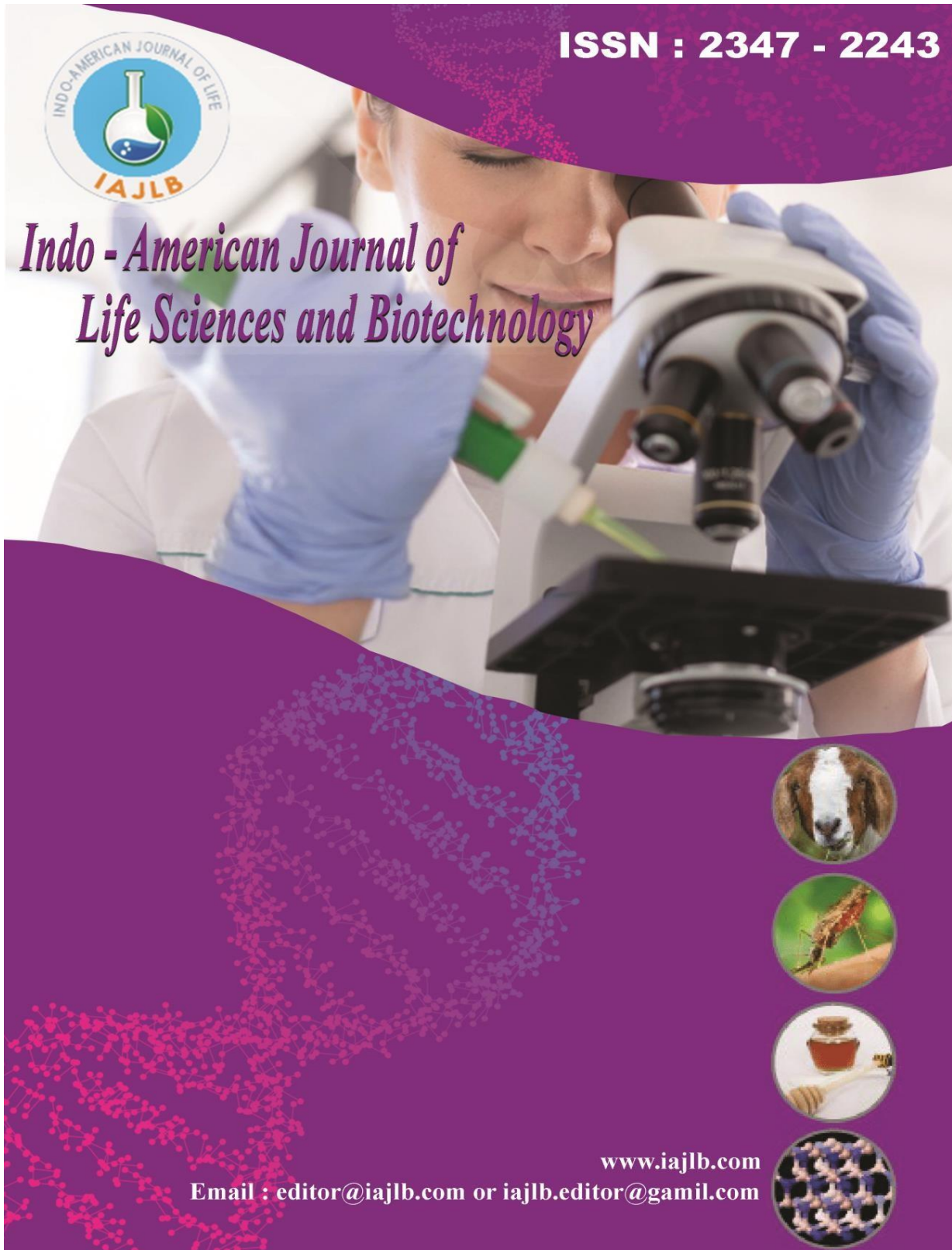




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Chewable Tablets Made From Momordica Charantia [Bitter Melon] A Hypothesis Driven Strategy For Managing Diabetes Mellitus

M Kishore Babu¹, Ch. Vineela², S Keerthana Madhuri³, Ch. Devadasu⁴

1. Professor , Department of pharmaceutics , QIS College of pharmacy , Ongole , A.P

2.Assistant Professor , Department of Pharm chemistry , QIS College of pharmacy , Ongole , A.P

3Assistant .Professor , Department of Pharm analysis , QIS College of pharmacy , Ongole , A.P

4.Assistant Professor , Department of Pharm analysis , QIS College of pharmacy , Ongole , A.P

ABSTRACT: Diabetes Mellitus, the metabolic disorder that causes persistently high blood sugar levels, is a major public health concern across the world. More than 61 million people in India deal with diabetes, earning the country the nickname "Capital of Diabetes." complications caused by diabetes. Phytochemicals and essential medications are abundant in plants, making them an excellent natural resource. The bitter melon, or *Momordica charantia* (MC), is a useful remedy for diabetes mellitus due to its high phytochemical content. One name for *Momordica charantia* is "vegetable insulin" due to the hypoglycemic effects caused by its alkaloids and peptides, which are similar to insulin and Charantin. Much has been said and written about bitter melon's action mechanism. Because of their slow disintegration or dissolving in the mouth, the active ingredient in medicated *Momordica charantia* lozenges is released gradually. This is due to the fact that the lozenges dosage form has a good oral retention time in, increases bioavailability, and decreases gastrointestinal irritation. Both topical and systemic administration are possible with this dose type. The development of chewable lozenges containing *Momordica charantia* as a medication for type 2 diabetes is central to our working hypothesis. The article touches on a few bits of data from bitter melon investigations, both in the pre-clinical and clinical stages. Multiple investigations in the fields of physiology, pharmacology, and biochemistry have provided credence to our theory. The paper also details the process that was utilized to create the chewable lozenges. Additionally, the essay has covered many bitter melon and herbal lozenge formulations that are available for purchase.

Keywords:

Diabetes Mellitus, *Momordica, charantia*, Chewable lozenges, Hypoglycaemia, Drugs

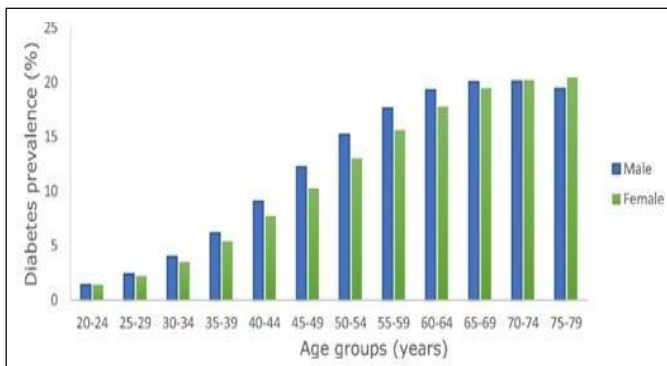
- Corresponding Author
Kishore babu
kishorebabu@gmail.com

INTRODUCTION:

1. Diabetes Mellitus: The increasing prevalence of diabetes mellitus is a serious concern for world health. Many consider it to be among the top killers on Earth. An estimated 366 million people would have diabetes by 2030, up from 171 million in 2000 1. Still, with over 61 million people living with diabetes in India, the country has firmly established itself as the Global Capital of Diabetes. When the beta cells in the islets of Langerhans malfunction or when insulin absorption in peripheral tissues is hindered, the result is hyperglycemia and insulin insufficiency (to varying degrees), together with insulin resistance (number 51).



Diabetic cells have trouble breaking down sugar because insulin, a peptide hormone, is either ineffective or not produced at all. Inadequate insulin synthesis or non-utilization by the body is the main reason of sugar not being metabolized. This leads to the using the body's own fat and glycogen to reduce sugar levels, which may lead to major complications and dysfunction of many organs, accompanied by symptoms including poly-urea, impaired eyesight, and decreased weight 51.



2.
FIG. 1: GRAPH SHOWING DIABETES PREVALENCE PERCENT BY AGE AND SEX OF PEOPLE IN 2019 ⁸

The two major forms of diabetes mellitus are ^{2, 5};

Because the β -cell of the pancreatic islets of Langerhans does not function, type 1 diabetes mellitus (IDDM) occurs. Insulin resistance, likely caused by an inadequate number of insulin receptors, causes type 2 diabetes, also known as non-insulin-dependent diabetic mellitus (NIDDM). IDDM mostly results from a combination of hereditary susceptibility, environmental variables such diet, viral and allergen exposure, and autoimmune processes that destroy insulin-producing β -cells in the pancreas. Environmental and genetic variables are the two primary determinants of NIDDM. ².

The prevalence of type 2 diabetes mellitus (T2DM) among the elderly is a major issue in global public health. A worrying trend is the increasing prevalence of type 2 diabetes among younger generations. This might be due to pathogenic or accelerated aging changes occurring at the molecular level, as well as a decline in linked functions. ³. At now, type 2 diabetes is a complicated and expensive illness in adults, impacting over half a billion people worldwide and being responsible for 90% of all cases of diabetes. A change in lifestyle and appropriate medical care are essential for this illness ⁸⁹. Herbal remedies for diabetes mellitus have been advocated alongside more traditional forms of treatment. Because of their effectiveness, lack of side effects, and inexpensive cost, plants have been used in traditional medicine for a long time all over the globe. That being said, looking into conventional

has grown in importance as a therapeutic plant agent ⁶.

2.1 *Momordica charantia* (MC): The phytochemicals and essential medicines found in plants are an extraordinary natural resource. One perennial climber that helps with the hypoglycemia symptoms of type 2 diabetes mellitus is *Momordica charantia*, more often known as bitter melon, balsam pear, bitter melon, or bitter gourd. It's in the Cucurbitaceae family. Originating in the tropics and subtropics of the world, it may be found all over the place. As a powerful agent in diabetic mellitus prevention diets, it has a wealth of phytochemicals. The bioactive components found in abundance in *M. charantia* include minerals, alkaloids, vitamins, steroidal saponins, polypeptide, and aromatic volatile oil. Bitter melon's range of bioactive



components allows it to exert pharmacological effects, including hypoglycaemic and hypolipidemic effects (52). Some of the proposed mechanisms of action include improving beta-cell integrity, increasing insulin secretion, exerting insulin-like actions outside of the pancreas, and other similar processes. The brush border of the small intestine is also involved in the inhibition of glucose transfer. In addition, by activating enzymes in the glycolytic pathway, MC enhances glucose metabolism in the livers of diabetic mice. Because it contains insulin-like alkaloids and peptides as well as Charantin, a group of steroidal saponinins, which give M. charantia its hypoglycemic effect, it is sometimes called "vegetable insulin" 52, 54.



2.2

FIG. 2: MOMORDICA CHARANTIA WHOLE PLANT ⁵²

Several studies have shown that bitter melon may help avoid diabetes. A number of hypoglycaemia agents, including alkaloids, flavonoids, saponin, catechins, Charantin, and vicine, are present.

Several in-vivo investigations have shown bitter melon's hypoglycemic potential, thanks to its polypeptide-p fraction and other components. Numerous laboratory studies have examined Momordica charantia's hypoglycemic and antidiabetic properties. There is a wealth of information and theories on these impacts that have resulted from experiments using biochemical and animal models. Research has shown that Momordica charantia may enhance glucose tolerance, reduce postprandial hyperglycemia in rats, and alleviate unpleasant 37. Melon extract has the potential to increase insulin sensitivity and lipolysis. Pregnant women should stay away from bitter melon since it has a history of causing miscarriages, according to both human and animal research. Those with a history of severe allergies to cucurbitaceae fruits, including melons and gourds, may have an adverse response to bitter melon. Stay away from bitter melon seeds if you have glucose-6-phosphate dehydrogenase 7.

TABLE 1: ADVANTAGES AND DISADVANTAGES OF LOZENGES ^{40, 44}

S. no.	Advantages	Disadvantages
1.	Easy administration to children and geriatric patients.	Accidental swallowing of lozenge dosage
2.	Can be given to those patients who have difficulty in swallowing	Aldehyde candy bases are not suitable for certain drugs such as benzocaine
3.	Do not require water intake for administration	Mistakenly consumed by children as candy
4.	Local & Systemic effect through the oral cavity	The non-uniformity drug distribution within saliva affects the local therapy
5.	Better patient compliance	Only suitable for heat-stable drugs

1.3 Medicated Chewable Lozenges: Chewing them instead of putting them in your mouth dissolves the gelatine-based formulation that contains the medicine. They have a caramel foundation. The gummy candy lozenges 40 are another name for them. A very effective dose form for delivering medications for gastrointestinal absorption and systemic usage, these lozenges are developed particularly for pediatric patients.



The heated material is poured into molds or onto a uniformly thick 41 sheet to make these pastilles, which are based on gelatin.



FIG. 3: MEDICATED CHEWABLE LOZENGES ⁴⁰



FIG. 4: GUMMY-TYPE CANDY LOZENGES ⁴⁰

3. The Hypothesis Statement: The metabolic condition known as diabetes mellitus (DM) is marked by high blood sugar levels, insulin resistance, and beta cell dysfunction in the islets of Langerhans or decreased insulin uptake in peripheral tissues. Despite the availability of several synthetic medication groups for diabetes therapy, including sulfonylureas, biguanides, α -glucosidase inhibitors, and thiazolidinediones (TZDs), these medications come with side effects and are rather costly (51). Even

The main methods for controlling blood glucose and diabetes using synthetic and man-made hypoglycaemic medications have serious drawbacks, such as the fact that they do not adequately monitor the complications of the disease and come with a host of unwanted side effects. As a result, finding the other pharmacological families of antidiabetic drugs is crucial. The possibility for antidiabetic medications derived from plants has been known for quite some time. One plant that has been discovered to be useful for glycaemic control in diabetes is *Momordica charantia*, often known as Bitter Melon. Previous research has shown that bitter melon has substantial

effects on blood sugar and cholesterol levels. On the other hand, bitter melon enhanced glycaemic management and had a good safety profile, according to a recent meta-analysis 53. In addition to the bitter-melon juice or extract, there are many bitter-melon supplements on the market today, such as pills, capsules, powders, chips, biscuits, etc. (Table 6).

Not only that, but they all help diabetics control their blood sugar levels and have other positive effects on health. 81- 88. Difficulty swallowing is a big issue for patients of all ages, but notably for children and the elderly who use traditional pill or capsule medication forms. The most critical aspect of any dose form is patient compliance. Due to the lack of water, traditional items may be difficult to swallow in certain cases.

Another factor that decreases patient compliance is the harsh taste of bitter melon extract or juice, which is unpleasant to certain patients. Because of these issues, a new solid oral dose form was developed; therefore, there is an urgent need for a visually appealing formulation that can hide the taste. It was our expectation that



sugar-free chewable lozenges made from *Momordica charantia* (Bitter melon) would be an improved method of dosing diabetics of all ages, particularly those with Type-2 diabetes. However, particularly in pediatric patients because of the low barrier to compliance. Our extensive research has shown that there is currently no commercially available lozenge formulation for the management of elevated blood glucose levels. Consequently, the idea of producing such a formulation has the potential to result in a new and superior dosage form for lowering hyperglycemia in diabetes.

4. Evaluation of the Hypothesis

4.1 Phytochemistry of *Momordica charantia*: The Western Ghats and Himalayas are rich in plant species in India, one of the world's wealthiest countries regarding plant biodiversity. Approximately 7500 plant species out of 43,000 in the country have been documented in various medicines, with 1700 species recognized in Ayurvedic literature. Ayurveda is a 5000-year-old

57-58

Indian medicine primarily uses phytochemicals in its preparations and formulations. Phytochemicals are employed in various applications in India, including cosmetics, health and hygiene, scent, and food supplements. In China, India, and other Asian nations, *Momordica charantia* is commonly used to treat diabetes. The literature has identified several bioactive substances in *Momordica charantia* fruit, including carbohydrates, proteins, lipids, and others. Triterpenoids, saponins, polypeptides, flavonoids, alkaloids, and sterols are found in *Momordica charantia* ⁶¹⁻⁶⁵.

TABLE: 2 MAJOR BIOACTIVE COMPONENTS OF *MOMORDICA CHARANTIA* WITH THEIR RELATED FUNCTION ⁵⁷

Major Bioactive Components	Functions	Distribution
Polysaccharides	Antioxidant, antidiabetic, immune enhancement, neuroprotective, antitumor	Various parts of plants
Peptides and Proteins	RNA N-glycosidase, polynucleotide adenosine glycosidase (PAG), DNase-like, phospholipase, superoxide dismutase, antitumor, immune suppression, antimicrobial	Seed
Lipids	Antitumor, antioxidant	Seed, Flesh
Terpenoids	Anticancer, antioxidant, antidiabetic, hypoglycemic, cancer chemoprevention	Stem, Leaves, Fruit
Saponins	Antihyperglycemic, hypolipidemic, antiviral	Fruit, Root, Seed
Phenolics	Antioxidant, anti-inflammation, immune enhancement	Fruit, Pericarp, Seed
Sterols	Antimicrobial	Pericarp, Fruit

Among the several bioactive components of *Momordica charantia*, polysaccharides stand out. There is evidence that the polysaccharides found in V fruits possess antibacterial, anticancer, neuroprotective, immune-enhancing, and antidiabetic characteristics. A recent study found that

Saponin was also discovered to improve insulin release in in-vitro pancreatic MIN6-cells in the research.

Polypeptides named "polypeptide-p" and Charantin are responsible for bitter melon's ability to lower blood sugar levels.

Sections 58–60.

4.1.1 Saponin's Mechanism of Action in Diabetes Mellitus: Many plants and plant-based products include saponins, which are n-glycosides that are either steroids or triterpenoid. They show promise in several areas of medicine, including hypoglycemic, anticarcinogenic, hypocholesterolaemia, and antidiabetic. 52. Saponins influence insulin-resistant diabetes-related peptide adipokines such as leptin, apelin, vastatin, and adiponectin. Because of their ability to control blood sugar levels and enhance insulin sensitivity, saponins show promise as antidiabetic medications.

26. There is charantia in bitter melon extract, which helps the liver store glycogen and promotes normal insulin production by the islets of Langerhans. Helps maintain healthy blood protein levels and glucose utilization in the periphery 17. When it comes to glucose consumption by the liver, bitter melon saponins block gluconeogenesis and fructose-1,6, biphosphates, two important enzymes, and enhance glucose oxidation by activating glucose-6-phosphate dehydrogenase via the shunt route, which is one of the many pathways involved.

Charantia also encourages the development of new beta cells that secrete insulin and improves insulin release from pancreatic islets of beta cells 16. A decrease in blood glucose and a rise in plasma insulin level constitute the antidiabetic mechanism of action of this chemical. Charantia is an antioxidant that protects diabetic metabolic problems from free radicals and oxidative stress (28).

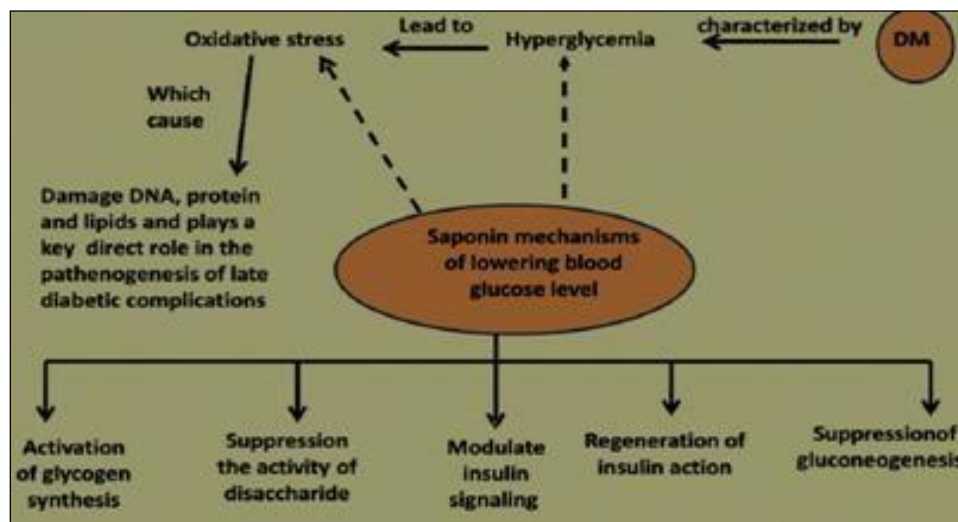


FIG. 5: ANTIDIABETIC MECHANISM OF SAPONINS ⁵²

4.2 Medicinal Properties of Bitter Melon: *Momordica charantia's* medicinal uses date back many years. It



possesses anti-inflammatory, antiviral, cholesterol-lowering, antidiabetic, and anti-cancer properties. It has anti-mutagenic and antioxidant phenolic chemicals in abundance. Hyperlipidaemia, gastrointestinal disorders, microbiological infections, and menstruation problems are just some of the conditions that bitter melon's many traditional medicinal uses have been put to use. Research has shown that *Momordica charantia* has powerful antiviral effects, including as boosting the immune system and activating natural killer cells, which may help fight infections like HIV/AIDS and white spot syndrome. *Momordica charantia* has also been shown to contain

cytotoxic effects and anti-carcinogenic characteristics, making it useful in the fight against a wide range of cancers. As shown by Ray et al. (12, 22), the *Momordica charantia* extract may be utilized as a dietary supplement to prevent breast cancer by modulating signal transduction pathways, which in turn inhibits the proliferation of breast cancer cells. The saponins found in bitter melon juice help regulate insulin levels and reduce blood sugar. Some of bitter melon's phytochemicals, including alkaloids and insulin-like peptides, have hypoglycaemic effects, meaning they raise glucose tolerance without raising insulin levels in the blood 19.

4.3 Antidiabetic or Hypoglycaemic Activity of *Momordica charantia*: Many hypotheses have been advanced on the origin of *Momordica charantia*'s hypoglycemic effects. The active ingredients of *Momordica charantia* extract seem to have the structural similarities of conical India, as determined by infrared-spectrum and electrophoresis

In the early examination, it was hypothesized that bitter melon had some insulin-like qualities (20). Natural glucose regulation is facilitated by its polypeptide - p content. A hypoglycemic protein known as polypeptide-p or p-insulin has been shown to reduce blood sugar levels. How much glucose administered sub-continuously into gerbils, langurs, and humans 18. There is some evidence that *Momordica charantia* may raise glucose levels in the bloodstream and liver while decreasing gluconeogenesis and increasing glycogen synthesis in the liver.

28. oxidation in fat cells and red blood cells 27. According to Welihinda et al., *Momordica charantia* stimulates the pancreas to release more insulin. One possible effect of *Momordica charantia* extract is to stimulate the pancreas to produce more beta cells. But research has not confirmed this process 16. A polypeptide named polypeptide P and a combination of two steroid glycosides termed Charantin 23 have garnered the most of the attention despite the fact that *Momordica charantia* contains many components with hypoglycemic effects.

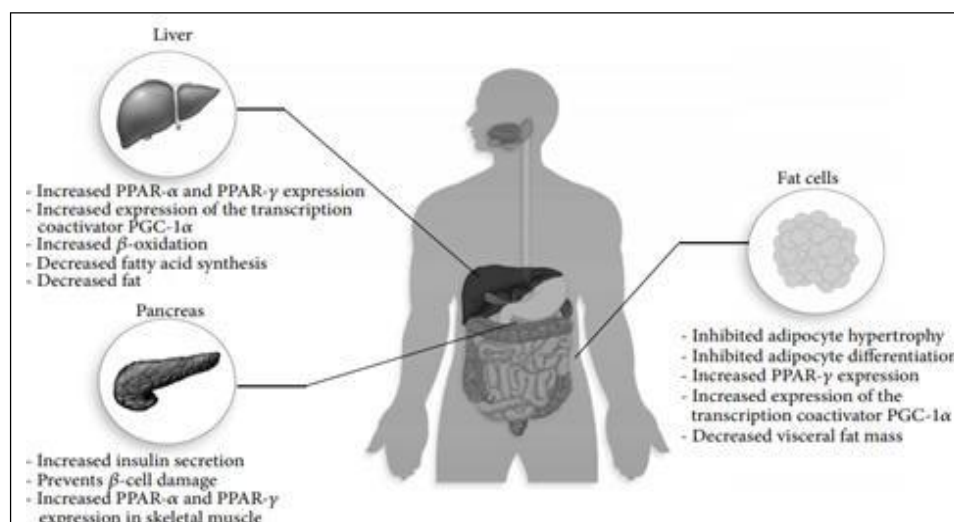


FIG. 6: EFFECT OF BITTER MELON ON VARIOUS ORGANS AND PROBABLE MOLECULAR TARGETS FOR



IMPROVING OBESITY AND DIABETES ⁷⁴



4.4 Mechanism of Action of *Momordica charantia*: To maintain homeostasis of blood glucose and lipid levels and forestall pathological diabetes, active phytochemicals regulate these metabolic processes via a variety of hypothesized mechanisms. These bioactive formulations have been backed by several studies in pharmacology, biochemistry, and physiological research. 51. *Momordica charantia* may have antidiabetic effects through a variety of pathways, including activation of enzymes involved in the HMP pathway, suppression of gluconeogenic enzymes, stimulation of skeletal muscles, inhibition of intestinal glucose uptake, restoration of islet β -cells, and inhibition of adipocyte differentiation. Glycosides, vicine, polypeptide p-insulin, and charantin all work to increase glycogen stores in the liver by blocking gluconeogenesis and increasing glucose oxidation via the pentose phosphate route, often called the shunt system. the liver. By restoring damaged β cells, they improve peripheral insulin sensitivity and increase insulin secretion. Momordicosides, cucurbitate glycosides, and their aglycones activate AMP-activated protein kinase (AMPK), which in turn increases insulin sensitivity through lectin linking of the two insulin receptors, inhibition of skeletal muscle protein tyrosine phosphatase 1B, an increase in the number and translocation of GLUT4 receptors, and an enhancement of the phosphorylation rate of the insulin receptor substrate. *Momordica charantia* stimulates glucose absorption into muscle cells and regulates glucose uptake into the jejunum brush border vesicles in a manner similar to insulin. The absorption of di- and monosaccharides in the gut is prevented by inhibiting enzymes like disaccharidase and glucosidase, respectively. Additionally, it promotes AMPK activity 51 by inducing the production of adiponectin from adipose tissue.

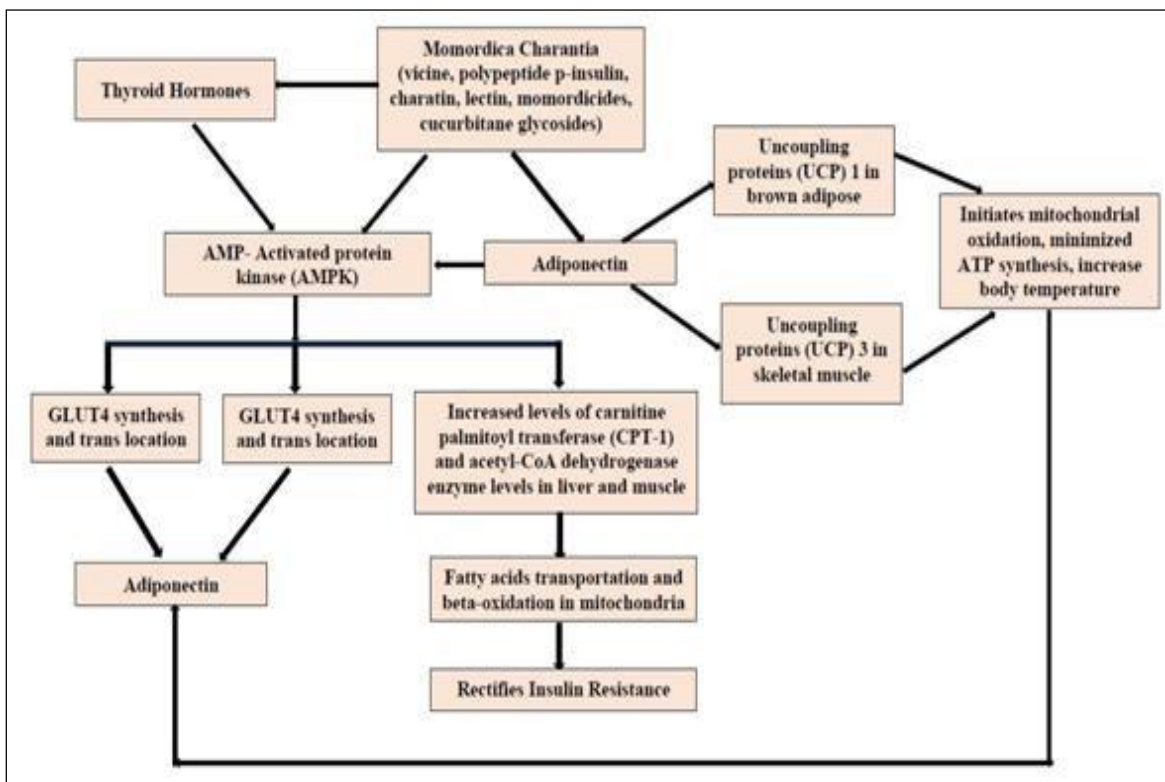


FIG. 7: THE SCHEMATIC DIAGRAM SHOWING MECHANISM OF ACTION OF *MOMORDICA CHARANTIA* ⁵¹

Consumption of *Momordica charantia* lowers the intestinal glucose absorption that is reliant on the Na^+/K^+ ATPase, which is much greater in individuals with diabetes. Reducing the activity of pancreatic lipase, intestinal sucrase, and maltase reduces the absorption of glucose and lipids. An insulin-tropic metabolic switch



known as AMPK promotes GLUT4 synthesis and translocation, which in turn controls glucose absorption. Research has shown that momordica charantia may activate AMPK by increasing adiponectin and thyroxine levels. In the liver, AMPK activates 3-hydroxy-3methylglutaryl-coenzyme reductase and inhibits cholesterol formation; it subsequently transports fatty acids to mitochondria for oxidation. Conversely, Adiponectin helps the body keep blood glucose levels healthy by promoting mitochondrial oxidation without producing ATP. By increasing glucose inflow and improving the activity of hepatic hexokinase, glucokinase, and phosphofructokinase, momordica charantia makes glucose oxidation easier. But by reducing expression of lipogenic genes, it stops adipocytes from making new fat. Additionally, the transportation of fatty acids and beta (β) oxidation are both enhanced by the liver and muscle enzymes known as acyl-CoA dehydrogenase and carnitine palmitoyltransferase (CPT). organelles called mitochondria. Restoring insulin resistance is achieved by the action of AMPK, which leads to a rise in the mRNA and protein levels of cytokine signaling-3, CPT-1, Akt, and c-Jun N-terminal kinase (JNK) in the liver. In addition to initiating fuel oxidation without ATP synthesis via electron-transporting proteins, AMPK enhances the uncoupling proteins (UCP) 1 in brown adipose tissue and skeletal muscle protein in mitochondria, respectively. Keeping one's core temperature at 51 degrees is the primary use of the energy produced by this process.

4.5 Pre-Clinical Studies: Many animal studies have shown that normal animals may experience hypoglycemia when exposed to MC in any form, including seeds, fruits, pulp, leaves, and the whole plant 1. Research on the Impact of Bitter Melon and a Chromium Propionate Complex on Insulin Resistance and Type 2 Diabetes Symptoms in Rat Models was conducted by Pandora White et al. The purpose of the research was to examine if streptozotocin (STZ)-induced diabetic rats that were given a high-fat diet might be treated more effectively by mixing the two nutritional supplements. After the experiment was over, samples of blood and internal organs were collected for analyses including biochemistry, haematology, and mineral (Cr) using standard analytical techniques. Cr³ (supplementary Cr (III)) had no

Unlike the prior research, this study found no discernible impact on glucose and lipid metabolism in diabetic rats caused by STZ who were given a high-fat diet. Supplementing with BM fruit powder in high-fat-fed rats showed some impacts on body mass, but when given with Cr³, these advantages were subdued. When Cr (III) and BM are together, they seem to act as substances that prevent the absorption of nutrients. Levels of glucose in the serum of both healthy and diabetic rats (mg/dL). The blood glucose level is called beginning glucose when the Cr and BM treatments begin. The final blood glucose values after 6 weeks of therapy with Cr and MC 29.

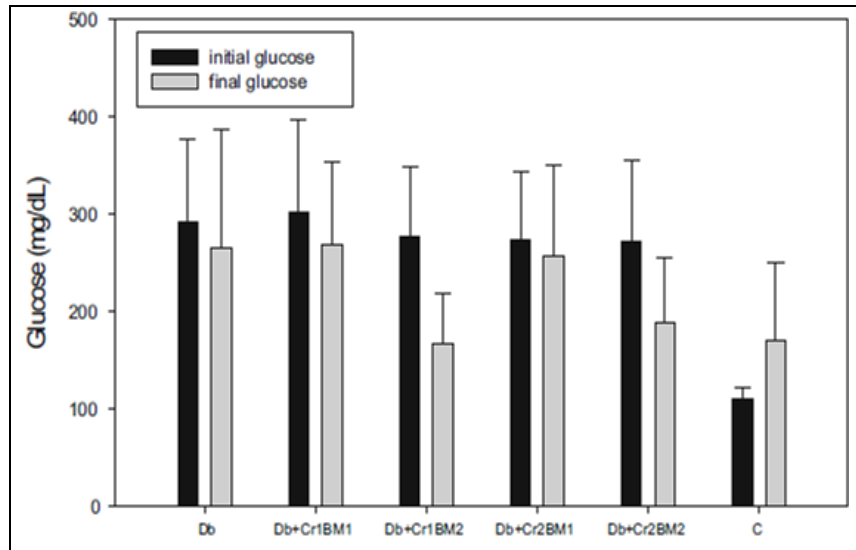


FIG. 8: DIABETIC CONTROL RATS(DB), DIABETIC SUPPLEMENTED WITH A LOW DOSE OF CR(III) RATS AND A LOW DOSE OF BM (DB+CR1BM1) RATS, DIABETIC SUPPLEMENTED WITH A LOW DOSE OF CR(III) RATS AND HIGH DOSE OF BM (DB+CR1BM2) DIABETIC SUPPLEMENTED WITH A HIGH DOSE OF CR AND A LOW DOSE OF BM RATS (DB+CR2BM1), DIABETIC SUPPLEMENTED WITH A HIGH DOSE OF CR(III) RATS AND HIGH DOSE OF BM RATS (DB+CR2BM2) ²⁹



In contrast, Jose Luis Perez's "Metabolite profiling and in-vitro biological activities of two commercial bitter melon (*Momordica charantia* Linn.) cultivars" set out to compare and contrast two commercial bitter melon genotypes in terms of their bioactivity and metabolite profile. Fifteen phenolic and forty-six triterpenoids were identified in that investigation of several bitter melon extracts using ultra-performance liquid chromatography–high resolution mass spectrometry (UPLC–HRMS). We used bitter melon extracts with a broad range of polarity from the pericarp and inner tissues. Researchers concluded that bitter melon extracts include chemicals with different levels of antioxidant and anti-hyperglycemic activity. A variety of dosages of extracts were evaluated for their inhibitory effects on α -glucosidase. In order to investigate the inhibition of α -glucosidase activity in vitro, the release of p-nitrophenol glucopyranoside from p-nitrophenyl α -D was used. There was a dose-dependent rise in inhibitory activity of 30 for all of the bitter melon extracts tested here. Another research found that after just one day of taking the MC ethanolic extract, participants' blood glucose levels dropped significantly. For two days, the animals were divided into two groups: one with normal blood sugar levels and another with diabetes. Next, 10 mice were assigned to each of the two diabetes groups. As a control, the first grouping did not undergo any therapy. The second grouping continued to take MC fruit extracts for another week. In addition to diabetic mice that had undergone treatment, we also maintained untreated diabetic animals for future studies. To find the LD50, mice were used. It was also decided upon by the MPD. Postmortem results and symptoms of acute poisoning were recorded. The infusion of MC ethanolic extract significantly reduced blood glucose levels compared to the zero time. In contrast, there was no drop in the control diabetic group after 31 days.

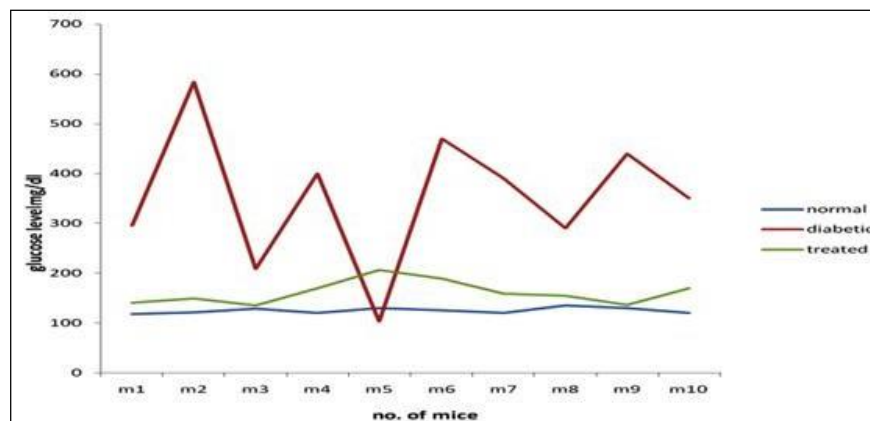


FIG. 9: GRAPH BETWEEN GLUCOSE LEVEL AND NUMBER OF MICE³¹

While MC improved postprandial blood glucose levels, according to another study by Eman Abbas Moussa et al. on "Hypoglycaemic effect of *Momordica charantia* (Karela) on normal and alloxan diabetic albino mice," MC caused a statistically significant decrease ($P < 0.05$) in blood glucose levels by the end of the experiment compared to the diabetic control group. Within that research, at least one

10 males and 10 females were administered 50 mg/kg BW alloxan intraperitoneally as a single dose to the animal group. Plasma glucose levels were randomly examined in order to ascertain whether or not certain groups of mice were diabetic. The present data indicate that *Momordica charantia* extract considerably decreased blood levels of cholesterol, creatinine, and AST and ALT activity (32).



TABLE 3: EFFECT OF TREATMENT WITH BMJ (10 ML/KG BODY WEIGHT 3 TIMES WEEKLY FOR 12 WEEKS) ON BLOOD GLUCOSE LEVELS (MG/DL) IN ALLOXAN DIABETIC MICE DURING GLUCOSE TOLERANCE TEST ³²

Time (minutes)	Pre-treatment* (mg/dl)	Post-treatment** (mg/dl)
30	280 ± 13.8	210 ± 10.5
60	385 ± 22.4	250 ± 8.9
90	420 ± 19.4	310 ± 14.8
120	400 ± 15.8	270 ± 17.5

The data represent the mean ± SD of 10 animals (5 males and 5 females) * Blood glucose level before the initiation of treatment with BMJ. ** Blood glucose level after treating 12 weeks with BMJ.

The increased risk of cardiovascular disease (CVD) associated with insulin resistance is likely due to reduced insulin sensitivity, which in turn causes an increase in apoB secretion and VLDL formation. One research that sought to examine the effects of BMJ on plasma apoB levels and the hepatic insulin signaling cascade in mice that were given a high-fat diet (HFD) was conducted by Pratibha V. Nerurkar et al. If this research is correct, MC may be able to normalize apoB-48 levels.

via regulating the insulin signaling pathway, plasma, and apo B-100 in mice subjected to a high-fat diet for a period of sixteen weeks. Statistically small as the relationships found in most research are, they nevertheless highlight tendencies that need more investigation ³³. Bitter melon has been shown in several trials to improve lipid parameters in animal models of diabetes and obesity.

TABLE 4: EFFECT OF BITTER MELON EXTRACTS ON LIPID PARAMETERS OF DIABETIC AND OBESE ANIMAL MODELS ⁷³

Model	Dose	Experimental Outcome
Cholesterol fed rats	0.5, 1 and 3% of diet	(i) Not changed TC level, but (ii) Increased HDL-C level in plasma
STZ-induced diabetic rats	10 ml, 100% fruit extract per kg body weight daily for 10 weeks	(i) Decreased elevated level of plasma cholesterol, TGs and phospholipids in STZ induced diabetic rats
Diabetic rats		(i) Decreased in TG and LDL, (ii) Increased in HDL
Rats fed a HF diet	7.5 g/kg or 0.75%	(i) Supplementation did not affect serum and hepatic cholesterol. (ii) Supplementation in HF diet rats led to a lowering of hepatic TAG and steatosis score in liver section



Wistar rats	Saponin fraction (50-100 mg/kg body weight)	(iii) Plasma epinephrine and serum FFA concentrations were increased. (iv) Lowered TAG concentration in red gastrocnemius and tibialis anterior.
Female C57BL/6 mice fed with HF diet	1.5% freeze-dried BMJ with diet	(i) Decreased pancreatic lipase activity and serum TG level in corn oil loaded rats. (i) Normalized plasma TAG, cholesterol and NEFA (ii) Normalized AST, ALT, and ALP in plasma. (iii) Decreased ApoB secretion and modulated the phosphorylation status of IR and its downstream signalling molecules.
Albino rats fed with sucrose	40, 80, and 120 mg/kg of body weight	(i) Reduced TG and LDL levels and increased HDL levels. (ii) Normalized hyperglycaemia (iii) Lowered TBARS and normalized levels of reduced glutathione.
Offspring rats fed high (60%) fructose diet	1% of diet	(i) Decreased plasma level of TG, cholesterol and FFA. (ii) Lowered the hepatic levels of stearyl-CoA desaturase and microsomal TG transfer protein mRNA. (iii) Increased PPAR γ coactivator 1- α and fibroblast growth factor 21 mRNA and fatty acid binding protein 1.
Female Zucker rats	3.0% ground BMS	(i) Supplementation increased the expression of PPAR- γ in the WAT. (ii) Decreased TC and LDL-C; increased HDL-C. (iii) Downregulated the expression of PPAR- γ nuclear factor-KB (NF-KB) and interferon γ mRNA in heart tissue.
HF diet fed mice	1.2% plant extract	(i) Decreased TC, TGs and LDL-C. (ii) Increased hepatic AMPK p, AMPK α 1, AMPK α 2 and Sirt1 content. (iii) FGF21 and insulin concentrations were significantly decreased. (iv) Hepatic FGF21 content was significantly downregulated, while FGF receptors 1, 3 and 4 (FGFR1, FGFR3 and FGFR4) were greatly upregulated.
Wistar rats fed high cholesterol diet		(i) Decreased serum TC, and LDL-C, HDL-C. (ii) Decreased mRNA levels of hepatic LXR α in rats. (iii) Increased the hepatic CYP7A1 mRNA level
C.57BL/6J mice 45% HF diet	0.1, 0.2 and 0.4 g/kg/day extracts	(i) Decreased serum TC and fatty acids. (ii) Normalized leptin and insulin concentration. (iii) Increased PPAR α level in liver. (iv) Increased GLUT4 expression in skeletal muscle. (v) Significantly increased the hepatic protein contents of AMPK phosphorylation and decreased phosphoenolpyruvate carboxykinase (PEPCK) expression.

4.6 Clinical Studies: In contrast to animal experiments, there have been few and few between clinical investigations on the hypoglycemic effects of MC 1. Using himself as a test subject, doctor Lakholia probably established the medical advantage of bitter melon for the first time in 1956. The first evidence that WBG improved MetS in people came from Chung-Huang Tsa et. al., which paved the way for future randomized controlled studies to evaluate the effectiveness of WBG supplementation. The results of this pilot research demonstrate that WBG has a beneficial effect on the prevalence of metabolic syndrome (MetS) in people. The recurrence rate of MetS was significantly decreased after three months of supplementation with a daily dosage of 4.8 g lyophilized WBG powder; this improvement remained for one month but did not persist for further months after supplementation was discontinued (35). Research on the hypoglycemic potentiation of oral hypoglycemic medications in

Thirteen type 2 diabetic patients were divided into three groups and studied for non-insulin-dependent diabetes mellitus (NIDDM) using phytochemical analysis and Momordica charantia fruit extraction (Tongia et al.). The individuals' FBS and PPS levels were measured before the intervention, and the findings served as controls. Following that, the FBS and PPS levels were evaluated after three groups had been administered metformin, in



glibenclamide, or metformin glibenclamide for seven days. For the next week, seven individuals were given half-dose oral hypoglycemic medications in addition to the usual dosage of MC fruit extract (200 mg twice day), and their FBS and PPS levels were reevaluated. Oral hypoglycaemics decreased FBS and PPS levels, while MC extract 36 further lowered these levels. Among newly diagnosed type 2 diabetics, Anjana conducted the first randomized controlled experiment to test the hypoglycemic impact of metformin with dried powder of bitter melon fruit pulp.

Wu et al. The purpose of this trial was to determine if three daily doses of metformin taken with bitter melon were safe and effective. Metformin (n = 33), bitter melon (n = 33), metformin (n = 31), or bitter melon (n = 32) at dosages of 500 mg/day, 2000 mg/day, or 1000 mg/day, respectively, were given to 129 patients who were randomly allocated to the experiment. There seems to be a small hypoglycemic effect of 2000 mg/day of dry powder of bitter melon fruit pulps, based on a reduction in fructosamine concentrations. In contrast, metformin 1000 mg/day had a greater hypoglycemic impact (37).

Analyzing 100 individuals with type 2 diabetes, Ahmad et al.

Fifty-eight men and forty-two women were part of the 44 who studied the effects of MC. This study used the same participants for both the controls and the trials, even though there was a huge sample size. Despite the fact that identified limitations, such as the lack of oversight for people to implement instructions at home, no signs of adverse impacts or attrition were detected. This study's methodology was flawed because of it. The case study nature precludes the use of the Jadad score. There is a wide range of actual dose and outcome metrics used in the studies. Regardless, when

4.7 available trials suggested that MC had a higher efficacy³⁹.

4.8 Medicated Chewable Lozenges Methodology:

4.8.1 **Materials and Method:** The materials used in the formulation of chewable lozenges are the candy base, fillers, lubricants, humectants, binders, whipping agents, colouring agents, flavouring agents, acidulants, preservatives, and medicament⁵⁰.

TABLE 5: MATERIALS FOR CHEWABLE LOZENGES FORMULATION^{40, 49-50}

S. no.	Ingredients	Description	Examples
1.	Candy bases sugar free base (for antidiabetic lozenges) Corn syrup	In a ratio of 50:50 to 75:50 sugar-free base to corn syrup. To mask the bitter taste of medicament. To prevent crystallization and obtain the desirable appearance of the lozenge	Mannitol, Sorbitol, PEG- 600 & 800
2.	Fillers	To improve the flowability	Microcrystalline cellulose, Dicalcium phosphate, Calcium carbonate, Calcium sulphate& Lactose
3.	Lubricants	To avoid the sticking of candy to the teeth	Calcium stearate, Magnesium stearate, Stearic acid, PEG, Vegetable oils & Fats.
4.	Humectants	To improve chew mouth feel properties	Propylene glycol, Glycerine& Sorbitol
5.	Binders	To hold the particles	Corn syrup, Acacia, Polyvinylpyrrolidone, Tragacanth, Gelatin & Methylcellulose



6.	Whipping agents	For obtaining the desired degree of soft chew	Gelatin, Milk protein, Xanthan gum, Pectin, Starch, Carrageenan & Algin
7.	Colouring agents	To enhance the appearance and organoleptic properties of lozenges	Lakolene dyes, Water-soluble dyes, FD & C colours, Red colour cubes & Orange colour paste
8.	Flavouring agents	To enhance the taste of lozenges	Spearmint, Menthol, Eucalyptus oil, Zinger, Clove, <i>etc</i>
9.	Acidulants	To fortify and strengthen the flavour profile of lozenges & to alter the pH to maintain the integrity of the drug	Citric acid, Malic acid, Fumaric acid and Tartaric acid
10.	Medicament	35-40 % of a medicament can be incorporated	Bitter Melon to treat diabetes



3.7.1 Selection Criteria for Formulation of Chewable Lozenges ⁴³:

- ❖ Selection of suitable drug candidates.
- ❖ Selection of appropriate drug carrier excipients.

3.7.2 Method of Preparation for Medicated Chewable Lozenges:

Heating and Congealing Technique: In a beaker, the syrupy base was made by dissolving the appropriate amounts of sugar in the water while heating on a hot plate. The temperature was kept at 105-110 °C until it thickened. After 30 minutes of heating, the medication and other excipients (except plasticizer) were manually added and thoroughly mixed. A plasticizer was added to the prepared mass after it was heated for another 45 minutes. The syrupy base was then transferred into a pre-cooled, pre-lubricated mold and left for 10-15 minutes. The lozenges were taken out from the mold and allowed to air dry. A process of plasticizer addition was eliminated from the technique for batches without plasticizer ⁵⁰.

Melting and Mold Technique: The melted PEG was mixed with the other materials to make a homogeneous mixture. The mixture was then poured into a stainless-steel mold of the desired shape and size to form a lozenge ⁵⁰.

3.7.3 Manufacturing of Chewable Lozenges:

- Candy base is cooked at 95°C-125°C.
- Transferred to a planetary or sigma blade mixer.
- Mixed mass is allowed to cool at 120°C.
- Below 105°C, the whipping agent is added to the above mass.
- Followed by incorporation of medicament between 95°C-105°C.
- The Colouring agent is dispersed in the humectant above 90°C and mixed to the above mass.
- Flavouring agent is then added below 85°C.
- Lastly, the lubricant is added above 80°C to the above mass.

5. Marketed Supplements of Bitter Melon:






- The formation of chewable lozenges takes place in the form of long rope, which is then cut into desired size and uniform thickness ⁴⁰.

Absorption of Drug through Chewable Lozenges: Lozenges are solid unit-dose medication delivery devices with flavors that are meant to be kept in the mouth, moistened with saliva, and then dissolved gradually until dissolved entirely. It helps the body absorb medications administered systemically and soothes sores or infections in the mouth or throat. They may also be employed for systemic effects if the drug is well-absorbed via the buccal linings. 6,8, and 71. Chewing the drug-containing lozenge in between your teeth before swallowing is the only certain way to get all of the medicine out of it. This causes the release of the medicine from the base into the saliva. Absorption of drugs may occur in two ways: first, via the oral mucosa; second, through the gastrointestinal system. They happen at the same time, at a 90-degree angle. Recent research indicates that bitter melon has a hypoglycemic






impact that begins one hour after consumption and continues for three to four hours. Absorption of bitter melon lozenges is facilitated by a number of digestive system enzymes, whereas bitter melon extracts are taken in by diffusion 78, 80.

TABLE 6: MARKETED SUPPLEMENTS OF BITTER MELON TO TREAT DIABETES

S. no.	Product Name	Description	Product
1.	Himalaya organic bitter melon capsules ⁸¹ .	Support glucose metabolism and blood sugar level.	
2.	Himalaya Karela Metabolic Wellness Tablets ⁸² .	maintain healthy glucose levels.	
3.	Vedic Karela Juice ⁸³ .	Supports natural detoxification of blood, supports liver and pancreatic health and maintains normal blood sugar levels.	
4.	Indian Herbal Valley Karela Powder ⁸⁴ .	Maintaining healthy blood sugar levels and healthy lipid levels.	
5.	The tea trove Organic Bitter Melon Tea ⁸⁵ .	Helps in regulating blood sugar levels.	
6.	Aramacs Bitter Gourd Oil ⁸⁶ .	Purifies blood, activates spleen & liver &	



		good for diabetes.	
7.	Snackwise Bitter Gourd (Karela) Chips ⁸⁷	-	
8.	Taste Good Karela Biscuit ⁸⁸ .	Maintain blood sugar.	

6. Marketed Herbal Lozenges:

TABLE 7: SOME HERBAL LOZENGES AVAILABLE IN MARKET⁶⁸

Type	Ingredient	Effect produced	Uses
Garlic and ginger lozenges	Sucrose, sodium chloride, polyvinyl, pyrrolidone, NaCMC	Taste masking with good release matrix type lozenges	Inhibitory activity against non-resistant <i>C. albicans</i> infection, non-resistant oral thrush
Marshmallow root extract lozenges	Xanthan gum as gummy base	Increase the disintegration time over 30 min and retain in vitro release rate 40% for 30 min of lozenges	Irritated oropharyngeal mucosa and associated dry cough
Liquorice and catechu lozenges	Galen IQ 990, liquid glucose, liquorice powder extract, black catechu powder extract	Combination of both drug produced synergistic effect	Recurrent aphthous stomatitis
Polyherbal extract based linkus lozenges	<i>Adhatodavasica glycyrrhiza glabra</i> , <i>Piper longum</i> , <i>Viola odorata</i> , <i>Hyssopus officinalis</i> , <i>Cordia latifolia</i> , <i>Alpinia galanga</i>	Suitable dosage form in symptomatic relief	Sore throat and cough
Eucalyptus oil and coleus aromaticus oil lozenges	<i>Magnesium stearate</i> , lactose, mannitol, gelatin, sucrose	Inhibitory activity against non-resistance <i>C. albicans</i> infection	Antimicrobial activity

DISCUSSION & CONCLUSION: We reviewed the literature on the traditional use of *Momordica charantia* as a treatment for diabetes mellitus and analyzed its potential in this notion. Over the next half-century, the global prevalence of diabetes is projected to rise. Healthcare expenditures are expected to be significantly affected by complications associated with diabetes, as well as diabetes in younger individuals, such as children and adolescents. This includes cardiovascular disease and other long-term consequences. Numerous investigations have shown that over a hundred different plant species from different families are utilized as antidiabetic medications on a global scale. Because of this, we think that herbal therapy is the best way to manage diabetes now. The effectiveness of these ethnomedicinal plants has to be confirmed by pharmacological means. This proves without a reasonable doubt that herbal medications may treat human illnesses. Hyperlipidaemia, gastrointestinal problems, microbial infections, and menstruation problems have all been traditionally treated



using bitter melon's fruit, stems, leaves, and roots. *Momordica charantia* has a wealth of bioactive substances, including vitamins, minerals, alkaloids, polypeptides, fragrant volatile oil, and steroidal saponins. Its adaptability is enhanced by this. Chewable lozenges with a variety of therapeutic uses can be made using various mechanisms that have been proposed to regulate blood glucose and lipid levels and prevent pathophysiological diabetes. This opens up new possibilities for the development and formulation of herbal lozenges for people with diabetes. According to numerous studies, *Momordica charantia* may have antidiabetic effects by stimulating enzymes in the HMP pathway, suppressing gluconeogenic enzymes, stimulating skeletal muscles, inhibiting intestinal glucose uptake, restoring islet β -cells, and preventing adipocyte differentiation. A large body of evidence from both pre- and post-clinical research shows that MC effectively lowers blood glucose levels after eating by enhancing postprandial glucose tolerance. There is a wide range of actual dose and outcome metrics used in the studies. The current experiments, however, indicated that MC performed better. Herbal lozenges with medicinal ingredients provide many benefits, such as a longer half-life in the mouth, higher bioavailability, less gastrointestinal distress, and no first-pass metabolism. We have concentrated on this notion to create a lozenge that is both popular and effective in its medicinal properties. Innovative and perhaps more palatable formulations include herbal chewable lozenges created from *Momordica charantia*, which may be particularly helpful for pediatric and elderly patients. Patient compliance, ease of use, comfort, low dose, rapid start of effect, decreased dosing regimen, and cost will all be improved with these. For minority groups with a high diabetes rate who, culturally speaking, value natural remedies more highly, this may be a workable solution. Formulating and developing herbal lozenges of MC for the treatment of DM requires immediate attention.

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