

Anti-Hyperglycemic Activity of Aqueous Extracts of Some Medicinal Plants on Wistar Rats

Ajay Kumar Sharma and Ritika Gupta*

Department of Biotechnology, Meerut Institute of Engineering and Technology, MIET, Meerut, India

*Corresponding author: Ritika Gupta, Department of Biotechnology, Meerut Institute of Engineering and Technology, MIET, Meerut, India, Tel: 7060134245; E-mail: guptaritika.27@rediffmail.com

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Abstract

Diabetes mellitus is a heterogeneous group of metabolic disorder characterized by high blood glucose level. The pancreatic β -cells and its secretory hormone i.e. insulin are central in the pathophysiology of Diabetes. In type 2 or non-insulin dependent Diabetes mellitus, muscle and fat cells are 'resistant' to the action of the insulin and compensatory mechanisms that are activated in the β -cell to secrete more insulin are not sufficient to maintain blood glucose levels within a normal physiological range. This state is also linked to other common health problems, such as obesity, polycystic ovarian disease, hyperlipidemia, hypertension and atherosclerosis. The epidemic of type 2 Diabetes and impaired glucose tolerance are main causes of morbidity and mortality worldwide, which result from defects in insulin secretion, or action, or both. Herbal medicines are widely used now a day's against various ailments. Some of the herbal plants and their active chemical constituents play an important role in the management of Diabetes mellitus.

The present investigation was carried out to study the anti-hyperglycemic effect of the various extracts of different medicinal plants including *Trigonella foenum-graecum* (Methi), *Cymbopogon citratus* (DC) Stapf. (Lemon grass), *Triticum aestivum* (Wheat grass), *Syzgium cumini* (Jamun), *Bauhinia Purpurea* (Kaniyar) & *Momordica charantia* (Karela) in streptozotocin induced Diabetic Wistar rat models.

Keywords: Phyto-medicinal; Diabetes mellitus; Anti-hyperglycemic; Streptozotocin; Wistar rat

Introduction

Diabetes mellitus is one of the most important non infective diseases to hit the globe in the present millennium. It has affected 5% of the people worldwide [1-4] and accounts for about 10% of total health care expenditure in many countries [5]. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000, and is expected to rise to 4.4% in 2030 [6,7]. Diabetes is one of the five leading causes of death in the world and about six deaths per minute are attributable to diabetes complications [8]. WHO (2002) estimated that globally 7.1 million deaths could be attributed to high blood pressure, 4.4 million to high cholesterol, and 2.6 million to excessive body weight. In adults, type 2 diabetes is more frequent than type 1 [1,4,9] and is mostly characterized by peripheral insulin resistance [1,9-11] and inadequate functional mass of β -cells [10,11].

An additional or alternative approach is to select in vivo models which have diabetes symptoms. In the drug discovery process, they are employed for a variety of purposes. Animal models are used to identify new compounds with no previous history of use for diabetes treatment (screening). They are also used to understand the physiological effects, pharmacokinetics and toxicity of drugs or compounds in development (characterization).

Type 2 diabetes (DM) is a metabolic disorder which is characterised by hyperglycaemia caused by insulin secretion deficiency and insulin secretion resistance in varied tissues. In type II diabetic patients, insulin can be produced and secreted by pancreas, but the body can

only partially, or even completely unable to use the insulin produced. Urination is also increased due to high blood glucose levels. Hyperglycaemia is thought to be one among the most contributors to oxidative stress by the direct generation of excessive reactive oxygen species (ROS), resulting from associate imbalance between antioxidants and oxidants [12-14].

In conventional medical practice, the present therapies of diabetes mellitus are reported to have side effects. Many oral therapeutic agents are the primary alternative treatments of type 2 DM. The glucose-lowering drugs include insulin secretagogues (sulfonyl-ureas, meglitinides), insulin sensitizers (biguanides, metformin, thiazolidinediones), α -glucosidase inhibitors (miglitol, acarbose). The aim of those oral hypoglycaemic agents is to ameliorate the underlying metabolic disorder, related to inadequate insulin resistance, insulin secretion, and augmented hepatic gluconeogenesis.

However, these agents have limited efficacy and sometimes produced severe side effects such as weight gain, hypoglycaemia, liver injury, channel disturbances, cardiopathy, and bloating [14,15]. Besides the side effects associated with the use of insulin, the side effects of most oral glucose-lowering drugs may include severe hypoglycemia at high doses, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache, dizziness and even death. Therefore, because of the side effects associated with the present antidiabetic drugs, there is need to develop effective, safe and cheap drugs for diabetes management. Such effective, safe and cheap drugs could be obtained by using medicinal plants which have been used by humans to prevent or cure diseases including diabetes since the dawn of civilization [16].

Trigonella foenum-graecum (also known as fenugreek, locally as methi), is a well-known traditional medicinal herb and its seeds have been used as traditional medicines not only in diabetes but also in high cholesterol, inflammation and gastrointestinal ailments [17]. *T. foenum-graecum* seeds have also previously been shown to have hypoglycemic and hypocholesterolemic effects on type 1 and type 2 diabetes mellitus patients and experimental diabetic animals [18,19].

Wheatgrass is the young grass of common wheat plant, which has been used as traditional herbal medicine and is highly valued for its therapeutic and nutritional properties [20,21]. Fresh juice of *Triticum aestivum* grass contains a number of aminoacids, vitamins, phytochemicals which is used as health improving adjuvants in several diseases. There are few reports of showing that *T. aestivum* has hypolipidemic properties in normal rat due to presence of such phytochemical shaving antioxidant properties [20-22].

Cymbopogon citratus (*C. citratus*), a perennial tropical plant of the family poaceae has diverse chemical constituents that include proteins, moisture, ash, crude fiber, fat and carbohydrates [23], and it is rich in minerals, vitamins [24], phytochemicals (tannins, saponins, flavonoids, alkaloids, phenols, and anthraquinones) and anti-nutrients [25]. The antioxidant activity of *Cymbopogon citratus* was assessed in various studies and found to possess good antioxidant activity [26-28]. The oral single dose or prolonged treatment for 21 days of lemongrass (*Cymbopogon citratus*) essential oil does not show any genotoxic or toxic effects in mice and shown to beneficial in reducing the blood cholesterol level [29].

The *Syzygium cumini* (or *Eugenia jambolana*) leaf extract showed hypoglycemic action in diabetic rats. *Eugenia jambolana* Lam., commonly known as black plum or "jamun" is an important medicinal plant in various traditional systems of medicine. It is effective in the treatment of diabetes mellitus, inflammation, ulcers and diarrhea and possess chemopreventive, radioprotective and antineoplastic properties [30]. Various extracts of fruit and seeds of *Syzygium cumini* were found to have antidiabetic, antiinflammatory, hepatoprotective, antihyperlipidemic, diuretic and antibacterial activities [31-33].

Momordica charantia (Karela) commonly known as bitter gourd, bitter melon or balsam pear is a well-known to possess antihyperglycemia, anticholesterol, immuno-suppressive, antiulcerogenic, anti-HIV, anti-ulcer, anti-inflammatory, anti-leukemic, anti-microbial, anti-cholesterol, immunosuppressive, and anti-tumor activities [34]. It is a potent hypoglycemic agent [35,36] and hypoglycaemic actions for potential benefit in diabetes mellitus are possible due to at least three different groups of constituents in bitter melon. Clinical studies with multiple controls have confirmed the benefit of bitter melon for diabetes [37]. The main active component related to the anti-diabetic effect of *Momordica charantia* is present in the butanol fraction, and it may be saponin [38]. This effect is important for the treatment of both Type I and Type II diabetic patients and helps to prevent high blood sugar levels after meals.

The plant *Bauhinia purpurea* is a moderate evergreen tree used by tribes of India as cattle feed [39]. *B. purpurea* a most important species used to treat several ailments in traditional system of medicine [40-43]. *B. purpurea* was reported for its antidiarrhoeal, anticancer, thyroid gland stimulating properties [44-46]. *Bauhinia purpurea* Linn possess antibacterial, antidiabetic, analgesic, anti-inflammatory, antidiarrheal, anticancerous, nephroprotective, and thyroid hormone-regulating activity [39]. The aerial parts of the plant are reported to exhibit various pharmacological activities such as CNS activity, cardiotoxic

activity, lipid-lowering activity, antioxidant activity, hepatoprotective activity, and hypoglycemic activity [47].

Streptozotocin

Streptozotocin [STZ; 2-deoxy-2(3-methyl-3-nitrosoureido)-D-glucopyranose] is an antibiotic isolated from *Streptomyces achromogenes* which also have oncolytic, oncogenic, and diabetogenic properties [48]. It has a serum half-life as 15 min, meaning that STZ is cleared from bloodstream in 15-24 minutes [49]. Administration of low doses (35 mg/kg) of STZ causes mild diabetes leading to acute ketoacidosis, moderate doses (55-65 mg/kg) results in high blood glucose levels and weight losses [50], while administration of high doses (100 mg/kg) ends up with death within 2 to 3 days.

Through previous literature studies, acute toxicity of all plant extracts were studied. It was found that no mortality is observed at 2000 mg/kg dose for all these six medicinal plants.

Materials

Plants used in the study

Trigonella foenum-graecum (Methi), *Cymbopogon citratus* (DC) Stapf. (Lemon grass), *Triticum aestivum* (Wheat grass), *Syzygium cumini* (Jamun), *Bauhinia Purpurea* (Kaniyar) & *Momordica charantia* (Karela) were collected from local area. The plants were identified and authenticated in the Department of Biotechnology at Meerut Institute of Engineering & Technology (MIET), Meerut.

Chemical reagents

Chemical reagents used to induce Diabetes mellitus; streptozotocin and standard anti-diabetic drug; glibenclamide were purchased from Sigma-Aldrich Co, India.

Animals used in the study

36 adult male Wistar rats weighing around 180-200 g were needed for the experiment. They were housed in clean polypropylene cages (six rats/cage) and maintained under controlled room temperature (25 ± 1°) with relative humidity of 45-55% under 12: 12 hr light and dark cycle for one week with free access to food and water ad libitum. All procedures using animals obtained the approval of the Institutional Animal Ethical Committee, and the experiment was carried out in compliance with the Guidelines for CPCSEA.

Methodology

Preparation of aqueous extract

150 g of fresh plant leaves were collected from the botanical garden at each visit. These were gently rinsed in normal saline and dried leaves were separated from the fresh ones. 100 g of the fresh leaves was cut into pieces, and simmered in a conical flask containing 500 ml of double-distilled water (DDW) for 1 h.

The decoction was allowed to cool for about 3 h after which it was filtered using a piece of clean, sterile, white cotton cloth. The filtrate was evaporated to complete dryness in an aerated oven (Genlab Ltd., Widnes, England) preset at 50°C for about 2 days. The sweet-scented, chocolate colored solid residue formed after the complete dryness was kept in an air-tight and water- proof container, which is stored in the

refrigerator for a week before it was used. From this, a fresh stock for daily use was prepared.

Induction of diabetes

Streptozotocin was dissolved in freshly prepared 0.1 M citrate buffer having pH 4.5. To induce diabetic condition in rat a dose of 50 mg STZ per kg body weight were injected intraperitoneal as done previously. STZ injection rapidly produced the characteristic signs of diabetes, such as increased intake of food and water, frequent urination and increased blood glucose concentration. STZ was selected to induce experimental diabetes because of its greater selectivity of β -cells, lower mortality and relatively longer half-life (15 min) of STZ in the body. Diabetes was confirmed 48 h after STZ administration with Accucheck glucometer. All animals with plasma glucose level >200 mg/dl were considered diabetic and included in the study.

Every Day Activity

Using electronic glucometer device accu-check. One drop of blood from tail vein, putting it on strip device gives the reading within 2-5 second. Ethanol is use to wipe and clean the tail, before taking the blood from tail vein. Weighing machine is used for measure the weight of rats during the course of treatment.

Dosage preparation

Dosage were prepared by mixture of aqueous extracts as shown in treatment protocol. Fusion of extracts were given to rats orally by cannula. Rats died during the induction of diabetes by STZ injection were disposed off. Cage of rats were changed within 3-4 days or on the same day when animal die within group.

Treatment protocol

The rats were divided into 6 groups, each containing 6 animals. Group I contains normal non-diabetic rats while all other groups contain diabetic rats. Antidiabetic activity of aqueous combined plant extract (500 mg/kg) was evaluated by estimation of blood glucose levels and body weight measurement on the day 0, day 7, day 14 and day 21 of the study by using commercially available kit (Accu-Chek Active Test Meter).

Group 1: Normal rats

Group 2: Diabetic rats as control

Group 3: Diabetic rats to be treated with glibenclamide (600 μ g/kg, orally)

Group 4: Diabetic rats to be treated with PE-1

Group 5: Diabetic rats to be treated with PE-2

Group 6: Diabetic rats to be treated with PE-3

PE-1: Combined extracts of *Momordica charantia* (karela) and *Bauhinia purpurea* (kaniyar) (1:1)

PE-2: Combined extracts of *Syzygium cumini* (jamun) and *Trigonella foenum-graecum* (methi) (1:1)

PE-3: Combined extracts of *Cymbopogon citratus* (lemon grass) and *Triticum aestivum* (wheat grass) (1:1)

Statistical analysis

The values are expressed as mean \pm standard deviation (SD) obtained from the number of experiments. The data was subjected to the analysis of variance (one way ANOVA) to determine the significance of changes followed by students "t"-test.

Results

This study is based on two parameters on which diabetes affected, first one is weight and second is blood glucose level for further comparison we check the body weight and blood glucose level of rats before the injection.

Blood glucose level of animals after STZ injection

The blood sugar level was increased as compared to the rats with normal blood sugar level. Group 1 rats had normal blood glucose level and they were considered as the non-diabetes group whereas group 2-6 were considered as diabetic animals.

It was shown that the blood glucose level >200 mg/dl were considered as diabetic. Rate of motility is high as in case of STZ used to induce the diabetes in rats because there were only 30 rats survived out of 36 rats. In our study we used 30 animals for the induction of diabetes, 6 animals were died after the injection.

In this study, diabetes was induced in rats by single intraperitoneal injection of streptozotocin (50 mg/kg b.wt.). After 72 hrs rats with marked hyperglycaemia (blood glucose above 200 mg/dl) were selected and used for the study. Antidiabetic effect was evaluated by oral administration of aqueous combined plant extract at doses of 500 mg/kg b.wt. for 21 days. The treatment with aqueous combined plant extract up to 21 days at the dose of 500 mg/kg significantly improve the alterations in blood glucose levels and body weight in streptozotocin induced diabetic rats.

However, at the end of 21 days of treatment, there was a decrease of blood glucose levels with the glibenclamide and aqueous combined plant extract (500 mg/kg) respectively when compared with diabetic control group as shown in Table 1.

Streptozotocin induced diabetic rats showed significant reduction in body weight as compared to normal group. At the end of 21 days treatment, the body weight of normal rats, treated with aqueous combined plant extract and standard drug treated group increased significantly, whereas body weight of diabetic control group rats decreased as shown in Table 2.

Groups	Pre-treatment	Post-treatment		
	Day 0	Day 7	Day 14	Day 21
Normal control	87.67 ± 5.42	89.67 ± 7.42	90.67 ± 4.63	91.67 ± 9.45
Diabetic control	279.5 ± 6.23	314.5 ± 12.47	379.5 ± 15.11	409.5 ± 19.68
Glibenclamide at 60 µg/kg, orally	262.17 ± 16.33	202.17 ± 12.41	152.17 ± 10.47	94.17 ± 8.75
Combined karela and kaniyar extract at 500 mg/kg, orally	221.33 ± 14.23	177.67 ± 9.65	121.33 ± 12.84	103.17 ± 11.17*
Combined jamun and methi extract at 500 mg/kg, orally	264.67 ± 16.84	206.33 ± 12.68	147.17 ± 15.41	102.67 ± 40.07*
Combined lemon and wheaat grass extract at 500 mg/kg, orally	265.33 ± 9.38	224.67 ± 18.12	154.67 ± 14.56	109.83 ± 23.74*

*P<0.001 when compared with control (no drug) animals

Table 1: Changes on blood glucose level (mean ± SD, mg/dl) in groups of normal and Streptozotocin (STZ) induced diabetic Rats (n=6).

Groups	Pre-treatment	Post-treatment		
	Day 0	Day 7	Day 14	Day 21
Normal control	168.67 ± 7.21	178 ± 9.51	193.17 ± 12.72	207 ± 16.86
Diabetic control	209.5 ± 19.15	203.5 ± 17.67	186.83 ± 14.58	161 ± 12.39
Glibenclamide at 60 µg/kg, orally	185.67 ± 8.96	192.5 ± 16.65	203 ± 14.63	215.33 ± 18.65
Combined karela and kaniyar extract at 500 mg/kg, orally	179.83 ± 9.83	179.33 ± 11.88	180 ± 8.98	180.33 ± 12.94*
Combined jamun and methi extract at 500 mg/kg, orally	234.67 ± 15.6	237.33 ± 19.52	252 ± 13.64	219.83 ± 20.68*
Combined lemon and wheaat grass extract at 500 mg/kg, orally	206.5 ± 9.79	207.17 ± 13.82	211.5 ± 11.79	216.33 ± 14.94*

*P<0.001 when compared with control (no drug) animals

Table 2: Changes on body weight (mean ± SD, g) in groups of normal and Streptozotocin (STZ) induced diabetic Rats (n=6).

When diabetes was successfully induced in the animal, then we used our treatment protocol to reduce the blood sugar level in diabetic animal. Figure 1 shows the effect of various combinations of the plant extracts in the mean fasting blood sugar of the non-diabetic rats in comparison with diabetic rats. The aqueous combined plant extract of jamun and methi at the dose of 500 mg/kg showed significant

antidiabetic activity against streptozotocin induced diabetic rats and the effect was comparable with that of the standard drug glibenclamide (600 µg/kg). After the treatment with aqueous combined plants extract, there was significant decrease in blood glucose level and glycosylated haemoglobin levels.

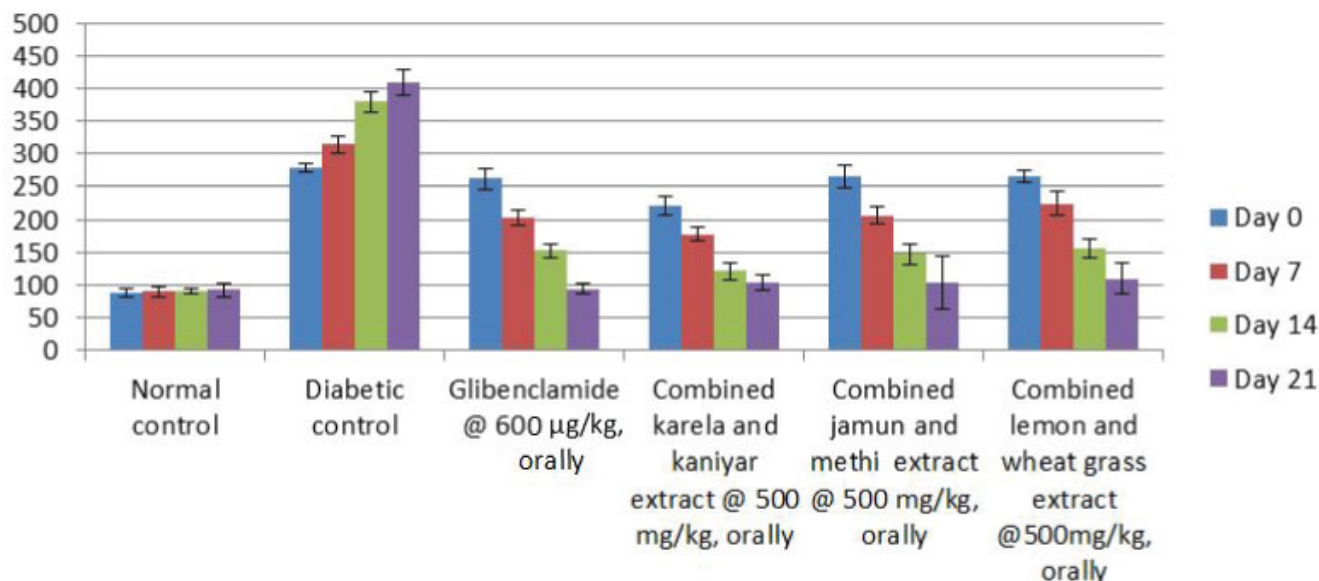


Figure 1: Changes on blood glucose level (mean \pm SD, mg/dl) in groups of normal and Streptozotocin (STZ) induced diabetic Rats (n=6).

Effect on body weight after the treatment

Figure 2 shows the effect of various combinations of the plant extracts in the mean body weights of the non-diabetic rats in comparison with diabetic rats. Induction of diabetes with streptozotocin is associated with a characteristic loss of body weight, which is probably due to muscle wasting and due to loss of tissue

proteins. All the aqueous extract of phytomedicinal plants were given at a dose of 500 mg/kg orally for a period of 21 days to different groups of diabetes animals. After 21 days it was found that there is significant increase in body weights which can be easily calculated with the help of unpaired t-test.

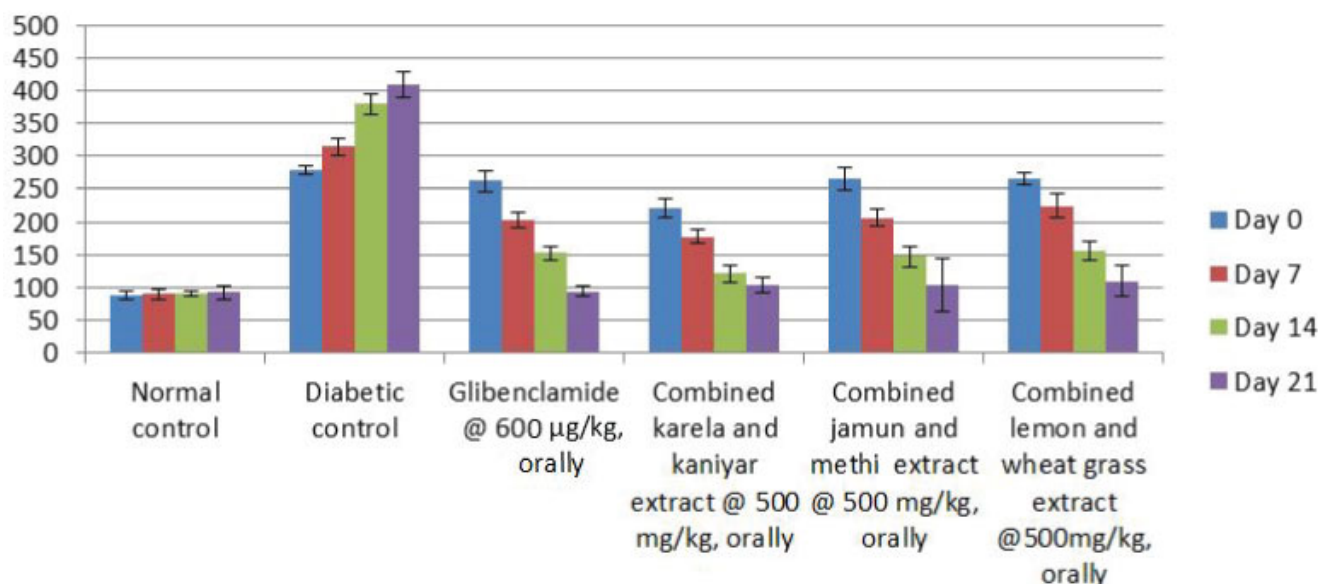


Figure 2: Changes on body weight (mean \pm SD, g) in groups of normal and Streptozotocin (STZ) induced diabetic Rats (n=6).

Discussion

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by high blood glucose level. Since ancient times plants have been extemporary source of medicine. Ayurveda and Indian

literature mention the use of plants in treatment of various human ailments. In light of these evidences, an attempt was made in the present project to identify some new combination of anti-diabetic agents using experimentally validated animal models of diabetes. The purpose of choosing streptozotocin as diabetes-inducing agent was

known to produce diabetes mellitus irreversibly with a single dose of intraperitoneal administration by relative necrotic action on the β -cells of pancreas leading to insulin deficiency. Insulin deficiency leads to various metabolic aberrations in animals viz., increased blood pressure level, decreased protein content, increased level of cholesterol and triglycerides were reported. The WHO expert committee has aptly suggested that research should be aimed at investigating the traditional methods of treatment for refractory diseases like diabetes.

Since ancient times, plants and plant extracts were used cost-effectively worldwide to treat diabetes. In fact, in many parts of the world, especially poor countries, this may be the only form of therapy available to treat diabetes patients. Therefore, traditional medicine offers promising solutions to face the global increasing demands for new therapeutic agents. Insufficient data exist for most plants to guarantee their quality, efficacy and safety [51].

Akilmoludun et al. (2007) described medicinal effects of plants which are often attributed to the antioxidant activity of the phytochemical constituents, mainly the phenolics. He also explained the synergistic relationship amongst phytochemicals is responsible for the overall beneficial effect derivable from plants [52].

The perusal of the proposed study shows that many of the plant species which are being used by the rural people for treatment of diabetes mellitus are very common, easily available either at low or no cost. Further, their mode of preparation as well as administration should also be simple and convenient and without any side effects. However, the adverse effects of phytotherapeutic agents are less frequent compared with synthetic drugs, but well-controlled clinical trials have now confirmed that such effects really exist [53].

Mentreddy (2007) has reviewed many medicinal plants possessing experimental and clinical antidiabetic activity that have been used in traditional systems of medicine. It has been estimated that about 80-85% of population both in developed and developing countries rely on traditional medicine for their primarily health care needs and it is assumed that a major part of traditional therapy involves the use of plant extracts or their active principles [54].

STZ-induced diabetic rats were found to exhibit significant hyperglycemia as compared to control rats. In the present study, six medicinal plants were selected for antidiabetic studies owing to its traditional uses. Therefore, the study was undertaken to justify its claimed uses. Wistar rats were selected as experimental animals for the antidiabetic activity. The extracts were screened for streptozotocin-induced antidiabetic activity. The aqueous extracts of plant showed significant ($P < 0.0001$) antidiabetic activity at dose, that is, 500 mg/kg of body weight.

Treatment of these compounds showed significant blood glucose lowering effect in diabetic rats which was comparable showed significant blood glucose lowering effect in diabetic rats which was comparable to the blood glucose lowering effect of known standard anti-diabetic drug. The fusion of phytomedicinal plants (jamun and methi) was found to be very effective in the treatment of diabetes. They inhibit the postprandial rise in hyperglycemia in STZ-induced diabetes comparable to that of standard anti-diabetic drug.

Conclusion

In conclusion, this study shows that the phytoconstituents in kaniyar, karela, wheat grass, lemon grass, jamun and methi exerts promising antihyperglycemic effects in STZ-induced β -cell damaged

diabetic rats. From the above discussion it conclude that aqueous plant extracts of *Syzium cumini* and *Trigonella foenum-graecum* at dose (500 mg/kg) exhibited significant antihyperglycemic activity in STZ-induced diabetic rats. These extracts also showed improvement in parameters like body weight so might be of value in diabetes treatment. Thus, these antihyperglycemic agents can be explored for development of anti-diabetic lead molecules and further studies carried out in this direction to find out mechanisms of action may results in effective treatment and control of diabetes. The study can suggests that the combined extract had synergetic hypoglycemic effect revealed by increased serum insulin levels, decreased serum lipid levels and therefore attribute to therapeutic value of the combined plant extracts to combat the diabetic condition in rats. However, further pharmacological and biochemical investigations are needed to elucidate the exact mechanism of hypoglycemic effects of combination of jamun and methi seeds aqueous extracts.

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