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Review Article

A SYSTEMATIC REVIEW OF FIVE HERBAL INGREDIENTS FOR THE MANAGEMENT OF DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus (DM) is becoming a common metabolic disorder which has serious threatening to public health that leads to huge economic loss in the developing countries. There are some antidiabetic drugs available that helps in controlling diabetes but there is no permanent remedy which reliefs to get completely cure from this disorder. By conducting huge number of research study, numerous herbal medicines have been found for diabetes. Extracts isolated from different natural resources especially plants have always been a rich arsenal for controlling and treating diabetes and its complication. Herbs used in the preparation of the polyherbal formulation were *Cassia auriculata*, *Gymnema sylvestre*, *Syzygium cumini*, *Trigonella foenum-graecum*, *and* Cinnamomum zeylanicum. Phytochemical qualitative analysis indicated the presence of flavonoids, alkaloids, terpenoids, tannins, steroids, carbohydrates and glycosides. So this review helps to understand the importance of five herbal ingredients present traditionally which can be used to treat DM.

Keywords: Diabetes mellitus, Polyherbal formulation, Phytochemicals, Traditional medicine.

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INTRODUCTION

Change in lifestyle and food habits, especially looking and adapting others cultures this has resulted changes in status of health and disease. Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from deficiencies in insulin secretion, insulin action or both [1]. Prevalence of metabolic disorders like DM has risen to epidemic levels [2]. DM is a growing health disorder in world that causes economic status loss, depression, psychological stress, morbidity, and mortality [3-5]. In the year 2000, prevalence of diabetes among adults is 151 million [6] whereas in 2021 the number has been increased to approximately 537 million in worldwide. Due to demographic changes the world is expected the occurrence of diabetes to be 643 million in 2030 and expected to be 783 million in year 2045 [7]. In India the number of people with diabetes has raised from 26 million in 1990 to 65 million in 2016. In the year 2020, the prevalence of diabetes is approximately 77 million, which makes it the second most affected diabetic country in the world, after china as per international diabetes federation, the number is projected to grow by 134 million in the year of 2045 [8]. High in population and lack of nutrient supplement makes India becoming the diabetes hub of the world, one in six people with diabetic in the world is from India [9]. Tamil Nadu and Kerala, one of the main states in economically and epidemiologically giving high incidence of diabetes in India. The major reason for the rise of this disease burden among peoples include rapid urbanization, socioeconomic change, population aging, dietary, and nutritional factors [10-14].

Three major types of DM Type 1, Type 2, and gestational DM (GDM). Type I DM also called juvenile diabetes is a chronic illness characterized, due to the autoimmune destruction of the β cells in the pancreas, it cannot produce insulin. Although the age of symptomatic onset in usually during childhood or adolescence, symptoms can sometimes develop much later. Type II DM (T2DM) also called non-insulin dependent (NIDDM) or adult-onset diabetes is a chronic condition that affects the way the body processes blood sugar. With T2DM, the body either resists insulin or doesn't produce enough insulin. T2DM is more mutual in older adults, because of increased amount of children's with obesity has led to more cases of T2DM in younger people. T2DM has been observed in majority of diabetic patients (85%) and results in peripheral insulin resistance, thereby results in decreased insulin sensitivity to the liver, skeletal muscles, and adipose tissues [15]. Another category known as GDM is the result of hormonal changes during pregnancy. Women during pregnancy gain too much weight are more likely to get gestational diabetes, women who develop gestational diabetes during pregnancy are at high risk of developing type 2 diabetes later in life [16]. Studies shows that high body mass index baseline as well as increase in waist-to-hip ratio is both shows high chances of onset of diabetes by many folds [17-19].

Different categories of anti-diabetic medications are available in the market, which includes insulin analogs, biguanides, sulfonylureas, thiazolidiones, a-glucosidase inhibitors, meglitinides, and dipeptidyl peptidase-4 inhibitors, where the mechanism of counteracting this increased glucose level is different for different categories [20]. These drugs have little progress inaction against the voluminous increase in prevalence of diabetes used in management of DM. Most of the drugs used in treatment of DM address only the issue of hyperglycemia. However, recent research found that, many factors other than carbohydrate metabolism play important role in pathogenesis of DM [21]. Factors such as chronic inflammation, activation of immune system, oxidative stress, derangement of protein, and lipid metabolism all play important roles in disease progression and development of diabetic complications [22]. Studies suggested that anti-hyperglycemic agents which are presently used do not sufficiently give protection against DM. Thus, from many years of clinical experience and by several research studies it is clear that diabetic complications are multifactorial in nature and addressing only one aspect of the pathogenesis cannot sufficiently prevent the disease progression and development of diabetic complications. This may be the probable explanation for failure of present anti diabetic agents in prevention of long-term complications of DM.

From ancient time, till now many plants have been used in medicine for its traditional activity. By the development of allopathic medicine, herbal medicine usage has been decreased but still it continued to be

used in many parts of the world. This is due to many reasons, some of them being their effectiveness and better safety profiles. Moreover, investigation on traditional medicinal herbs has been recommended by the WHO expert Committee [23]. Many scientists propose the multiple mechanisms possessed by an herbal drug to be responsible for their beneficial effects in chronic diseases. Combination of chemical constituents present in plants may exert synergistic effect and possess multiple mechanisms such as improving insulin sensitivity, beta cell protection, decreased hepatic glucose output, anti-oxidant activity, anti-inflammatory activity, and anti-hyperlipidiemic activity. Such multiple effects of plants may prove beneficial effects if used in treatment of DM. However, long-term treatment, cost efficiency and side effects of the available hypoglycemic medications, leading huge demand for complementary alternative medicine, because of its decreased side effects and affordable agents for the treatment of diabetes [24,25].

SELECTION OF THE POLYHERBAL FORMULATION

Based on the literature survey a new polyherbal formulation with five different plant ingredients having significant hypoglycemic, hypolipidemic, and antioxidant properties was selected. As a formulation it was not scientifically proven yet, it was thought worthy to study about this traditional antidiabetic polyherbal formulation to create scientific evidence. The polyherbal formulation contains the following ingredients [26].

ANTIDIABETIC STUDIES ON INDIVIDUAL INGREDIENTS

CASSIA AURICULATA

Kingdom: *Plantae*
Order: Fabales
Family: *Fabaceae*
Genus: Senna
Species: *S. auriculata*

Kumar *et al.* studied shows the antidiabetic activity of *C. auriculata* flower extract in in liver, plasma, and pancreas in type 2 diabetes rats and assessed that the extract showed momentous development in the glucose, insulin, and lipid levels in plasma and have substantial antioxidant activity [27]. Guruprasad *et al.* studied the antidiabetic effect of *C. auriculata* flower extract in streptozotocin (STZ)-induced type 2 diabetic rats. Results displayed reduction of fasting glucose level with different doses in STZ-induced diabetic rats [28]. Sivaraj *et al.* evaluated the combined plant extract of *C. auriculata* and *Aegle marmelos* in STZ induced diabetic albino rats and the result shows a significant reduction in blood glucose level compared to glibenclamide (control drug). These mixture of plant extract supports in restoration of β-cells [29].

Hakkim *et al.* revealed that compared with aqueous extract, water soluble fraction of the ethanol extract showed more efficient anti-hyperglycemic effect in alloxan induced diabetic rats [30]. The assessment of anti-diabetic activity of *C. auriculata* Linn seeds for alloxan induced diabetic rats was studied by Aruna and Roopa found that ethyl acetate and petroleum ether extract of *C. auriculata* Linn seeds treated with alloxan induced diabetic rats displayed significant antidiabetic activity [31].

Srivastava *et al*. reviewed the polyherbal formulations based on Indian medicinal plants as antidiabetic phototherapeutics. This review focuses on the pharmacological investigations and the potential of different polyherbal formulation in the treatment of diabetes [32]. Kalaivani *et al.* assessed the anti-hyperglycemic and antioxidant properties of *C. auriculata* and the results indicate significant hold of anti-diabetic and antioxidant activity in diabetic conditions [33]. Surana *et al*. reveals the antihyperglycemic activity of several segments of *C. auriculata* Linn in alloxan diabetic rats. The n-butanol section showed significant decrease in blood glucose level [34].

Jeyashanthi and Ashok shows that the anti-oxidative effect of 200 mg/kg b.wt was significantly >100 mg/kg b.wt on STZ induced diabetic rats reference drugs used were metformin and tolbutamide [35]. In DM the *in vitro* antiglycation activity of different medicinal plants used were evaluated. The results displayed that Phyllanthusemblica and *C. auriculata* have significant anti glycation activity [36]. Nilam *et al*. estimated the antioxidant, phytochemical analysis, and carbohydrate hydrolyzing enzyme inhibitor property of *C. auriculata*, Delonixregia and Vincarosea Linn: an *in vitro* study and confirmed that the methanol extract of *C. auriculata* flowers displayed high carbohydrate hydrolyzing enzyme inhibitor activity and antioxidant activity [37].

The *C. auriculata* comprises preliminary phytochemical constituents such as proteins, carbohydrates, alkaloids, glycosides, phenols, flavonoids, saponins, tannins, and anthraquinone [38]. The plant has also been recognized to possess hepatoprotective [39], anti-inflammatory [40], antioxidant [41], antiperoxidative, antihyperglycemic [35], antiviral activity, and anti-spasmodic activity [42].

GYMNEMA SYLVESTRE (GS)

Kingdom: *Plantae*
Order: Gentianales
Family: *Apocynaceae*
Genus: Gymnema
Species: *G. sylvestre*

Galletto *et al.* shows the antidiabetic and hypolipidemic potential of dried powdered leaves of GS with oral dosage of 30 mg/kg. The sub-acute and chronic treatment with GS in non-diabetic and alloxan-diabetic rats did not change the body weight gain, food and water ingestion and the blood level of glucose and lipids. Thus, we concluded

that GS have antidiabetic activity and require further experimental and clinical trials [43].

Aralelimath and Bhisea study shows that GS with the dose of 200 and 400 mg/kg was administered orally to STZ induced diabetic rats for 40 days shows significant change in the all biochemical parameters when compared to control group. The histopathological study shows the significant recovery of damaged β-cells in diabetic GS treated rats, when compared to diabetic control ones [44].

Laha and Paul investigated the antidiabetic activity along with antioxidant potential of GS. Results show that bio-components possess both antidiabetic and antioxidant activity [45]. Mishal *et al.* shows the anti-diabetic activity using STZ induced diabetic Wistar albino rats. Oral administration of leaf extract at a dosage of 500 mg/Kg body weight shows the anti-diabetic activity of GS in STZ-induced diabetic rats [46].

Baskaran *et al.* studies the effectiveness of GS in controlling hyperglycemia. Twenty-two Type 2 diabetic patients were administered with (400 mg/day) for 18–20 months as a supplement to the conventional oral drugs. During GS supplementation, the patients exhibited a significant decrease in blood glucose, glycosylated hemoglobin, and glycosylated plasma proteins level [47]. Ahmed *et al.* investigates treatment of diabetic rats with GS leaves extract. Most of the studies of GS on diabetes revealed that there is a remarkable improvement in the condition of damaged β -cells in histological study of the pancreas with GS leaves extract treated diabetic albino rats [48].

Thakur *et al.* shows that Gymnemic acids are thought to be responsible for its anti-diabetic activity and it is the major component of an extract shown to stimulate insulin release from the pancreas. The commercial exploitation of this plant and their secondary metabolites are some of the major prospective of this rare medicinal herb. The focus of the present review is to achieve the potential of therapeutic value of this herb and mechanism and action of their secondary metabolites [49].

The plant has been stated to possess antimicrobial [50], anti-sweetener [51], antihypercholesterolemia [52], ethno veterinary medicinal properties [53], hepatoprotective, and anti-saccharine activities [54,55]. The aqueous extract of GS stimulates the pancreas activity, therefore rise in insulin release and decreasing blood sugar level in type-II diabetes (NIDDM) [56].

SYZYGIUM CUMINI

Kingdom: *Plantae*
Order: Myrtales
Family: *Myrtaceae*
Genus: Syzygium
Species: *S. cumini*

Kumar *et al.* examined the compound mycaminose isolated from SC seed extract to evaluate the anti-diabetic activity against STZ-induced diabetic rates with standard drug, glibenclamide (1.25 mg/kg). The results indicate that ethyl acetate and methanol extracts possess anti-diabetic effects against STZ-induced diabetic rats [57].

Prabakaran carried out to evaluate the phytochemical bioactive compounds from *S. cumini* seed extract and it is *in vitro* anti-diabetic activity. The phytochemical screening showed appreciable amount of flavonoid and steroid in the seed extract. The result suggested that significant amount of flavonoid in *S. cumini* seed is responsible for antidiabetic properties and it is further confirmed by higher intensity of alpha amylase inhibitory effect [58].

Amudha *et al.* showed that the Inner kernel of *S. cumini* seeds was extracted and formulated into a novel phytosome formulation using cholesterol and lecithin with suitable method. *S. cumini* seed extract (100/200 and 400 mg/kg b.wt) and its *S. cumini* phytosome formulation (100/200 and 400 mg/kg b.wt) shows a significant control in blood sugar level in comparison with standard drug Glibenclamide in a dose dependent manner. Further, the research proves that phytosome formulation is superior in controlling blood sugar than *S. cumini* seed extract [59].

Mulkalwar *et al.* indicates that *S. cumini* extract at a dosage of (SC 100 mg/kg and 200 mg/kg, metformin 90 mg/kg and SC 200 mg/kg with metformin 90 mg/kg) reduces blood sugar levels in diabetic rats. *S. cumini* also caused decrease in HbA1c levels but the reduction was more significant when used in supplementation with metformin. However, more non-clinical and clinical studies need to be conducted to confirm the findings [60].

Schoenfelder *et al.* showed that the ethanolic crude extract (ECE) of leaves from *S. cumini* (L) was screened for its hypoglycemic and hypolipidemic activity (125, 250, and 500 mg/kg v.o). Hypolipidemia was evaluated in rats with alloxan-induced diabetes. The acute treatment with *S. cumini* ECE caused a significant decrease in the blood glucose in hyperglycemic normal rats (250 mg/kg), and in glucose (125 and 250 mg/kg), triglyceride (125 and 500 mg/kg), and cholesterol (125 mg/kg) levels of diabetic rats, but no effect was observed in the normal treated rats [61].

The *S. cumini* seeds also contains anti-oxidant activity, anti-inflammatory activity [62], antimicrobial activity [63], anti-diarrheal, anti-fertility [64], gastro-protective [65], anti-ulcerogenic, and radioprotective activity [66]. Seeds of *S. cumini* contain total phenols, terpenoids, tannins, saponins, phytosterols, carbohydrates, flavonoids and amino acids [67].

TRIGONELLA FOENUM-GRAECUM

Kingdom: *Plantae*
Order: Fabales
Family: *Fabaceae*
Genus: *Trigonella*
Species: *T. foenum-graecum*

Soneji and Khan evaluated the anti-diabetic activity of *T. foenum-graecum* leaves in different solvent extracts. The results of the work indicate that both extracts of plant possessed considerable *in vitro* antidiabetic activity by inhibition of α-amylase, ethanol extract of plant shows maximum inhibition (73.4%) of glycosylation of hemoglobin, while extracts of *T. foenum-graecum* provide uptake of glucose by yeast cells which differ with the sample and glucose concentration, maximum increase in 5 mM glucose concentration. Hence, from study it is concluded that *T. foenum-graecum* leaves might be considered as herbal remedies for diabetes [68].

Rehman *et al*. that Fenugreek seeds powder 20 g/day to treat type 2 DM as a natural supplement. Blood glucose levels such as fasting blood glucose, random blood glucose, and HbA1c were taken at baseline, at the end of study. T2DM patient's shows significant reduction in their glucose levels after 30 and then 60 days of treatment [69].

Premanath *et al.* shows the effectiveness of *T. foenum graecum* leaves on blood glucose levels, islets cells of pancreas in STZ induced type 2 diabetic rats. The result suggests that the ethanol leaf extract of *T. foenum graecum* has significant antidiabetic activity against diabetic rats [70]. Geberemeskel *et al*. study investigated the effect of *T. foenum-graecum* seed powder solution on the lipid profile of newly diagnosed Type II diabetic patients. The results showed that the administration of *T. foenum-graecum* seed powder solution had pronounced effects in improving lipid metabolism in Type II diabetic patients with no adverse effects [71]. Baset *et al.* study investigates the antidiabetic potential of fenugreek (*T. foenum-graecum*) seed extract at a dose of 100 mg/kg in a Streptozocin-induced diabetic model. Results show that oral and injectable fenugreek showed improvement in blood glucose, renal and liver functions. Although triglyceride levels decreased significantly, no significant changes in cholesterol levels were seen after fenugreek use [72].

Scientific studies have shown that fenugreek has several therapeutic benefits such as hepatoprotective, antioxidant [73], anticancer [74], antimicrobial [75] anti-inflammatory, antiulcer, antilithogenic, anticarcinogenic, antibacterial, and neuroprotective effects, such activities have been proven in both experimental animals and clinical trials [76-78].

CINNAMOMUM ZEYLANICUM

Beji *et al.* investigates the oral administration of cinnamon blocked the increase of blood glucosein alloxan-induced diabetic rats. In diabetic rats, cinnamon action returned the activities of SOD, CAT, and GPx. These findings proposed that cinnamon has an anti-hyperglycemic effect, recovers lipid profiles, and protect against damage induced by oxidative stress [79].

Kingdom: *Plantae*
Order: Laurales
Family: *Lauraceae*
Genus: Cinnamomum
Species: *C. zeylanicum*

Antidiabetic potential of the ethanolic extract of *C. zeylanicum* leaves was studied by Tailang *et al*. Oral induction of extract in three different doses 100, 150, and 200 mg/kg body weight to Wistar albino rats suggestively reduced the blood sugar level in alloxan induced type 2 diabetic rats under acute and sub-acute studies [80].

Shen *et al.* determining the insulin-independent effect of cinnamon. STZ induced diabetic rats were divided into four groups and orally administered with an aqueous cinnamon extract (CE) for 22 days. CE exhibited its anti-diabetic effect independently from insulin by two mechanisms: (i) Upregulation of mitochondrial UCP-1, and (ii) enhanced translocation of GLUT4 in the muscle and adipose tissues. These activities may allow cinnamon to be used in the daily care of DM by its dietary or supplementary use [81].

Kamble and Rambhimaiah combine cinnamon with glibenclamide to treat alloxan induced type 2 diabetic rats and the result shows more significant decrease in blood glucose level than either drug is given alone in diabetic albino rats [82].

Shang *et al.* shows water soluble extracts of *C. zeylanicum* containing 45 and 75% gallic acid equivalents (GAE). These polyphenol enhanced extracts were shown to offered better antioxidant potential, hypoglycemic effect, hypolipidimic effect, and significant decrease in other biochemical parameters as compared to the standard aqueous extract containing 15% GAE, when administered to STZ-induced diabetic rats at 200 mg per kg b.wt for 30 days [83].

Cinnamom shows health effects such as antibacterial activity [84], antimicrobial activity [85], anti-obesity [86], anti-inflammatory [87], reducing cardiovascular disease, boosting cognitive function, and reducing risk factor of colonic cancer [88,89].

CONCLUSION

In the developing countries increased cost effectiveness of modern medicine and their side effects made people to look into herbal medicine. This systematic review shows that *C. auriculata*, GS, *S. cumini*, *T. foenum-graecum*, *and* C. zeylanicum have antidiabetic activity in nature. The mixture of this compound, when used in single formulation it enhance the beneficial effects through synergistic amplification and offer advantage over a single isolated ingredient. Due to the lack of good quality trial the effectiveness of polyherbal formulations remains to be validated. Still, advanced well designed clinical trials with a bigger sample size are essential to determine the better therapeutic efficacy of polyherbal formulations in managing blood sugar in diabetic patients. From this review article, it may be useful to the health professionals, scientists and research scholars to develop antidiabetic herbal drug to cure different kinds of diabetes problem using polyherbal formulation.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTEREST

There is no conflict of interest from the authors.

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