

ANTIDIABETIC POLYHERBAL FORMULATION AND ITS EVALUATION

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ABSTRACT

Chronic metabolic disease known as diabetes mellitus is characterized by an imbalance in the metabolism of fat, protein, and carbohydrates that leads to hyperglycemia. Insulin malfunction or insufficient insulin secretion are the major causes of this.[1] Patients with diabetes mellitus are dramatically rising globally, particularly in wealthy nations.

The International Diabetes Federation (IDF) estimates that 537 million persons worldwide will have this heterogeneous metabolic disease in 2021. It is predicted to increase by 643 million adults by 2030.[2] Diabetes mellitus should be identified and treated effectively; otherwise, it can worsen and cause a host of micro- and macrovascular complications, including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, cardiovascular diseases, atherosclerosis, and stroke.[3] Weight gain, hypersensitivity responses, hepatotoxicity, gastrointestinal problems, lactic acidosis, vitamin B12 insufficiency, ocular abnormalities, lipodystrophy, and many other adverse effects are reported with synthetic antidiabetic medications. Consequently, a polyherbal antidiabetic formulation that demonstrates an efficient and powerful action in contrast to synthetic formulations is required in order to avoid the difficulties and side effects of synthetic preparations. Consequently, a

polyherbal antidiabetic formulation utilizing capsule forms of Cucurbita maxima, Moringa oleifera, Acalypha indica, Phyllanthus emblica, Nigella sativa, Trigonella foenum-graecum, Murraya koenigii, Ocimum sanctum, Curcuma longa, Cinnamon cassia, and Zingiber officinale was attempted to be created in the current study. The developed formulation passed the tests for moisture content, stability, homogeneity in weight, bulk density, tapped density, angle of repose, Hausner's ratio, Carr's index, and disintegration and dissolution.

Important words: anti-diabetic, Cucurbita maxima, Moringa oleifera, polyherbal, capsules..

I. INTRODUCTION

Diabetes mellitus is a category of metabolic illnesses characterized by chronic hyperglycemia, caused by decreased insulin action or secretion. It is divided into two types: Type 1 and Type 2. Type 2 diabetes accounts for more than 90% of diabetes cases and causes problems with glucose, lipid, and protein metabolism. Controlling hyperglycemia effectively in diabetic individuals is crucial for lowering the risk of micro and macrovascular disease.[5]

The link between the formation of free radicals, particularly reactive oxygen species (ROS), and the pathophysiology and progression of diabetes mellitus has increased. Metabolic stress arising from alterations in energy metabolism,

inflammatory mediators, and reduced antioxidant defence mechanisms may all contribute to the production of free radicals in Diabetes mellitus.[6] Hyperglycemia causes oxidative stress by producing too many reactive oxygen species, resulting in an imbalance between free radicals and the cell's antioxidant defence mechanism. It has been shown that oxidative stress, which affects glucose, lipid, and protein metabolism, increases in diabetic individuals, and causes endothelial cell failure and atherosclerosis progression. High blood glucose levels in diabetes are known to cause cell death by inducing oxidative stress. These individuals have a higher risk of cardiovascular disease.[7] A preventative strategy of maintaining normal blood glucose, reducing oxidative stress through some polyherbal formulations should be explored.

In the present study, an attempt was made to formulate polyherbal antidiabetic formulation, using *Cucurbita maxima*, *Moringa oleifera*, *Acalypha indica*, *Phyllanthus emblica*, *Nigella sativa*, *Trigonella foenum-graecum*, *Murraya koeniggi*, *Ocimum sanctum*, *Curcuma longa*, *Cinnamon cassia*, *Zingiber officinale* in the form of capsules.

Cucurbita maxima(Pumpkin) contains D-chiro-inositol which assists in increase of insulin secretion. D-chiroinositol makes the receptors more receptive to insulin thus favoring regulation of blood sugars.[8] In addition to this, it also contains Carotenoid mainly Beta-carotene, Beta-cryptoxanthin, Lutein, Zeaxanthin which helps in reducing oxidative stress caused by lack of physical activity.[9] It also contains lipid soluble antioxidant Tocopherol, which reduces the tissue damage caused by toxic free radical oxygen release as a result of oxidative stress. Presence of phenolic phytochemicals such as Flavonoids helps in inhibition of two enzymes (α Amylase and α -

Glucosidase)which is responsible for increase of postprandial hyperglycemia. [10]

*Moringa oleifera*contains several phytoconstituents such as Flavonoids, Terpenes, Saponins, Alkaloids, Phenolic acids, Steroids, Tannins, Glucosinolates etc. [11] Antidiabetic properties of flavonoids aid in carbohydrate digestion, insulin signalling, insulin production, glucose absorption and adipose deposition. They target a number of molecules involved in the control of many pathways including improvement of β -cell proliferation, increase of insulin secretion, lowering apoptosis and alleviating hyperglycemia by regulating glucose metabolism in the liver. The hydroxyl group and ketones in flavonoids are responsible for majority of the bioactivity.[12]

Acalypha indica (Indian nettle) contains Flavonoids such as Quercetin-3-O-rutinoside (rutin), kaempferol-3-Orutinoside and isorhamnetin-3-O-glucoside, Organic acids like Caffeic acid and its esters, ferulic acid, chlorogenic, citric, fumaric, phosphoric acids etc. Minerals and trace elements such as Calcium, Potassium, Magnesium, Phosphorus, Iron, Sulphur, Zinc, Manganese, Copper, Nickel and Selenium are also present. It also contains vitamins like vitamin A (retinol), vitamin B2 (riboflavin), vitamin B5 (pantothenic acid), vitamin B9 (folic acid), vitamin C (ascorbic acid), vitamin K (phylloquinone). Other constituents such as Tannins, chlorophyll and carotenoids are also present. [13] When compared to glibenclamide, methanol extract significantly reduces serum blood glucose levels. Methanol extract of *Acalypha indica* reduced FBS levels in diabetic mice by 51%, while glibenclamide reduced sugar levels by 67%. In diabetic rats, methanol extract caused a significant (P

Phyllanthus emblica (Amla) contains flavonoids such as Quercetin and Kaempferol. Quercetin shows active interaction with a variety of

molecular targets in small intestine, pancreas, skeletal muscle, adipose tissue, and liver to regulate glucose homeostasis throughout the body. Quercetin exhibits pleiotropic mechanisms of action which include reduction of intestinal glucose absorption, insulin secretory and insulin-sensitizing actions and enhanced glucose utilization in peripheral tissues.[15] It also contains excess amount of Ascorbic acid (Vitamin C). Ascorbic acid, an antioxidant vitamin, is essential in preventing free radical damage. Antioxidant activity of vitamin C is important in the treatment and prevention of diabetes and its complications, because it can include suppressing Reactive Oxygen Species (ROS) formed either by inhibiting enzymes or by chelating trace elements involved in free radical generation.[16] Alkaloids like Phyllembain, Phyllantine, Phyllantidine, Amino acids including Glutamic acid, Proline, Alanine, Lysine, Aspartic acid, Cystine and sterols namely β sitosterol-3-O- β -D-glucoside and Stigmasta-7,22-dien-3-O- β -D glucoside also have anti diabetic effect.[17]

Nigella sativa (Black Jeera) contains active chemicals like thymoquinone, thymohydroquinone, dithymoquinone, p-cymene, carvacrol, 4-terpineol, tanethol, sesquiterpene longifolene, α -pinene, thymol etc. It also includes two types of isoquinoline alkaloids, nigellicimine and nigellicimine N-oxide, and pyrazole alkaloids or imidazole alkaloids such as nigellidine and nigellicine. Furthermore, seeds of *Nigella sativa* contain alpha-hederin, a water-soluble pentacyclic triterpene, and saponin.[18] Among quinines present, Thymoquinone (TQ) is the most prevalent constituent responsible for majority of pharmacological activities. TQ reduces hepatic gluconeogenesis and protects β -cells from oxidative stress. It inhibits insulin resistance, protein glycation, and diabetic nephropathy. Pharmacologically significance of TQ in *Nigella*

sativa in the treatment of diabetes may be due to their antioxidant, cytoprotective, and immunomodulatory properties.[19] Meta-analysis of animal studies showed TQ has reduced the Serum glucose level significantly in the STZ-induced diabetes model. Furthermore, a meta-analysis of the effect of TQ on Body weight revealed that TQ has a statistically significant effect on Body weight of diabetic animals.[20]

Trigonella foenum-graecum (fenugreek) has Polyphenols, steroids, lipids, alkaloids, saponins, flavonoids, hydrocarbons, carbohydrates, galactomannan fiber, and amino acids. [21] In type 2 diabetic rats, fenugreek powder considerably decreases postprandial sugar levels. It also helps to normalise other clinical symptoms linked with diabetes, such as polyuria, polydipsia, weakness, and weight loss. According to majority of studies, the gum component of the seeds is primarily responsible for decreasing plasma glucose levels, thus having a considerable positive influence on serum lipid profiles. These mostly due to a decrease in glucose, cholesterol, and bile acid absorption from the intestine. [22] 4-Hydroxyisoleucine, a novel amino acid derived from fenugreek seeds, enhanced insulin release in isolated islet cells from rats, mice, and humans. *Trigonella foenum-graecum* has been shown in vitro and in vivo to trigger glucose-induced insulin release. The amino acid hydroxyisoleucine, which accounts for 80 percent of the free amino acids in *Trigonella foenum-graecum* seeds, may have insulin-stimulating characteristics.[23] *Trigonella foenum-graecum* seeds may improve insulin sensitivity due to the effects of fibre, which slows carbohydrate metabolism, resulting in lower insulin and blood glucose levels. The anti-hyperglycemic effect of *Trigonella foenum-graecum* seed and leaf extracts, powder, and gum has been attributed to delayed stomach

emptying caused by the high fibre content, inhibition of carbohydrate digesting enzymes and stimulation of insulin secretion.[24]

Murraya koeniggi (Curry leaves) has shown to possess hypoglycemic effect in rats with alloxan-induced diabetes. Increased insulin secretion and stimulation of the glycogenesis process are two possible mechanisms of action. The extracts were effective in modulating biochemical indicators related with diabetes, such as glucokinase and glucose-6-phosphatase activity. It also protects the pancreas by reducing oxidative stress and preserving pancreatic cell integrity. Alkaloids found in *Murraya koeniggi* leaves have been studied and found to have inhibitory effects on the aldose reductase enzyme, glucose utilisation and other enzyme systems, potentially contributing anti-diabetic effects. *Murraya koeniggi* was evaluated for α -glucosidase inhibition and it exhibited inhibition of α -glycosidase. Alpha-glucosidase inhibitors are commonly used in the treatment of type 2 Diabetics. [25] *Murraya koeniggi* was found to have antihyperglycemic effects in STZ-induced diabetic rats in another investigation. Oral treatment of an ethanolic extract of *Murraya koeniggi* at a dose of 200 mg/kg/b.w./day for 30 days dramatically reduced blood glucose, glycosylated hemoglobin, urea, uric acid and creatinine levels in diabetic treated mice. The extract's insulin stimulating impact was revealed by measuring plasma insulin levels. *Murraya koeniggi* appears to have statistically significant hypoglycemic potential in STZ-induced diabetic rats, according to the findings. *Murraya koeniggi* extract was found to be more effective than glibenclamide, a well-known drug in diabetes treatment.[26]

2. MATERIALS AND METHODS

Dry herbs of *Cucurbita maxima*, *Moringa oleifera*, *Acalypha indica*, *Phyllanthus emblica*, *Nigella sativa*, *Trigonella foenum-graecum*, *Murraya koeniggi*, *Ocimum sanctum*, *Curcuma*

longa, *Cinnamom cassia*, *Zingiber officinale* was collected from local market and powdered. According to the formula given below, herbal ingredients were weighed as per ascending order of its weight. Weighed ingredients were triturated using mortar and pestle. The powdered herbal materials were sieved through the mesh size of 120. The powdered polyherbal formulation was encapsulated. Size #0 capsule was selected for encapsulating the desired strength (150 mg) of the drug (blended extract). The composition of developed formulation is summarized in Table 1.

Table 1: Formulation of polyherbal capsule.

SL.NO	INGREDEINTS	QUANTITY (Per Capsule)
01.	<i>Cucurbita maxima</i>	30mg
02.	<i>Moringa oleifera</i>	20mg
03.	<i>Acalypha indica</i>	15mg
04.	<i>Phyllanthus emblica</i>	15mg
05.	<i>Nigella sativa</i>	10mg
06.	<i>Trigonella foenum-graecum</i>	10mg
07.	<i>Murraya koeniggi</i>	10mg
08.	<i>Ocimum sanctum</i>	10mg
09.	<i>Curcuma longa</i>	10mg
10.	<i>Cinnamom cassia</i>	10mg
11.	<i>Zingiber officinale</i>	10mg

EVALUATION

The formulated antidiabetic capsule was subjected to physical and physicochemical evaluation as below.

A. PHYSICAL PARAMETERS

1. Determination of Bulk Density

Weighing about 10g of sample and placing it in a dried graduated measuring cylinder, the volume was recorded as V1 mL. The measuring cylinder containing the sample was placed in the bulk density instrument and tapped for 50 times. The powder's volume was recorded as V2 ml and computed using the given formula.[36]

Bulk density = Untapped density - Tapped density

2. Determination of Hausner's ratio

The Hausner's ratio is a measure of the ease with which powder flows; it is determined using the following formula:[37]

Hausner's ratio = Tapped density / Untapped density

3. RESULTS AND DISCUSSION

The results of formulated anti-diabetic polyherbal capsule subjected to evaluation are as below:

A. Physical Evaluation

The physical evaluation such as Bulk Untapped density, Tapped density, Angle of repose, Hausner's ratio, Carr's index, Loss on drying(%) was carried out as per standard method and tabulated in Table 2.

Table 2: Results of Physical evaluation

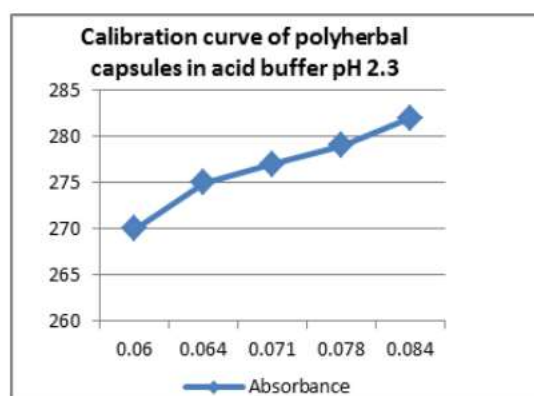
Sl.no	Parameters	Observation
01.	Bulk Untapped density (gm/ml)	15 gm/ml
02.	Tapped density	11 gm/ml
03.	Hausner's ratio	0.733
04.	Carr's index	36.6
05.	Angle of repose	19±0.122°
06.	Loss on drying (%)	9%

The formulated polyherbal anti-diabetic capsule showed, Bulk untapped density of 15 and Tapped density of 11 and the difference between these two values is 4, which shows good porosity value. Hausner's ratio was 0.733. From density data % compressibility was calculated and was found to be 36.6. Angle of repose was 19±0.122° which shows good flow property of encapsulated powder. 9% of loss on drying value shows a good stability.

B. Physicochemical evaluation The results of physicochemical evaluation, such as Uniformity weight variation, Dissolution test, disintegration test was carried out as per standard method and tabulated in table 3, table 4 and table 5 respectively.

Table 3: Dissolution test observation.

SL.NO	ACID BUFFER (pH 2.3)		NEUTRAL BUFFER(pH 6.8)	
	Wavelength	Absorbance	Wavelength	Absorbance
01.	270 nm	0.060 Au	270 nm	0.076 Au
02.	275 nm	0.064 Au	271 nm	0.078 Au
03.	277 nm	0.071 Au	274 nm	0.079 Au
04.	279 nm	0.078 Au	276 nm	0.081 Au
05.	282 nm	0.084 Au	278 nm	0.076 Au



Anti-diabetic polyherbal formulation in hard gelatin capsule form shows steady release of drug content from capsules, especially in acid buffer solution within the time period of 30 minutes, therefore drug contents are well dissolved in gastric pH. In Neutral buffer solution, drug release shows slight unstable drug release patterns compared to acid buffer solution, which indicates that acid buffer is much better and drug release in gastric pH is comparatively good.

4. CONCLUSION

The polyherbal anti-diabetic pill that was created has virtually all of the parameter values satisfied and is within the allowed ranges. The created polyherbal capsules were determined to be good based on evaluations of their angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index. Tests for stability, disintegration, and dissolution of the prepared polyherbal capsules have shown positive results.

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