"FORMULATION AND EVALUATIONS OF POLY HERBAL ANTI DIBETIC TABLET FOR ORAL DRUG DELIVERY SYSTEM"

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ABSTRACT: Diabetes mellitus is a multifactorial disease, for diabetes develop various complications like hepatic toxicity, retinopathy, neuropathy, nephropathy and immunodeficiency, etc. Medicinal herb with antidiabetic activities is being more desired to lesser side effects and low cost. Marketed herbal drugs comprises of irrational combinations, which makes their quality control more difficult. In the present study, polyherbal formulation comprises of lyophilized hydroalcoholic (50%v/w) extract of Momordica charantina, Trigonella foenum-graecum and Withania somnifera 2:2:1, respectively, named HA optimized based on oral glucose tolerance test model in Wistar rat. Present review high light various novel and controlled drug delivery System that have been investigated by different researchers for achieving sustained and controlled drug delivery of oral hypoglycemic and for overcoming the limitations related with the conventional dosage forms of oral hypoglycemics. Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia due to resistance or both. Oral antidiabetic agents remain the cornerstone of therapy for Type 2 diabetes mellitus (T2DM).

KEYWORDS: Medicinal plant, adenanthera pavonine, Kigelia africane, Pharkia, Biglandulosa, Syzygium jambose, Poly herbal tablet.

INTRODUCTION:

Diabetes mellitus is systemic metabolic disease characterized by hyperglycemia, hyperlipedemia, hyperaminoacidemia, and hypoinsulinaemia it leads to decrease insulin secretion and insulin action. Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonyl ureas, bigaunides, a-glucosidase inhibitors and glinides. In developing countries products are expensive and not easily accessible[1]. Prevalence of diabetes is rising all over word but alarming rate. India stood

at the first position with highest number of diabetic subjects[2,3,4].

Types of diabetes mellitus:

1. Type I DM
2. Type II DM

Type I diabetes mellitus results from immune mediated destruction of the beta-cell of the pancreas, resulting in eventual absolute insulin deficiency. Roughly 5-10% of people with diabetes have type I disease. Patients of type I disease more likely to develop ketoacidosis than are people with type II diabetes.

Type II diabetes mellitus has usually some degree of insulin resistance with variable insulin resistance with variable insulin secretion. Insulin secretion is said to be relatively deficient because many patients may have normal to elevated level to insulin; however, their blood sugar remain elevated because of tissue resistance to the action of insulin[5,6,7,8].

Mechanism of DM:

Fig. no. 1

Mechanism of DM

Glucose metabolism:

Glucose metabolism is the source and fuel for human cells. It is gotten from the diet consumed, processed within body, and transfer from the circulation into the target cell. The movement of glucose across the plasma membrane is important[9]. Lipids, proteins, and carbohydrates eventually break down to form glucose, which serves as fuel for the metabolic processes of the body. Glycogenolysis are only a few of the multiple processes that make up the glucose metabolism. An enzyme catalyzed metabolic mechanism called glycolysis promotes glucose catabolism in

cells and conversion of glucose tolerance pyruvate [10]. In order to maintain steady blood sugar and glucose level during the fasting state, the cytosol and mitochondria of hepatocytes undergo a series of metabolic activities that result in the synthesis of glucose from non-carbohydrate substrate. Insulin, glucagon, and cortisol are control it [11]. Furthermore, the pancreas's release of glucagon during fasting triggers the start of glycogenolysis. A biological procedure called glycogenolysis involves the breakdown of glycogen to produce glucose and glucose-1-phosphate. The process of synthesizing glycogen is known as glycogenesis, and glucose molecules connect the glycogen links for storage.

Material and methods:

1. Fenugreek

Fig no. 2

Fenugreek

It is medicinal herb used to treat various diseases such as diabetes, inflammation, cancer, hypercholestermia, reproductive dysfunction, and neurodegenerative disorders. For centuries, fenugreek seeds have been used as carminative, demulcent, expectorant, laxative, and stomachic agent [12].

History of fenugreek: Fenugreek can be grown in all seasons and has medicinal values known from ancient times. It's seeds, leaves, and stem have been used for various purpose. The seeds are popularly have been used for various purpose. The seeds are popularly known as methi dana, which is commonly used as a spice in Indian curries and pickles and also as a flavouring agent it baking breads, cheese, syrups, etc. Its leaves and young plants are cooked as winter dishes. Earlies, Romans and Greeks used it for cattle food. In Egypt, it was used to ease labor and enhance milk flow. Many Egyptian women used it to reduce menstrual pain. Its medicinal properties are extensively documented in Ayurveda, Chinese, Arabic, Greek, and Latin Pharmacopoeia [13].

• **Synonyms:** Fenugreek, Methi, Saga methi, Kasuri methi.

• **Biological source:** Trigonella foenum-graecum.

• **Family:** Fabaceae

• **Chemical constituents:** Choline, Trigonelline, Gentianine, Carpaine, Flavonoids apigenin, Orienting, luteolin, Quercetin, Vitexin, and Free amino acids.

Mechanism of action:

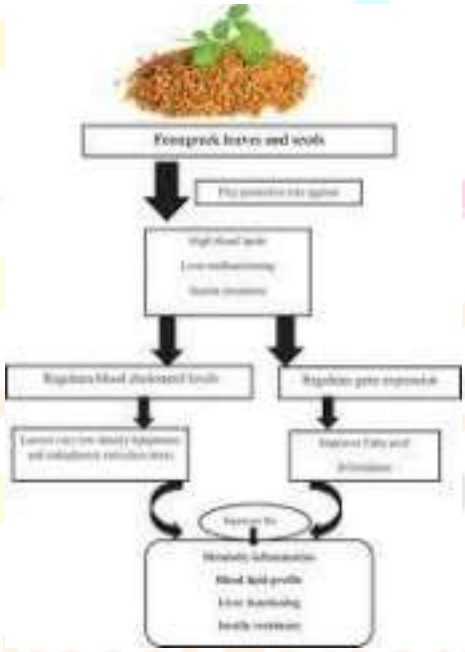

Fig. no. 3
Mechanism of fenugreek

Health benefits:

1. **May help *control diabetes and blood sugar level :*** People with type II diabetes who took 5g of Fenugreek seed powder twice daily for 2 months experienced a reduction in fasting blood sugar levels, belly fats, body mass

2. Appetite control: Reduction in fat intake and appetite.

3. Cholesterol control: Some evidence indicates that Fenugreek can lower cholesterol and triglycerides level.

4. Heartburn: People with frequent heartburn found that Fenugreek reduced their symptoms. ***5.*** **Inflammation:** This herb was demonstrated anti inflammatory effects in rats and mice.

2. Bitter gourd

Fig. no. 4

Bitter gourd

In the present age of advancing medicine and technology, man's quest has been to explore natural products to treat diseases. According to World Health Organization (WHO) about 80% of the world population still depends on the traditional system of medicine[16]. Among the oldest Indian and Chinese traditional culture systems of medicine, the therapeutic potential of numerous plants and their products have been researched. These ancient texts have documented the medicinal potential of *Momordica charantia.*

History of Bitter gourd: In the field of medicine, herbal medicine is becoming more popular day by day in recent years, because they are naturally present in the environment and have fewer side effects on human health[17,18].

• **Synonyms:** Bitter meison, Gouya, Cerassee, Goya, Bitter apple, Bitter gourd, Bitter squash, Balsam-pear, Karela.

• **Biological source:** Bitter gourd is the plan of Momordica charantia.

• **Family:** Cocurbitacea

• **Chemical constituents:** Several bioactive compound of M. Charantia fruit have been recorded in the literature; they are classified as carbohydrates, proteins, lipids and more[19,20,21]. M. Charantia contains Triterpenoids[22,23,24,25], saponin[26,27,28], Polypeptides[29], Flavonoids[30], alkaloids[31], and sterols. And main chemical contains in the Momordicin and charatin.

Mechanism of action:

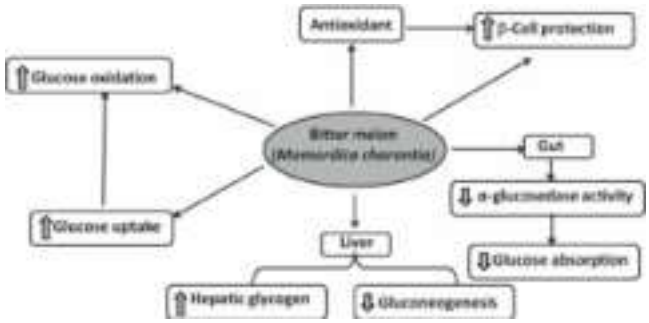

Fig. no. 5

Mechanism of bitter gourd

Health benefits:

1. Antioxidant activity: Phenolic compounds are a very good source of natural antioxidant which help in the reduction of cholesterol, blood pressure and helpful in prevention of cancer and cardiovascular disease. One of the most efficacious free radical scavenger and antioxidant from bitter gourd are flavonoids[32].

2. Antidiabetic activity: Diabetes mellitus, one of the fastest growing diseases throughout the world, could be a cluster of metabolic disorder, characterized by symptoms ensuring from defects in insulin hormone secretion and hormone action[34].

3. Antimalarial activity: M. Charantia has some antimalarial activities. The extract or bitter melon has modest in vivo activity against ordent malaria, Plasmodium vinckei Petteri, and a very good antimalarial activity in vitro on P. Falciparum[34].

4. Antimicrobial activity: Antimicrobial activity is a process in which inhibition of disease causing microbial occurs[35]. Bacterial resistance can be a major problem throughout the world and it is a belief by 2050 it could be a major cause of demise in the world[36].

5. Blood sugar managements: It contains compounds like charantin and polypeptide-p that may help lower blood sugar levels and improve glucose tolerance.

3. Guduchi:

Fig. no. 6

Guduchi

Traditional Medicines are being researched extensively, especially in China, India, and other South Asian countries, in COVID-19 clinical trials due to their established anti-viral, anti inflammatory, and immune-modulatory properties[37]. The popularity of herbal products globally is because they are perceived as being safe, effective, and natural even though not rapid in action, Currently, there are no effective drugs against the COVID-19 pandemic caused by the SARS Cov2-virus[38].

History of Gucuchi: Gucuchi as it is called in Sanskrit, has been documented as a major drug of use in the early treaties of Ayurveda,- about 3000 BCE[39]. Guduchi is described in the treatment of various disorder in Sushruta Samhita, under Tikta-Saka Varga, including Svasa (asthma), Maha Jvara (fever) Aruci (anorexid), and Kushta (leprosy). There is no strong evidence for its use in the treatment of Jvara (fever), Vata Rakta (arthritic condition), and Kamala (jaundice) in Ashtanga Hridaya and Charaka Samhita[40].

- **Synonyms:** Giloy, Galo, Amarvel, Gulavel.
- **Biological source:** Tinospora cardifolia.
- **Family:** Menispermaceae
- **Chemical constituents:** Tinospora cardifolia contains diverse phytochemicals, including alkaloids, phytosterols, glycosides, tinosporide etc[41]. Diterpenoid lactones, essential oil, mixture of fatty acids, sesquiterpenoid, aliphatic compound[42].

Mechanism of action:

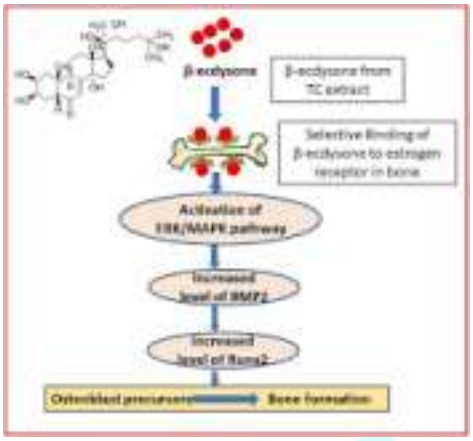

Fig. no. 7

Mechanism of guduchi

Health benefits:

1. Prevent diabetes: Phytochemicals like alkaloids, tannins, cardiac glycosides, flavonoids, saponins and steroids that are isolated from different parts of T. cardifolia are responsible for curing the diabetes. Stem extract of T. cordifolia enhances the efficiency of insulin secretion from beta-cell of the pancreas and enhances glycogenesis and inhibiting the glucose formation thus have a strong antidiabetic[43].

2. Boosts Immunity: Goly's stem strengthen the immune system by altering the levels of enzyme catalase thus stimulating the lymphocytes. T. cordifolia contains polysaccharide (G-4A) enhances the production and differentiation beta-cell and T-cells thus boosting the immunity[44,45].

3. Anti-inflammatory activity: Gucuchi contains powerful anti-inflammatory and anti arthritic properties, which are beneficial for reducing pain and swelling in conditions like arthritis and gout.

4. Anti-allergic activity: Tinospora cordifolia is used for the treatment of Kasa (cough) and swash (asthma), which is described in various texts of Ayurveda T. cordifolia is traditionally used for the treatment of asthma, and the juice is also employed for the treatment of chronic coughs[46].

5. Memory enhancement: It enhances the stimulation of immune system and synthesis of acetylcholine[45]. It is having a beneficial effect against anxiety[47]. It helps in relieving stress[48].

4. Ginger:

Fig. no. 8

Ginger

Notably, a prominent number of randomized clinical trials(RCTs) have been conducted to examine ginger's antiemetic effect in various condition such as motion sickness, pregnancy, and post anesthesia[49]. More than approximately 100 compounds have reportedly been isolated from ginger[50]. Among them, gingerols are considered as the primary components, reported to possess several bioactivities, reported to possess several bioactivities[51]. As a result, many related biological activities have been explored such as those of antioxidant, antimicrobial, and anti neuroinflammation, just to name a few[52].

History of Ginger: Belonging to Zingiberaceae family, has been used alone or in compounds as a spice or remedy in ancient recipes of Iranian Traditional medicine (ITM) manuscripts. This plant is endemic to India and cultivated in South and South-East Asia, Africa, Latin America and Australia[53].

• **Synonyms:** Ginger root, Zingiber officinale,

• **Biological source:** Zingiber officinale

• **Family:** Zingiberaceae

• **Chemical constituents:** Bisapolene, Zingiberene, Zingiberol, Sesquphellandrene, Curcumene. Galanolactone, gingesulfonic acid, Zingerone, Geraniol.

Mechanism of action:

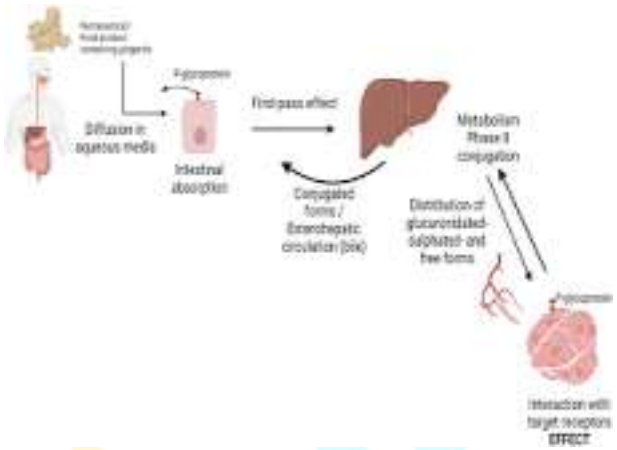

Fig. no. 9

Mechanism of ginger
Health benefits:

1. Relieves nausea: Ginger is effective at easing nausea and vomiting related to motion sickness, morning sickness, and chemotherapy.

2. Reduces inflammation: Ginger contains gingerol, which has anti-inflammatory properties that can help block inflammatory pathways in the body.

3. Eases pain: The anti-inflammatory effects can also reduce pain from conditions like osteoarthritis and menstrual cramps.

4. Supports heart health: Ginger can help improve blood circulation and may lower levels of "bad" LDL cholesterol and triglycerides.

5. Immunity Boosts: Ginger contains antioxidants and has properties that help fight microbes, supporting the immune system.

6. Anti-fungal activity: A molecule with strong antifungal effects found in ginger is called caprylic acid. Apply a cup of boiling water infused with one ounce of ginger root directly to the foot's effected area twice a day, as suggested by fixer[54] and hexing Wang[55]

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5. Jamun

Fig. no. 10

Jamun

The diabetic is a metabolic disorder characterized by hyperglycemia and glucose intolerance. The malfunctioning of pancreas is the major cause of this metabolic disorder. This may be due to lack of insulin production, defective insulin action or both. The diabetes is four types depending on the etiology and clinical presentation. The insulin dependent diabetes mellitus (DDM, Type I) and non-insulin dependent diabetes mellitus (NIDDM, Type II). The other types of diabetes include gestational diabetes, and other specific types[56]. The type I diabetes (IDDM) is an autoimmune disease produced due to the destruction of beta-cell of islets of Langerhans by the body's T lymphocytes leading to local inflammation and suppression of insulin secretion and this needs insulin replacement therapy[57].

History of jamun: Jamun has a long history, originating in India and deeply intertwined with Indian mythology, where it is called the "Fruit of the Gods". It is mentioned in ancient texts and linked to figures like Lord Rama and Lord Krishna. It uses as a food source is believed to have started in Neolithic times, and its wood, bark, and leaves have been historically used for medicinal purposes, natural dyes, and construction.

• **Synonym:** Black plum, Indian blackberry, Jambul, Syzygium cumini.

• **Biological source:** Syzygium cumini

• **Family:** Myrtaceae

• **Chemical constituents:** Flavonoids, Tannins, terpenoids, Polyphenols and Phenolic acids, Alkaloids and Glycosides, Vitamins, Minerals, and other compounds.

Mechanism of action:

Health benefits:

1. Anti-diabetic activity: The hypoglycemic effect of different part of Jamun to control diabetes in preclinical models have been investigated by several investigators who have shown that jamun alleviates blood sugar levels . These preclinical studies have been negative where no hypoglycemic effect of jamun was observed in alloxan-induced diabetic rats[58]. However, majority of the preclinical reports have indicated that different parts of Jamun reduced blood sugar levels in rodent models of diabetes and clinical setting. The seed powder extracted in water has been shown to reduce blood sugar level in diabetic rabbits[59].

2. Anti-hyperlipidemic activity: The ethanol extract of Jamun seed kernel has been found to reduce the (Low Density Lipoproteins) LDL and VLDL cholesterol levels in streptozotocin-induced diabetic rats, which was accompanied by an elevation in the HDL cholesterol[60]. The aqueous Jamun fruit pulp extract has been reported to attenuate triglycerides and total cholesterol levels and elevate the HDL cholesterol level in the streptozotocin-induced diabetic rats[61]. The activity principle isolated by passing ethanol seed extract fraction of Jamun on Sephadex gel did decrease triglycerides and total cholesterol and raised the HDL cholesterol level in the alloxan-induced diabetic rats[62].

3. Anti-Inflammatory activity: Herbs were the main focus of ancient medical practitioner's efforts to strengthen the body immune systems. Products made from ginger boost immunity in several nations. The inhibition of 5 lipoxygenase or prostaglandin synthetase, gingerol, shogaol, and other structurally similar compounds in ginger prevents the formation of prostaglandins and leukotrienes[63]. Furthermore, they can prevent the manufacture of pro inflammatory cytokines such IL-1, TNF-a, and IL-8. In a different study, Pan et al. demonstrated that shogaol can suppress the expression of the inflammatory INOS and COX-2 genes in macrophages. According to Jung et al., Z. officinale rhizome hexane fraction extract prevented the overproduction of NO, PGE (2), TNF-a, and IL-1 beta[64].

4. Skin and oral health:

Improves skin: The antioxidants and vitamin C help combat acne, Wrinkles, and other skin blemishes.

Boost oral hygiene: Its antibacterial properties can help prevent gum infection and bad breath.

5. Other benefits:

Improves blood health: The iron in Jamun can help increases hemoglobin levels. **Strengthens bones:** It contains calcium, iron, and potassium that are essential for bone health.

Supports blood sugar management: The fruit has compounds like jambolana that may help manage blood sugar levels.

6. Cinnamon bark

Fig. no. 11 Cinnamon bark

The bark of various cinnamon species is one of the most important and popular spices used worldwide not only for cooking but also in traditional and modern medicines. Overall, approximately 250 species have been identified among the cinnamon genus, with trees being scattered all over the world [65,66]. Cinnamon is mainly used in the aroma and essence industries due to its fragrance, which can be incorporated into different varieties of foodstuffs, perfumes, and medicinal products [67]. The most important constituents of cinnamon are cinnamaldehyde and *trans*-cinnamaldehyde (Cin), which are present in the essential oil, thus contributing to the fragrance and to the various biological activities observed with cinnamon [68].

History of Cinnamon bark:

Synonyms: Cinnamon, Dalchini, Canela

Biological Source: Cinnamomum

Family: Lauraceae

Chemical constituent:
Chemical Constituents: Cinnamal-dehyde, Eugenol, Cinnamyl acetate, Benzaldehyde. **Health benefits**:

1. Lower blood sugar levels: Cinnamon is well known for its blood-sugar-lowering properties. Apart from the beneficial effects on insulin resistance, cinnamon can lower blood sugar through serval other mechanisms. First, cinnamon has been shown to decrease the amount of sugar that enters your bloodstream after a meal. It does this by

interfering with numerous digestive enzymes, which slows the breakdown of carbohydrates in your digestive tract.

2. Antioxidant Activity: Antioxidant compounds present in foodstuffs play a vital role in human life, acting as health-protecting agents. In addition to this role, antioxidants are one of the key additives used in fats and oils. Even in the food processing industry, antioxidant have been used to delay or prevent food spoilage. Spices and medicinal plants have received rapid consideration as source of beneficial antioxidants against various diseases [69].

3. Anti-Inflammatory Activities: Several studies on medicinal plants and their components have indicated the anti-inflammatory activities of cinnamon. Various studies reported the anti-inflammatory activity of cinnamon and its essential oils.

4. Anticancer Activity: A cell proliferation assay was used to test the anticancer efficacy of the water-soluble polysaccharide and other cinnamon extracts against macrophage cell lines in an in-vitro investigation.

5. Anti-Diabetic Activity: Cinnamon methanol extract and 50 green teas have anti-diabetic action in 50 diabetic rats caused by streptozotocin (STZ). The treatment lasted six weeks.

Conclusion:

The present study successfully demonstrated that a polyherbal antidiabetic tablet can be formulated using selected medicinal plant extracts with proven antihyperglycemic potential. The optimized tablet formulation exhibited acceptable physiochemical properties, including uniform weight, hardness, friability, disintegration time, and drug content, all of which complied with standard pharmacopeial limits. Evaluation parameters confirmed that the herbal actives were stable within the formulation and were effectively released in a controlled manner suitable for oral administration.

The combined herbal extracts showed synergistic potential, providing multiple mechanism of antidiabetic action such as enhancement of insulin secretion, improvement of insulin sensitivity, inhibition of carbohydrate – metabolizing enzymes, and protection against oxidative stress.

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