IJPSR (2023), Volume 14, Issue 2 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 May 2022; received in revised form, 14 July 2022; accepted, 03 August 2022; published 01 February 2023

MOMORDICA CHARANTIA (BITTER MELON) CHEWABLE LOZENGES- A HYPOTHESIS-BASED APPROACH TO THE TREATMENT OF DIABETES MELLITUS

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Keywords:

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

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ABSTRACT: Diabetes Mellitus is a prevalent global health problem commonly known as diabetes, a metabolic disease resulting in high blood sugar levels. India considered as "Capital of Diabetes" and more than 61 million Indians suffer from diabetes. Plants are incredible natural reservoirs of phytochemicals and vital medicines. *Momordica charantia* (MC), commonly known as bitter melon, has high phytochemical content and is effective against diabetes mellitus. *Momordica charantia* is also considered as "vegetable insulin" because it contains alkaloids and peptides which resemble insulin and Charantin, which are responsible for the hypoglycaemic activity. The mechanism of action of bitter melon has been discussed and mentioned. Medicated *Momordica charantia* chewable lozenges are intended to dissolve or disintegrate slowly in the mouth and release the active constituent slowly because the Lozenges dosage form has good oral retention time in, increases bioavailability, and decreased gastrointestinal irritation. This dosage form can be used for both local and systemic therapy. Our hypothesis revolves around the formulation of *Momordica charantia* chewable lozenges for treating diabetes mellitus. Various shreds of evidence have been discussed and mentioned in the article involving pre-clinical and clinical studies on bitter melon. Several physiological, pharmacological, and biochemical studies have supported our hypothesis. Additionally, the article includes the methodology used to formulate chewable lozenges. Moreover, different marketed formulations of both bitter melon and herbal lozenges have been discussed in the article.

INTRODUCTION:

1. Diabetes Mellitus: Diabetes Mellitus is a major global health problem becoming more prevalent. It is regarded as one of the world's biggest leading causes of death. Globally, the number of diabetics is expected to increase from 171 million in 2000 to 366 million in 2030 [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(2).622-38

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(2).622-38

However, India has become the Capital of Diabetes as more than 61 million Indians are suffering from diabetes [51]. Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia, complete and comparative insulin insufficiency caused by the dysfunction of the beta cell of islets of Langerhans or by impaired insulin intake in the peripheral tissues as well as insulin resistance [51].

Because of the poor action or lack of the peptide hormone insulin in diabetes, body cells are unable to digest sugar efficiently. The major cause for non-metabolization of sugar is the production of inadequate insulin by the pancreas or its non-utilization by the body, which induces the

breakdown of the body's own fat and glycogen to lower the sugar content, which may result in serious problems and malfunction of various organs with symptoms such as poly-urea, blurred vision and weight loss [51].

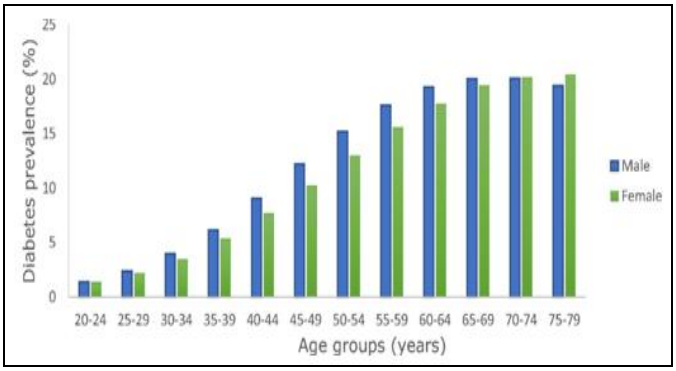

FIG. 1: GRAPH SHOWING DIABETES PREVALENCE PERCENT BY AGE AND SEX OF PEOPLE IN 2019 [8]

The two major forms of diabetes mellitus are [2, 5];

Type 1 – Known as insulin-dependent diabetes mellitus (IDDM), due to non-functioning of the β-cell of the pancreatic islets of Langerhans. Type 2 – Known as non-insulin-dependent diabetes mellitus (NIDDM), due to insulin resistance, probably due to too few insulin receptors. IDDM is majorly caused due to genetic predisposition, environmental factors such as nutrition, exposure to viruses and allergens, and autoimmunity leading to the destruction of insulin-producing pancreatic β-cells. The main two causes of NIDDM are genetic and environmental factors [2].

Type 2 diabetes mellitus (T2DM) is a public health concern worldwide, especially in older adults. The rise in the number of young people with T2DM is also caused for concern, as it implies pathogenic or accelerated aging alterations at the molecular level and loss of related function [3]. Presently, T2DM is a complex and costly disorder in adults, affecting about half a billion individuals globally and accounting for 90% of diabetes incidents. This condition necessarily requires proper medical treatment and a change in lifestyle [89].

Besides conventional therapeutic options, many herbal medicines have been proposed to treat diabetes mellitus. Plants have long been utilized in traditional medicine worldwide due to their efficiency, minimal side effects, and low cost. Therefore, the investigation into traditional medicinal plant agents has become more significant [6].

1.1 *Momordica charantia* (MC): Plants are incredible natural reservoirs of phytochemicals and vital medicines. *Momordica charantia* (bitter melon), also named karela, balsam pear, bitter melon, or bitter gourd affiliated to the Cucurbitaceae family is a perennial climber effective against hypoglycaemic effects of type 2 diabetes mellitus [51]. It is native to tropical and subtropical regions in Asia, Africa and other parts of the globe. It holds rich phytochemistry and effective agent in dietary regimens to prevent diabetes mellitus [52]. *M. charantia* is abundant in various bioactive components such as minerals, alkaloids, vitamins, steroidal saponins, polypeptide, and aromatic volatile oil. Due to the presence of various bioactive components, bitter melon has some pharmacological actions, such as hypoglycaemic and hypolipidemic actions [52]. Mechanisms of activity have been attributed to enhancement of beta-cell integrity, promotion of insulin release, insulin-like activity and extra-pancreatic effects. It also includes the inhibition of glucose transportation at the brush border of the small intestine. Furthermore, MC has been proved to improve the carbohydrate metabolism in the liver of diabetic mice through the stimulation of glycolytic pathway enzymes [3]. *M. charantia* is also considered "vegetable insulin" because it contains alkaloids and peptides resembling insulin and Charantin, a collection of steroidal sapogenins due to which it has hypoglycaemic property [52, 54].

FIG. 2: *MOMORDICA CHARANTIA* WHOLE PLANT [52]

Bitter melon is effective in the prevention of diabetes in various studies. Because of the presence of several hypoglycaemia agents such as alkaloids, flavonoids, saponin, catechins, Charantin, vicine,

and polypeptide-p fraction, various *in-vivo* studies have proved the hypoglycaemic potential of bitter melon. The antidiabetic and hypoglycaemic effects of *Momordica charantia* have been extensively studied in laboratories. Experiments using biochemical and animal models have produced a lot of data and hypotheses to elucidate such effects. According to these research studies, *Momordica charantia* improves glucose tolerance, lowers postprandial hyperglycaemia in rats and that bitter melon extract can promote insulin sensitivity and lipolysis [39]. Based on historical use and animal study, pregnant women should avoid bitter melon since it may cause a miscarriage. Bitter melon can trigger allergic or hypersensitive reactions in people who are allergic or hypersensitive to members of the Cucurbitaceae family (gourds and melons). Individuals with glucose-6-phosphate dehydrogenase deficiency should avoid bitter melon seeds [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: These are the gelatine-based formulation containing the medicament which is being incorporated within a caramel base that is chewed rather than dissolved in the mouth. Also known as the 'gummy type candy lozenges [40]. These lozenges are designed especially for paediatric patients and are a highly effective dosage form to deliver drugs for gastrointestinal absorption and systemic use. These gelatin-based pastilles are prepared by pouring the melted mixture into moulds or onto a sheet of uniform thickness [41].

FIG. 3: MEDICATED CHEWABLE LOZENGES [40]

FIG. 4: GUMMY-TYPE CANDY LOZENGES [40]

2. The Hypothesis Statement: Diabetes Mellitus (DM) is a metabolic disorder characterized by hyperglycaemia, complete and comparative insulin insufficiency caused by the dysfunction of the beta cell of islets of Langerhans, or impaired insulin intake in the peripheral tissues, as well as insulin resistance. Although there are various synthetic groups of medicine for the treatment of diabetes, such as sulfonylureas, biguanides, α-glucosidase inhibitors, and thiazolidinediones (TZDs), the treatment of diabetes with synthetic medicines has shown side effects and is very expensive [51]. Even though synthetic and man-made hypoglycaemic medicines are the chief ways to control blood glucose and diabetes, they cannot properly monitor its complications besides having significant side effects. Hence, it is necessary to determine the alternative medicinal families of antidiabetic agents. Plants have been regarded as prominent sources of potential antidiabetic medicines for a long time. *Momordica charantia* (Bitter melon) is one herb that has been found as effective for glycaemic management in diabetes. Earlier studies identified bitter melon as having significant

antidiabetic as well as hypolipidemic activities. In contrast, a recent meta-analysis indicated that bitter melon improved glycaemic control and had a positive safety profile [53]. Currently, there are several bitter melon supplements available, including bitter-melon extract or juice, bitter melon tablets, bitter melon capsules, bitter melon powders, bitter melon chips, bitter melon biscuits, *etc*. (shown in **Table 6**).

All of them are effective in sugar management in diabetes along with several other health benefits [81-88]. But among the major problem of all age groups, especially the paediatrics and elderly patients with a conventional tablet or capsule dosage form, is difficulty in swallowing. Patient compliance remains an important factor for any dosage form. Sometimes it may be difficult to swallow conventional products due to the non-availability of water.

Also, the bitter melon extract or juice has a bitter flavour that some patients find unpalatable, which again reduces patient compliance. These problems led to the development of a novel type of solid oral dosage form; hence, an attractive, taste masking formulation is the need of the hour. We hypothesized that the formulation of chewable lozenges of *Momordica charantia* (Bitter melon) with a sugar-free base could prove to be a better dosage form for the treatment of diabetes (especially Type-2 diabetes) for all age groups but mainly for paediatric patients due to ease of patient compliance. After studying a lot, we found that no lozenge formulation is available in the market for managing high blood glucose levels. Therefore, the concept of manufacturing such a formulation could lead to an improved and emerging dosage form for reducing hyperglycaemia in the case of diabetes.

3. Evaluation of the Hypothesis

3.1 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

Polysaccharides are one of *Momordica charantia*most important bioactive components. Polysaccharides from *V* fruits have been demonstrated to have antioxidant, antidiabetic, immune-enhancing, neuroprotective, anticancer, and antibacterial properties. According to a recent study, saponin was also found to enhance insulin release in pancreatic MIN6-cells *in-vitro*.

Bitter melon's antidiabetic action is due to polypeptides such as "polypeptide-p" and Charantin [58-60].

3.1.1 Saponin's Mechanism of Action in Diabetes Mellitus: Saponins are steroid or triterpenoid n-glycosides available in many plants and plant products. They exhibit a variety of medical potential including Antidiabetic, Hypocholesterolaemia, anticarcinogenic and hypoglycaemic among others [52]. Saponins modulate peptide adipokines including leptin, adiponectin, adipsin, vastatin and apelin present in insulin-resistant diabetes. It regulates blood glucose levels and improves insulin sensitivity making saponins a potential antidiabetic drug or medicines [26]. The bitter melon extract contains charantia, which supports healthy insulin secretion by the islets of Langerhans and improves liver glycogen storage. Promotes appropriate serum protein levels and peripheral glucose utilization [17]. Saponins of bitter melon of glucose utilization by the liver decrease gluconeogenesis *via* inhibition of the two key enzymes glucose-6- phosphate and fructose-1-6, bisphosphates, and improve glucose oxidation by activating glucose-6-phosphate dehydrogenase via the shunt pathway [15].

Charantia also upgrades insulin release from beta cells pancreatic islets and promotes the new growth of insulin-secreting beta cells [16]. The antidiabetic mechanism of this compound is to lower blood glucose and increase plasma insulin level charantia also acts as an antioxidant that neutralizes oxidants and oxidative stress from diabetic metabolic complications [28].

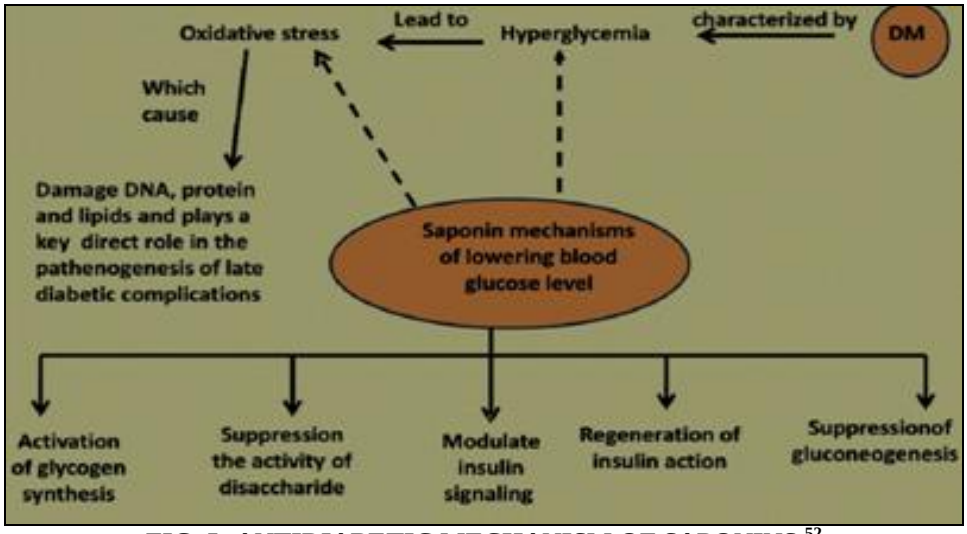

FIG. 5: ANTIDIABETIC MECHANISM OF SAPONINS [52]

3.2 Medicinal Properties of Bitter Melon: *Momordica charantia* has long been known for its therapeutic benefits, including antidiabetic and anti-cancer capabilities, anti-inflammatory, antiviral and cholesterol-lowering effects. It contains many phenolic compounds that are antioxidants and antimutagenic [9]. The fruit, stems, leaves & roots of bitter melon have all been used in traditional medicine to help treat ailments such as hyperlipidaemia, digestive disorder, microbial infection, and menstrual problem [25]. *Momordica charantia* has been proven to have potent antiviral properties, including stimulating the immune system and activating the body's natural killer cells, which can aid in the battle against viruses, including the white spot syndrome virus and the human immunodeficiency virus [21]. Studies have also shown that *Momordica charantia* has anti-carcinogenic properties and can be used as a cytotoxic agent against many types of cancer. Ray *et al.* showed that the extract of *Momordica charantia* modulates signal transduction pathways for inhibiting breast cancer cell growth and can be used as a dietary supplement to prevent breast cancer [12, 22]. Bitter melon juice contains saponins that keeps insulin under check and lower blood sugar level. The phytochemicals of bitter melon, alkaloids, and insulin-like peptides are responsible for hypoglycaemic properties, increasing glucose tolerance without increasing blood insulin levels [19].

3.3 Antidiabetic or Hypoglycaemic Activity of *Momordica charantia*: Multiple mechanisms have been proposed as the cause of *Momordica charantia* hypoglycaemic properties. Momordica charantia extract's components appear to have

conical India's structural secularities, as measured by electrophoresis and infrared–spectrum analysis [20]. Some insulin-like properties of bitter reloan in the preliminary investigation have been suggested. It contains polypeptide – p and is used to control diabetes naturally. Polypeptide – p or p-insulin is an insulin-like hypoglycaemic protein shown to lower blood. Glucose levels in gerbils, langurs, and humans when injected sub-continuously [18]. Evidence indicates that *Momordica charantia* may decrease hepatic gluconeogenesis, increase hepatic glycogen synthesis and increase peripheral glucose oxidation in erythrites and adipocytes [27]. Welihinda *et al.* reported that *Momordica charantia* increases pancreatic insulin secretion. It has been theorized that *Momordica charantia* extract increases beta–cell production in the pancreas. Studies, however, have not proven this mechanism [16]. Although several constituents of *Momordica charantia* have been found to have hypoglycaemic properties, most interest has focused on a polypeptide isolated from the seeds called polypeptide P and a mixture of two steroid glycosides referred to as Charantin [23].

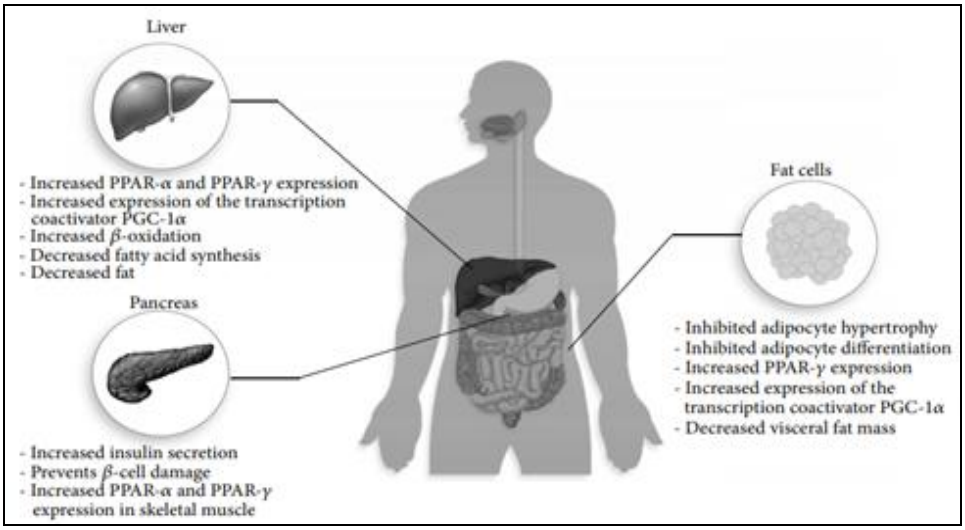

FIG. 6: EFFECT OF BITTER MELON ON VARIOUS ORGANS AND PROBABLE MOLECULAR TARGETS FOR IMPROVING OBESITY AND DIABETES [74]

3.4 Mechanism of Action of *Momordica charantia*: Active phytochemicals control glucose and lipid metabolisms through diverse proposed mechanisms to balance blood glucose and lipid levels in the body and prevent pathophysiological diabetes. Various physiological, pharmacological, and biochemical studies have supported these bioactive formulations [51].

HMP pathway key enzyme stimulation, gluconeogenic enzyme suppression, stimulation of skeletal muscles, peripheral glucose utilization, intestinal glucose uptake inhibition, islet β-cell restoration, and adipocyte differentiation inhibition are some of the possible antidiabetic mechanisms reported in *Momordica charantia*. Vicine, polypeptide p-insulin, Charantin, and glycosides have been proven to inhibit gluconeogenesis and promote glucose oxidation through the pentose phosphate pathway, also known as the shunt pathway, which elevates glycogen levels in the liver. They increase insulin secretion and enhance peripheral insulin sensitivity by repairing impaired β cells. Other mechanisms that increase insulin sensitivity include activation of AMP-activated protein kinase (AMPK) by momordicosides, cucuriate glycosides and their aglycones, lectin linking of the two insulin receptors, skeletal muscle protein tyrosine phosphatase 1B inhibition, increased in the translocation and number of GLUT4 receptors and also by the enhancement of phosphorylation rate of insulin receptor substrate. *Momordica charantia* works similarly to insulin in regulating glucose uptake into the jejunum brush border vesicles and increases glucose uptake into muscle cells. It appears to block the absorption of di- and monosaccharides in the intestine by blocking enzymes like disaccharidase and glucosidase, respectively and induce the secretion of adiponectin from adipose tissue, which increases AMPK activation [51].

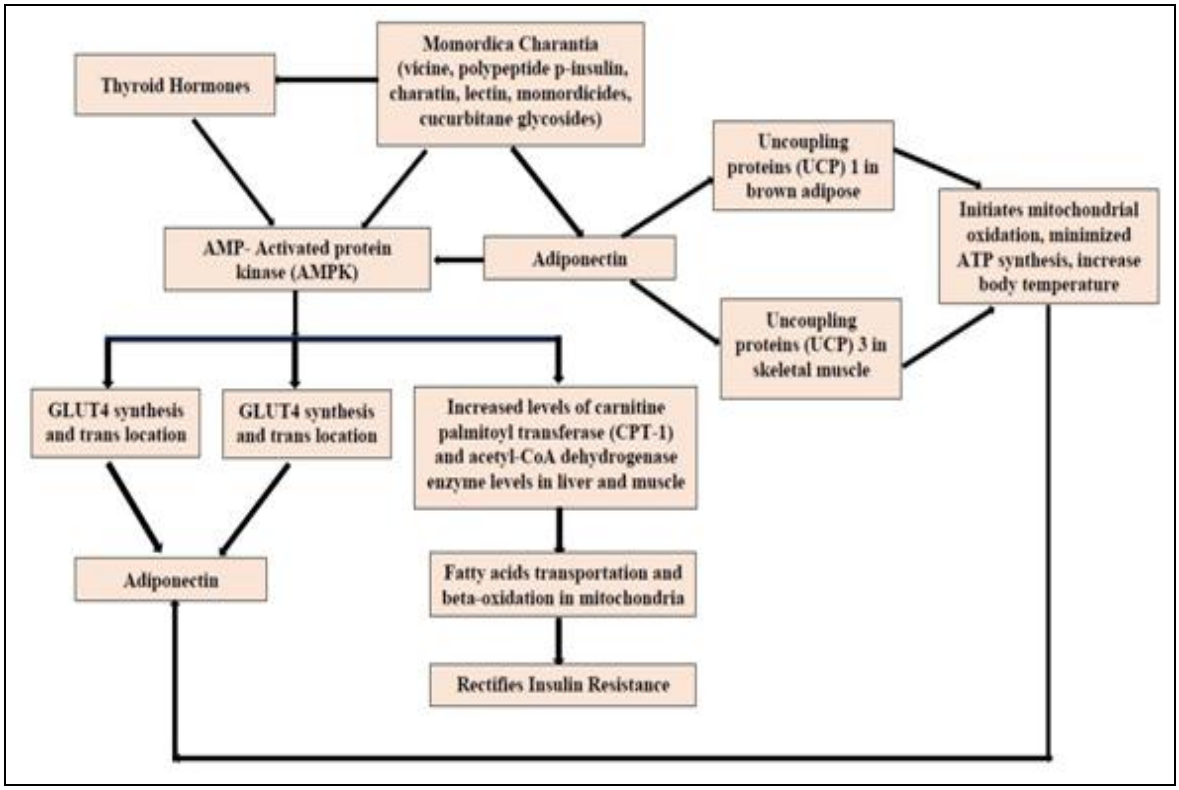

FIG. 7: THE SCHEMATIC DIAGRAM SHOWING MECHANISM OF ACTION OF *MOMORDICA CHARANTIA* [51]

Intake of *Momordica charantia* reduces Na+/K+-ATPase-dependent intestinal glucose absorption, which is considerably higher in diabetic patients. Suppressing the activities of intestinal sucrase, maltase, and pancreatic lipase lowers glucose and lipid absorption. AMPK is an insulin tropic metabolic switch that regulates glucose uptake by promoting GLUT4 production and translocation. *Momordica charantia* has been shown to increase adiponectin and thyroxine, which activate AMPK. AMPK then transfers fatty acids to mitochondria for oxidation while activating 3-hydroxy-3methylglutaryl-coenzyme reductase in the liver and preventing cholesterol synthesis there. On the other hand, Adiponectin promotes mitochondrial oxidation without generating ATP, allowing the body to maintain a healthy blood glucose level.

Momordica charantia facilitates glucose oxidation by enhancing the activity of hepatic hexokinase, glucokinase and phosphofructokinase, in addition to increased glucose influx. However, it inhibits lipogenesis in adipocytes by down-regulating lipogenic gene expression. Moreover, acyl-CoA dehydrogenase and carnitine palmitoyltransferase (CPT) enzymes in the liver and muscle increases fatty acid transportation and beta (β) oxidation in mitochondria. By the impact of AMPK, increased production of cytokine signaling-3, CPT-1, Akt, and c-Jun N-terminal kinase (JNK) at both mRNA and protein levels in the liver restores insulin resistance. AMPK also increases the uncoupling proteins (UCP) 1 and 3 in brown adipose tissue and skeletal muscle protein in mitochondria, respectively, and initiates fuel oxidation without ATP production through electron-transporting proteins. The energy generated in this process is mostly utilized to maintain body temperature [51].

3.5 Pre-Clinical Studies: Several animal studies have frequently demonstrated that seeds, fruits, pulp, leaves and the entire MC have hypoglycaemic effects in normal animals [1]. According to Pandora White *et al.*, the findings of a study done on the effect of Bitter Melon and a Chromium Propionate Complex on Symptoms of Insulin Resistance and Type 2 Diabetes in Rat Models. The study aimed to see if combining the two nutritional supplements could have an additive effect on curing these conditions in streptozotocin (STZ)-induced diabetic rats fed a high-fat diet. Blood and internal organs were taken after the experiment ended for biochemical, haematological and mineral (Cr) studies using approved analytical procedures. Supplemental Cr (III) (given as Cr3) had no

detectable effect on glucose and lipid metabolism in high-fat-fed STZ-induced diabetic rats, contrary to the previous study. In high-fat-fed rats, supplementing with BM fruit powder had some effects on body mass, but these benefits were muted when BM was given in combination with Cr3. Cr (III) and BM are present; they appear to operate as nutritional antagonists. Control and diabetic rat's serum glucose levels (mg/dL). At the start of the Cr and BM treatments, blood glucose is referred to as initial glucose. The glucose levels in the final serum after 6 weeks of Cr and MC treatment [29].

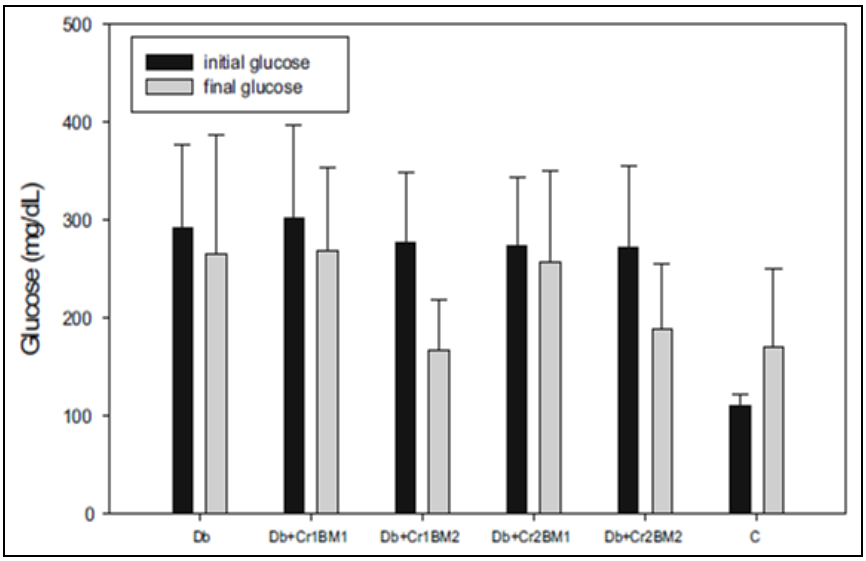

FIG. 8: DIABETIC CONTROL RATS(DB), DIABETIC SUPPLEMENTED WITH A LOW DOSE OF CR(III) RATS AND A LOW DOSE OF BM (DB+CR1BM1) RATS, DIABETIC SUPPLEMENTED WITH A LOW DOSE OF CR(III) RATS AND HIGH DOSE OF BM (DB+CR1BM2) DIABETIC SUPPLEMENTED WITH A HIGH DOSE OF CR AND A LOW DOSE OF BM RATS (DB+CR2BM1), DIABETIC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

Whereas another study by Jose Luis Perez, on "Metabolite profiling and *in-vitro* biological activities of two commercial bitter melon (*Momordica charantia* Linn.) cultivars" intended to determine the bioactivity and metabolite profile of two commercial bitter melon genotypes (*Momordica charantia Linn.*). In that study of diverse bitter melon extracts, UPLC-high resolution mass spectrometry (HRMS) was employed to discover 15 phenolic and 46 triterpenoids. Extracts from the pericarp and inner tissues of bitter melon with a wide range of polarity were.

The findings implied that bitter melon extracts include chemical components with varying antioxidant and anti-hyperglycaemic properties. The inhibitory actions of extracts at various doses against α -glucosidase were tested. From p-nitrophenyl α-D, the release of p-nitrophenol glucopyranoside was used to test the inhibition of α-glucosidase activity *in-vitro*. The several bitter melon extracts used in this study showed a dose-dependent increase in inhibitory activity [30].

In another study, there was a significant reduction in blood glucose level, within 24 hours of receiving the ethanolic extract of MC. The animals were split into two groups, one normal and the other diabetic for two days. The diabetic groups were then separated into two subgroups, each with ten mice. The first subgroup received no treatment and was kept as a control.

For the next 21 days, the second subgroup was given extracts of MC fruit. In addition, diabetic mice that had not been treated with diabetes were kept for additional research alongside diabetic mice that had been treated. Mice were used to determine the LD_{50}.

The MPD was determined as well. Acute toxicity symptoms and post-mortem findings were documented. In comparison to the zero time, the injection of MC ethanolic extract resulted in a considerable reduction in serum glucose levels. The control diabetes group, on the other hand, showed no decline over 21 days [31].

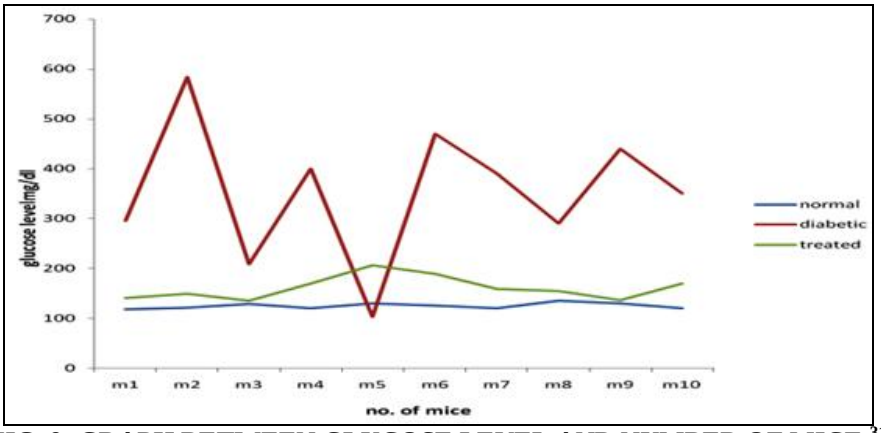

FIG. 9: GRAPH BETWEEN GLUCOSE LEVEL AND NUMBER OF MICE [31]

While in another study, by Eman Abbas Moussa *et al.*, on "Hypoglycaemic effect of *Momordica charantia* (Karela) on normal and alloxan diabetic albino mice" showed that MC improved postprandial blood glucose levels because it induced a significant drop (P0.05) in blood glucose levels at the end of the experiment when compared to the diabetic control group. In that study, each animal group (10 males and 10 females) received a single dosage of 50 mg/kg BW alloxan intraperitoneally. To determine the diabetes status of different groups of mice, random plasma glucose levels were monitored. *Momordica charantia* extract significantly reduced AST and ALT activity, creatinine and cholesterol levels in the blood, according to the current findings [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.

Increased apoB secretion and VLDL production in insulin-resistant states present a high risk of CVD and are probably a result of decreased sensitivity to insulin. One such study by Pratibha V. Nerurkar *et al.* aimed to study how BMJ affected plasma apoB levels and the hepatic insulin signalling cascade in mice fed a high-fat diet (HFD). According to this study, MC can potentially normalize apoB-48 plasma and apo B-100 in mice on an HFD for 16 weeks by modulating the insulin signalling system. While the associations discovered in most studies are statistically insignificant, they reveal trends that should be investigated further [33]. Many studies proved the effect of bitter melon on lipid parameters of diabetic and obese animal models.

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

		(iii) Plasma epinephrine and serum FFA concentrations were increased. (iv) Lowered TAG concentration in red gastrocnemius and tibialis anterior.
Wistar rats	Saponin fraction (50-100 mg/kg body weight)	(i) Decreased pancreatic lipase activity and serum TG level in corn oil loaded rats.
Female C57BL/6 mice fed with HF diet	1.5% freeze-dried BMJ with diet	(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 stearoyl-CoA desaturase and microsomal TG transfer protein mRNA. (iii) Increased PPARy 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-y in the WAT. (ii) Decreased TC and LDL-C; increased HDL-C. (iii) Downregulated the expression of PPAR-y nuclear factor-KB (NF-KB) and interferon y 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 α1, AMPK α2 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 (FGFRI, 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 LXRα in rats. (iii) Increased the hepatic CYP7A1 mRNA level
C.57BI./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 PPARα 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.

3.6 Clinical Studies: Clinical studies on the hypoglycaemic effects of MC have been limited and infrequent when compared to animal trials [1]. In 1956, Lakholia, a physician, was likely the first to establish the medicinal benefit of bitter melon, using himself as a test subject [34]. Chung-Huang Tsa *et. al* were the first to show that WBG improved (on the rate of metabolic syndrome) MetS in humans, laying the groundwork for future randomized controlled trials to assess WBG supplementation's efficacy. This preliminary study's findings show that WBG positively affects the rate of metabolic syndrome (MetS) in humans. After three months of supplementation, a daily dose of 4.8 g lyophilized WBG powder considerably reduced the MetS occurrence rate, and this improved status lasted for one month but not for additional months after the supplementation was stopped [35]. In a study to determine hypoglycaemic potentiation of oral hypoglycaemic drugs in diabetes Mellitus (NIDDM) by phytochemical determination and extraction of *Momordica charantia* fruit by Tongia *et al.* fifteen, T2D patients were taken and split into three groups. Before the intervention, the subjects' FBS and PPS levels were assessed, and the results were utilized as controls. After that, the three groups were given metformin, glibenclamide, and metformin glibenclamide for 7 days before the FBS and PPS levels were assessed. 7 subjects were given half-dosage oral hypoglycaemic drugs for the next 7 days, as well as a standard dose of MC fruit extract twice daily (200 mg twice a day) and FBS and PPS levels were assessed again. FBS and PPS levels were reduced after oral hypoglycaemics, with a further reduction with MC extract [36]. The first randomized controlled trial to compare the hypoglycaemic effect of dried powder of bitter melon's fruit pulp with metformin in newly diagnosed type 2 diabetes patients was by Anjana

Fuangchan *et al.* This study aimed to evaluate the efficacy and safety of three bitter melon doses of metformin. The trial enrolled a total of 143 participants, with 129 being randomly assigned to metformin (n = 33), bitter melon 500 mg/day (n = 33), bitter melon 2000 mg/day (n = 31) or bitter melon 1000 mg/day (n = 32). Based on a decrease in fructosamine concentrations, dried powder of bitter melon fruit pulps 2000 mg/day appears to have a minor hypoglycaemic impact. Its hypoglycaemic effect, on the other hand, was less than metformin 1000 mg/day [37].

In a case series of 100 T2D patients, Ahmad *et al.* (44) investigated the effect of MC (fifty-eight males and forty-two females). Despite the large sample size, this investigation utilized the same people as controls and trials. Although the authors noted constraints, such as the absence of supervision for individuals to carry out instructions at home, there was no indication of negative effects or dropouts. As a result, the methodological design of this study was incorrect. Because it is a case study, the Jadad score cannot be applied. The actual dosage and result measures in the research vary significantly. However, the available trials suggested that MC had a higher efficacy [39].

3.7 Medicated Chewable Lozenges Methodology:

3.7.1 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 medicament [50].

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, *etc*
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.
- 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 flavored solid unit-dose drug delivery devices designed to be held in the oral cavity, wetted with saliva, and slowly dissolved until completely dissolved. It is used to treat local irritation or infection of the mouth or throat and to aid in the absorption of systemic drugs. If the medicine is well absorbed through the buccal linings, these can also be used for systemic effects [66, 68, 71].

Drug absorption through chewable lozenges could be achieved as a result of chewing since it must be chewed in between the teeth before swallowing. As a result, the medication enclosed within the base is released into the saliva. Drug absorption could take place by two possible outcomes- either it can absorb by the oral mucosa or it can be absorbed through the gastrointestinal tract. Both the processes occur simultaneously [90]. According to current studies, the hypoglycaemic effect of bitter melon starts within an hour after ingestion and lasts for 3-4 hours. Bitter melon extracts are absorbed through diffusion, and the action of several enzymes found in the gastrointestinal tract serves to absorb Bitter melon lozenges [78, 80].

4. Marketed Supplements of Bitter Melon:

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.	

5. Marketed Herbal Lozenges:

TABLE 7: SOME HERBAL LOZENGES AVAILABLE IN MARKET [68]

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 *C. albicans* 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	*Adhatodavasica glycyrrhiza* glabra, *Piper longum*, *Viola odorata*, *Hyssopus officinalis*, *Cordia latifolia*, *Alpinia galanga*	Suitable dosage form in symptomatic relief	Sore throat and cough
Eucalyptus oil and coleus aromaticus oil lozenges	*Magnesium stearate*, lactose, mannitol, gelatin, sucrose	Inhibitory activity against non-resistance *C. albicans* infection	Antimicrobial activity

DISCUSSION & CONCLUSION: In this hypothesis, we discussed and reread the use of the traditional plant *Momordica charantia* to treat diabetes Mellitus. Diabetes is increasing in prevalence worldwide, and this trend is expected to continue for the next 50 years. Diabetes-related problems and diabetes in younger people, children, and adolescents are predicted to substantially impact healthcare costs, including cardiovascular disease and other chronic repercussions. According to the findings of many studies, more than 100 plant species from various families are used as antidiabetic drugs worldwide. This leads us to believe that herbal therapy is still the most effective treatment for diabetes in this day and age. Pharmacological validation of the efficacy of these ethnomedicinal herbs is required.

This is enough to prove the therapeutic potential of herbal drugs in human diseases. Bitter melon's fruit, stems, leaves and roots have all been used in traditional medicine to treat hyperlipidaemia, digestive disorders, microbiological infections, and menstrual issues. *Momordica charantia*is abundant in various bioactive components such as minerals, alkaloids, vitamins, steroidal saponins, polypeptide, and aromatic volatile oil. This makes it even versatile. Diverse proposed mechanisms to balance blood glucose and lipid levels in the body and prevent pathophysiological diabetes are evidence that these can be used in making chewable lozenges with a wide range of therapeutic benefits and therefore opening new boundaries for formulation and development of herbal lozenges in diabetes.

Many studies have found that the possible mechanism of action of MC ids due to HMP pathway key enzyme stimulation, gluconeogenic enzymes suppression, stimulation of skeletal muscles, peripheral glucose utilization, intestinal glucose uptake inhibition, islet β-cell restoration, and adipocyte differentiation inhibition are some of the possible antidiabetic mechanisms reported in *Momordica charantia*. There are abundant data available on pre-clinical and clinical studies that proved the efficacy of MC in improving postprandial blood glucose levels by inducing a significant drop in blood glucose levels at the end of the experiment. The actual dosage and result measures in the research vary significantly. However, the available trials suggested that MC had a higher efficacy. The advantages of medicated herbal lozenges are that they prolong the time the dosage form is retained in the oral cavity, increase bioavailability, reduce gastrointestinal discomfort, and bypassing the first-pass metabolism. We have focused on this idea to make a widely acceptable and highly therapeutic lozenge. Herbal chewable lozenges made with *Momordica charantia* are an innovative idea and can be a more acceptable formulation, especially for paediatric and geriatrics patients. These will further benefit patient compliance, convenience, comfort, low dose, immediate onset of action, reduced dosage regimen, and cost. It can be a feasible option for ethnic minorities who have a high prevalence of diabetes but prefer treatment based on natural products according to their cultural beliefs. Shortly, great efforts are needed to formulate and develop herbal lozenges of MC for the treatment of DM.

ACKNOWLEDGEMENT: Authors are grateful to Mr. Pankaj Kumar Jaiswal and Miss. Princy Malik as an Assistant Professor of IEC College of Engineering and Technology, for providing moral support and guidance for completing this research manuscript and Department of Pharmaceutical Technology, IEC College of Engineering and Technology, Greater Noida, Uttar Pradesh.

CONFLICTS OF INTEREST: The authors declare that there is no conflict of interests regarding the publication of this paper.

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How to cite this article:
Tiwari C, Khatoon M, Kumar A, Mahima, Kishor N, Jaiswal PK and Malik P: *Momordica charantia* (Bitter melon) chewable lozenges- a hypothesis-based approach in the treatment of diabetes mellitus. Int J Pharm Sci & Res 2023; 14(2): 622-38. doi: 10.13040/IJPSR.0975-8232.14(2).622-38.