

A REVIEW ON HERBAL DRUGS WITH ANTIDIABETIC ACTIVITY

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is very common metabolic disorder affecting people of all age groups. The change in life style and environmental factors are the considerable factors which are involved in the development of the disorder. The different parts of medicinal plants vary in their composition of bioactive compounds. Traditionally bud of *C.auriculata L.* is used to treat diabetes rather than flower. The compounds present in the bud and flower parts were identified using LC-ESI/MS analysis. Among the herbal medicines used stands out cinnamon, which can serve as an adjuvant in the control of diabetes. Cinnamon is one medicinal universal plant which has been used daily by people all over the world, which has the probable to decrease the growth of diabetes and its problem. Although almost all the animal models have indicated a pronounced anti-diabetic activity of both cinnamon species, conflicting results were observed with regard to the few clinical trials available. *Syzygium cumini* (Myrtaceae) is widely used traditional system of medicine to treat diabetes in India. The present study was carried out to isolate and identify the putative antidiabetic compound from the *S.cumini* [SC] seed. A compound, mycaminose was isolated from SC seed extract. *S.cumini* seed (200 and 400 mg/kg) was undertaken to evaluate the anti-diabetic activity against streptozotocin (STZ)- induced diabetic rates. The hot water (0.8 g/kg b.w.) and ethanol extracts (2 g/kg b.w.) of *A. paniculata* reduced the elevated glucose level by 41.51 and 41.82%, respectively in glucose-loaded rats as compared to the respective diabetic control rats.

KEYWORDS: Diabetes mellitus, *C.auriculata*, mycaminose, streptozotocin, *A. paniculata*, *S.cumini*.

INTRODUCTION

Diabetes is a chronic metabolic disorder affecting people of all age groups. It is a metabolic disorder which is characterized with high blood glucose, high insulin production, high insulin resistance and glucose or insulin intolerance. World Health Organization (WHO) has estimated that nearly 422 million people were affected with T2DM worldwide in 2014 and the condition may double in 2030.^[1] In 2017, it was expected that 425 million people (20–79 years of age) suffered from Diabetes mellitus (DM), and the number is expected to rise to 629 million by 2045. The global use of medicinal plants for the management of diseases like diabetes has promptly increased over the last decade. Moreover, a large number of medicinal plants are believed to possess anti-diabetic activities and have been utilized to control diabetes.^[2] However, DM is also treated in Indian traditional medicine using anti-diabetic medicinal plants. Hence, there is a need to search for newer anti-diabetic agents that retain therapeutic efficacy and are devoid of side effects that could be important sources of such agents.^[3] According to the ethno botanical survey report more than 25,000 plant based drug formulations from 800 plants may be a good source of effective antidiabetic agents in Indian folk medicines.^[4] Indigenous drugs, since long, have been used for the treatment of diabetes.^[5] Most of these medicinal plants have not been well validated for their effectiveness and possible side effects. It is therefore various parts of plants have been used in herbal medicines for the treatment of diabetes, and reportedly carry no adverse effects.^[6]

Gymnema sylvestre plant preparation was used in different formulations for the treatment of diabetes. Several studies were conducted with the use of dexamethasone for induction of insulin resistance. Hence, the present study was undertaken to investigate protective role of aqueous extract of *Gymnema sylvestre* on serum glucose, insulin and lipid profile in dexamethasone induced insulin resistant rats.^[7]

A. paniculata is used as herbal medicine in countries such as China, Hong Kong, Bangladesh, Indonesia, India, Malaysia, and Thailand. The aerial parts of *A. paniculata* are the most frequently used parts. Its extracts contain diterpenoids, diterpene, glycosides, lactones, flavonoids and flavonoid glycosides. This study was conducted to investigate the anti-diabetic activities of the ethanolic extract of the twigs of *Andrographis paniculata* on STZ-induced diabetic Albino rats. This study will go through the anti-diabetic action of *Andrographis paniculata*, which has been employed as an anti-diabetic treatment in traditional medical systems.^[8]

The *Syzygium cumini* (or *Eugenia jambolana*) tree belongs to the Myrtaceae family. This is also called as Jamun, Jambul and Jambol in India and Malaya. The present study was designed to evaluate the anti-diabetic activity of isolated compound mycaminose. The effect of SC extracts was compared to glibenclamide, which is often used as a standard drug.^[3] *S. cumini* and its different parts are popular for its medicinal and nutritional value and traditionally utilized as anti-diabetic.

Cinnamon hypoglycaemic activity may be recognized to numerous mechanisms of action, comprising the stimulation of insulin release and insulin receptor signaling, the activation and regulation of enzymes involved in carbohydrate metabolism, glycolysis, gluconeogenesis, stimulation of cellular glucose uptake and increased glucose transporter-4 receptors synthesis.^[2] The effects of 'cinnamon extract' on insulin resistance and body composition have been studied by using Wistar rats of induced metabolic syndrome. Their results also concluded that 'cinnamon' alters the body composition in association with improved insulin sensitivity.^[9]

One such plant which has been used in the traditional medicine is *Cassia auriculata* L. The plant belongs to the family Fabaceae, and is widely distributed in India and Sri Lanka. The herbal tea prepared from the five parts of the plant such as roots, leaves, flowers, bark and unripen fruits were used in the preparation of herbal tea known as Kalpa herbal tea (Avarai panchaga chooranam). This tea is mainly consumed by the people in the Asian countries to reduce the blood sugar level and to control the symptoms of diabetes. The various parts of *C. auriculata* L. such as leaves and flowers have been reported for their antidiabetic activity. However, the bud part of the plant has been traditionally consumed by the people for the management of the diabetes.^[1]

HERBAL DRUGS WITH ANTI DIABETIC ACTIVITY

Cassia auriculata

C. auriculata flower extract exhibited $66.0 \pm 1.79\%$ glucose uptakes over control. *C. auriculata* flower extract increased the expression of GLUT4 in rat L6 myotubes. The effect of *C. auriculata* flower extract on the viability of the L6 myotubes was analyzed by colorimetric MTT assay. After overnight fasting with serum free DMEM, the cells were treated with various concentrations (62.5, 125, 250, 500, 1000 μg) of *C. auriculata* flower extract at 37°C with 5% CO_2 in an incubator for 24 h. After treatment, culture medium was removed from the wells, and 100 μl of MTT (5 mg/ml in D-PBS) was added to each well. After 4 h incubation at 37°C , MTT in D-PBS was removed and then the formazan crystals were solubilised in 100 μl of 2-propanol. The absorbance of dye was measured at a wavelength of 570 nm. The results were expressed as percentage of control cell viability.^[1]

To evaluate the effectiveness of *Cassia auriculata* (Avaram poo) flower extract in reducing blood glucose among pre diagnosed Type 2 Diabetes Mellitus. To administer the *Cassia auriculata* (Avaram poo) flower extract to the study group, To assess the post test level blood glucose among the control and experimental group, The research approach selected for the study was Quantitative approach, quasi Experimental design (pretest and post test with control group). The study was conducted in selected PHC Kalapet, at approach selected for the study was Quantitative approach, quasi Experimental design (pretest and post test with control group). The study was conducted in selected PHC Kalapet, at Puducherry. Sample size was 60, 30 in experimental and 30 in control group were randomly assigned. The standardized glucometer was used to assess the blood glucose level. Pretest was done to assess the level blood glucose (FBS and PPBS) for both the groups. Experimental group received *Cassia auriculata* Flower (Avaram poo) extract for 30 days and control group did not receive any measures. Post test level of blood Glucose (FBS and PPBS) was evaluated on 30th day for both experimental and control group. The results of the study were the result revealed that the pretest mean score of fasting blood glucose was 133.50 ± 37.43 and after the administrations of *Cassia auriculata* flower extract the post test mean score was 109.93 ± 18.14 . The mean difference score was 23.57. The calculated paired 't' value of $t=5.478$ was found to statistically highly significant at $p < 0.001$ level. This clearly indicates that the *Cassia auriculata* flower extract was found to be effective in reducing the fasting blood glucose level among type 2 diabetes mellitus.^[10]



Cassia auriculata

The preliminary in vitro antioxidant and in vitro antidiabetic activity suggest that the *C. auriculata* L. bud and flower ethanol extract possess the antidiabetic activity was performing the in vivo antidiabetic activity using high fat diet and STZ induced diabetic rat models. The weight of the non diabetic control group and the non diabetic vehicle control group animals remains slightly increased throughout the study. On treatment with CAFE 500, CAFE 500 and metformin, the animals gained their weight to normal and the level of consumption of water and feed rate decreased significantly ($p < 0.05$). On induction of diabetes using HFD and STZ resulted in the increase of blood glucose in all the group animals. High fasting blood glucose is one of the important indicators of diabetes. In the non diabetic control group and the non diabetic vehicle control group (DMSO), the blood glucose remained normal. In diabetes-induced groups, treatment with CAFE 500 significantly decreased the level of blood glucose from the 14th day till the end of the study, as compared to the disease control ($p < 0.05$). CAFE showed significant reduction in the blood glucose levels compared to the CAFE ($p < 0.01$). The standard metformin treated group animals showed the reduction of the blood glucose on 14th day of the treatment.^[11]

Cinnamomum verum

Established on the study of that cinnamon supplementation (500 mg capsules twice daily) can develop anthropometric considerations, glycemic indices, and lipid profile of patients with type 2 diabetes. The administration of 1 g of cinnamon powder for 12 weeks decreases fasting blood glucose level and glycosylated Hb among un-controlled type 2 diabetes patients.

The effect of oral administration of cinnamon extract to hyperglycemia induced rats. The Study showed that oral administration of cinnamon extract produced a significant decrease in the blood glucose level in the model of induced diabetes rats.^[12]

Effect of methanolic extract of *Cinnamomum verum* on sucrose absorption from the gut. Postprandial hyperglycemia is an abnormally high increase in blood sugar after eating. For this experiment, 16 Long Evans rats (both male and female) were selected randomly, then divided into a control and test group, each group containing eight rats. A sucrose solution (2.5 g/kg body mass) was administered orally with MECV (500 mg/kg) to the test group and only sucrose solution to the control group. Both test and control groups were killed to determine the unabsorbed sucrose content at 30, 60, 120, and 240 min time intervals, and then the GI tract was excised and separated into six segments: the stomach, upper 20 cm, middle and lower 20 cm of the small intestine, the cecum, and the large intestine. After

washing the segments with 10 ml ice-cold normal saline, 2N H₂SO₄ was added to acidify it and finally centrifuged at 3000 rpm for 10 min. Then the supernatant was boiled for 2 h in paraffin oil, and then after the addition of 1 N sodium hydroxide to neutralize the H₂SO₄ content, the final volume was recorded. The GI sucrose content was determined using the in-situ gut technique from the volume of released glucose.^[13]



Cinnamomum verum

The insulin-sensitizing property of 'cinnamon' in the rat epididymal fat cell assay have used the insulin secretory effect of 'cinnamon' to evaluate the influence of bovine serum albumin on insulin activity. Research conducted in 2004 by the same group has suggested that early administration of 'cinnamon extract' to high-fructose diet-fed rats prevents the development of insulin resistance at least in part by enhancing insulin signalling. The effects of 'cinnamon extract' on insulin resistance and body composition have been using Wistar rats of induced metabolic syndrome. Their results also concluded that 'cinnamon' alters the body composition in association with improved insulin sensitivity.^[14]

Syzygium cumini

The various parts of SC were investigated for antidiabetic potential in animal models and the bark, leaves, fruit pulp and seeds were found to be effective in controlling experimental diabetes. Recent studies using hydro-alcoholic and methanolic extracts of SC seeds in Alloxan-induced diabetic rat model shown positive results in lowering blood glucose levels. Hydro-alcoholic exhibited antidiabetic effect at 500 mg/kg dose and significantly reduced the blood glucose level after 21 days of treatment. The methanolic extract study using 200 mg/kg for 14 days showed comparable blood glucose lowering effect as that of gliclazide 25 mg/kg dose in comparison with diabetic control group.^[3,15]

Studies using hydroethanolic extract of SC leaves in lean and MSG-induced obese rat model showed improved hyperinsulinemia and insulin resistance. Hydroethanolic extract of leaves also potentiated pancreatic function in islets via stimulating/modulating β cell insulin release isolated from both lean and obese rats.^[4]

The aqueous and methanol extracts of root, stem bark, leaf and seed extracts of Jamun has been reported to lower serum glucose levels in alloxan-induced diabetes in male Sprague Dawley rats in an earlier study. Supplementation of Jamun seed powder in human diabetic subject for 30 days reduced the fasting and post prandial blood glucose levels. Although *Syzygium cumini* (seed aqueous extract) can reduce blood glucose levels in high fructose diet induced diabetic rats, in a dose dependent (200mg/kg, 400mg/kg and 800mg/kg) manner, but in euglycemic animals it had no effect on the blood glucose levels.^[16]



Different stages of *S. cumini*; a: Flowering stage, b: Fruiting stage, c: Mature Fruit, d: Seeds of *S. cumini*

Andrographis paniculata

During the optimization of the DM therapy often used a combination of several herbal medicines. The effects of combination of n-hexane insoluble fraction of ethanolic extract of *Andrographis paniculata* (HIFA) with other herbal medicines to improve their antidiabetic effect. Other herbal that can be combined with *Andrographis paniculata* is *Centella asiatica L.* *Centella asiatica* effectively for anti-diabetic in diabetic rats induced by streptozotocin based on measurement of serum levels of glucose and their hepatic glycogen levels.^[5,6]

Andrographolide-enriched extract of *Andrographis paniculata* (AEEAP) combined with asiaticoside enriched extract of *Centella asiatica* (AEECA) gave an anti-diabetic effect on diabetic rats induced by high fructose fat fed. Metformin is a common antidiabetic medication that has been demonstrated to be effective at lowering blood sugar levels without causing hypoglycaemia. Pre- and postprandial blood glucose levels, as well as cholesterol, Low Density Lipoprotein (LDL), triglycerides, and body weight, as well as liver and kidney functions, were used to measure anti-diabetic activity. Active compounds from *Andrographis paniculata* exert a hypoglycemic effect in alloxan-induced rats. It was successful in decreasing blood glucose, triglyceride, and LDL levels. They had no effect on cholesterol levels, however, and more research is required to establish their mechanisms of action. According to the findings of the study, *Andrographis paniculata* leaf extract has high therapeutic potential for the treatment of diabetes.^[17]



Andrographis paniculata

In vitro anti-diabetic activity was assessed by alpha amylase inhibitory activity and alpha glucosidase inhibitory activity. The data were analysed by one-way-ANOVA to check the statistical significance among the groups and considered at the levels of $p < 0.05$. Both the ethanolic extracts of *Andrographis echiooides* and *Andrographis paniculata* showed significant anti-diabetic potential in a dose-dependent manner (100-500 μ g) and can be used as potential antidiabetic agents. Similar to antioxidant potential, *Andrographis paniculata* exhibited an increased anti-diabetic potential compared to *Andrographis echiooides*. Data shows that ethanolic extracts of *Andrographis echiooides* and *Andrographis paniculata* possessed antioxidant and anti-diabetic activity and hence our present findings conclude that both plants can be considered for the development of natural drugs for the management of diabetes. In the present study, *Andrographis paniculata* significantly ($p < 0.05$) increased the Alpha glucosidase inhibitory activity in a dose dependent manner (100-500 μ g/ml). However, 400 and 500 μ g concentrations exhibited the maximum activity in inhibiting the alpha amylase suggesting that the plant has potential anti-diabetic activity.^[18]

Gymnema sylvestre

The present study was undertaken to evaluate antidiabetic activity of *Gymnema sylvestre* leaf aqueous extract against dexamethasone induced insulin resistance in Albino rats. Leaves of *Gymnema sylvestre* improve the glucose utilization by increasing the activity of enzymes responsible for glucose utilization by insulin dependent pathways. It increases phosphorylase activity, decrease in gluconeogenic enzymes and sorbitol dehydrogenase enzyme. It is believed that one of saponin form of *Gymnema sylvestre* plant leaves, Gymnemic acid was responsible for development of hypoglycemia. Gymnemic acid molecules by filling the receptors on absorptive layers of intestine decreases absorption of glucose, resulting in low blood sugar levels.^[19]



Gymnema sylvestre

The hypoglycaemic effect of *G. sylvestre* is attributed to triterpenoid saponins known as gymnemic acids. Experimental studies have shown that *G. sylvestre* can inhibit carbohydrate digesting enzymes like alpha-amylase and alpha-glucosidase to reduce postprandial hyperglycemia. It can also stimulate insulin secretion, enhance glucose uptake by cells, and inhibit hepatic glucose production. Various phytochemicals present in *G. sylvestre* like phenolics, flavonoids and terpenoids are reported to possess antidiabetic properties. However, the efficacy of different extracts and formulations of *G. sylvestre* has not been extensively investigated and compared. The ethanolic extract showed higher total phenolic and flavonoid content compared to the aqueous extract. In vitro antidiabetic assays demonstrated dose-dependent inhibition of alpha amylase and alpha glucosidase enzymes by the extracts. The ethanolic extract exhibited

higher antidiabetic activity compared to the aqueous extract and formulations. Overall, the results indicate that *G. sylvestre* extracts possess phytochemicals and antidiabetic potential that can be further explored.^[20,21]

CONCLUSION

This study was to evaluate the effectiveness of *Cassia auriculata* (Avaram poo) flower extract administration on blood glucose level in patients with pre diagnosed type2 diabetes mellitus in selected centers. The result showed that the *Cassia auriculata* (Avaram poo) flower extract is effective in reducing blood glucose level in pre diagnosed type 2 Diabetes mellitus. The present study showed that MECV bark possessed hypoglycemic and antihyperglycemic activities in a Long Evans rat model by reducing the absorption of sucrose and activity of the disaccharidase enzyme. This study helps to determine the regional pharmaceutical value of *S.cumini* seeds as a traditional medicinal utilization for the management of diabetes. As a result, *Andrographis paniculata* may be developed as an alternate anti-diabetic medication. Treatment with aqueous extract of *Gymnema sylvestre* improved the altered glucose, insulin and lipid profile in insulin resistance rats.

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