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Antihyperglycaemic activity of six edible plants in validated animal models of diabetes mellitus

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Abstract: The fruits of edible hypoglycaemic plants of *Momordica charantia*, dried seeds of *Syzigium cumini*, seed oil of *Aegle marmelos* and dried fruit powder of *Coccinia indica*, dried powder of the roots and rhizomes of *Curcuma longa* and seeds of *Trigonella foenum-graecum* were tested on normoglycaemic as well as streptozotocin-induced diabetic rats for its antihyperglycaemic efficacy. The investigation confirms the traditional claim of antihyperglycaemic activity in these edible plants.

Keywords: Antihyperglycaemic activity, *Momordica charantia, Coccinia indica, Syzigium cumini, Aegle marmelos, Curcuma longa, Trigonella foenum-graecum.*

Introduction

Diabetes mellitus with its devastating consequences has assumed epidemic proportion in many countries of the world. There are an estimated 143 million people worldwide with diabetes, which is almost five times more than the estimation of ten year ago. This number will probably double by 2030 (King *et al*., 1998). Although diabetes is more prevalent in developed countries, it is likely that the developing world will bear the brunt of the epidemic in the future. In the US, almost 16 million people are thought to be afflicted and third of them are undiagnosed. The disease is considerably more common among the elderly and strikes African-Mexican and Native Americans. In India, it is estimated that presently 19.4 million individuals are affected by diabetes and likely to go up to 57.2 million by the year 2025 (King *et al*., 1998).

There are two main categories of this disease i.e. Type 1 (Insulin dependent diabetes mellitus) and Type 2 (Non-insulin dependent diabetes mellitus). Type 1 diabetes represents a heterogenous and polygenic disorder, with a number of non-HLA loci contributing to disease susceptibility (Lernmark & Ott, 1998). Though this form of diabetes accounts for 5 to 10% of all cases yet there is no identified agent substantially capable of preventing this type of disease (Atkinson & Eisenbarth, 2001). Type 2 diabetes mellitus is far more common and results from a combination of defects in insulin secretion and action, either of which may predominate. People with type-2 diabetes are not dependent on exogenous insulin, but may require it for control of blood glucose levels if this is not achieved with diet alone or with oral hypoglycemic agents. This type of diabetes accounts for 90 to 95% of all diabetic patients (DeFronzo, 1997). Treatment of type-2 diabetic is complicated by several factors inherent to the disease process, typically insulin resistance, hyperinsulinemia, impaired insulin secretion, reduced insulin-mediated glucose uptake and its utilization (DeFronzo, 1997; Polonsky *et al*., 1996; Groop *et al*., 1989). All forms of diabetes are characterized by chronic hyperglycemia and the development of diabetes-specific microvascular pathology in retina, renal glomerulus and peripheral nerve. As a convenience of its microvascular pathology, diabetes is a leading cause of blindness, and stage renal disease and a variety of debilitating neuropathies.

The management of type-II diabetes mellitus is considered a global problem and successful treatment is yet to be discovered. The modern drugs like sulfonylurea, biguanides, inhibitors of intestinal α- glucosidases, glitazones, repaglinide and aldose reductase inhibitors control the blood sugar levels as long as they are regularly administered but also produce a number of undesirable side effects and sub-optimal control of glucose levels (Upadhyay *et al*., 1996; Reynolds, 1997). Also an oral hypoglycaemic agent equivalent to insulin has yet to be found. These are some reasons why people are still searching for novel treatments. The treatment of diabetes mellitus has been attempted with various indigenous plants and polyherbal formulations (Chaurasia *et al*., 1994; Mitra et al., 1996; Upadhyay *et al*., 1996). No doubt, encouraging results have been obtained from plant extracts with respect to antidiabetic activity, but still only a meager percentage of the plant world has been explored (Arokiyaraj *et al*., 2008; Ahmad *et al*., 2008). There is dearth of information regarding the antidiabetic property in lot of edible vegetables.

Vegetables are among the numerous plant adjuncts tried for the treatment of the Diabetes mellitus. A few vegetables that are commonly consumed in India have been claimed to possess antidiabetic property. Considerable amount of work has been carried out in this regard with bitter gourd (*Momordica charantia*) and ivy gourd (*Coccinia indica*) both in experimental animals and human patients. The hypoglycaemic claim is claimed to be mediated through an insulin secretagogue effect or through an influence on enzymes involved in glucose metabolism.

With this background, an attempt has been made first to evaluate the antihyperglycaemic effect of the crude powders of the parts of the six edible vegetables i.e. *Momordica charantia*, *Syzigium cumini*, *Aegle marmelos*, *Coccinia indica*, *Trigonella foenum-graecum and Curcuma longa* in animal models of diabetes mellitus to validate their traditional claims.

Materials and Methods

The fruits of *M. charantia*, dried seeds of *S. cumini*, seed oil of *A. marmelos*, leaves and fruits powder of *C. indica*, the roots and rhizomes of *C. longa* and seeds of *T. foenum-graecum* were purchased from the local market and shade dried before powdering them. Streptozotocin (STZ) was purchased from Sigma-Aldrich (USA).

Animals

Male Sprague-Dawley strain of albino rats weighing

Indian Journal of Science and Technology Vol.2 No 4 (Mar. 2009) ISSN: 0974- 6846

around 160 g was used in the experiments. Animals were fed the pellet diet and water *ad-libitum.* The following conditions were always maintained in the animal room 24-28 °C temperature, 60-70% relative humidity, 6 to 10 air changes per hour and 12h day and night cycle.

Evaluation on normoglycaemic rats

Prior to use, the animals were deprived of food for 12 hr. Rats showing fasting blood glucose between 60-80 mg/dl checked by glucostrips (Roche) were finally selected and divided into 6 groups. Each group consisted of 6 animals. Rats of the group I were taken as control given 1% Gum acacia whereas rats of experimental groups were dosed orally with the test extracts at 50, 100, 200, 375, and 500 mg/kg in 1.0% gum acacia, respectively. The rats were primed with sucrose (10.0 gm/kg orally) 30 minutes after dosing and blood glucose was again measured at 0, 30, 60, 90 and 120 min and 180 min post sucrose load. Food but not water was withheld from the cages during the course of experimentation. Comparing the AUC of experimental and control group determined the percent antihyperglycaemic activity.

Evaluation on streptozotocin-induced diabetic rats

Streptozotocin was dissolved in 100 mM citrate buffer (pH 4.5) and calculated amount (60mg/kg) of the fresh solution was injected intraperitoneally to overnight fasted rats. Blood glucose was checked 48 h later by glucostrips (Roche) and animals showing blood glucose value between 144-270 mg/dl were included in the experiments and termed as Diabetic. The diabetic rats were divided into 8 groups consisted of six animals in each. Group I served as control (untreated rats) given 1% Gum acacia whereas other groups were given the test extracts at an oral dose which was arbitrarily based on previous experiment.

The desired doses of the test extracts were evaluated in this model. The sucrose load (2.5 g/kg) was given 30 min post administration of the test/crude plant extract/vehicle and blood glucose was again measured at 0, 30, 60, 90, 120, 150, 180, 240, 300 min and at 24 hrs time interval post sucrose load. Animal not found diabetic after 48 hours post treatment of test sample were not considered and omitted for calculations and termed as non-responders. Food but not water was withheld from the cages during the course of (300 min.) experimentation. Comparing the AUC of experimental and control groups determined the percent antihyperglycaemic activity.

Statistical analysis

Statistical comparison was made by Dunnett's test. Results were expressed as mean ± S.E.

Results and discussion

Fig.1 to 6 depict the blood glucose profile at various time intervals post sucrose load in normoglycaemic rats treated with 250 mg/kg of the crude powders of *M. charantia* fruits, *A. marmelos* leaves, *T. foenum-graecum* seeds, *S. cumini* seeds, *C. longa* rhizome and *C. indica* leaves, respectively.

Table 1 depicts the average percent inhibition on the postprandial rise in hyperglycaemia in normoglycaemic rats by the crude powders of the various portions of these six edible plants.

The crude powder of the seeds of *S. cumini* showed maximum improvement i.e. 34.9 % followed by *C. longa* rhizome i.e. 16.5 %, *A. marmelos* leaves i.e. 15.6 %, *M. indica* fruits i.e. 13.0 %, *C. indica* leaves i.e. 12.4 % and *T. foenum-graecum* seeds i.e. 6.80 %. Fig. 7 A, B to 12 A, B shows the dose dependent inhibitory effect on the rise in postprandial hyperglycaemia in normoglycaemic rats. It is evident from the Fig. 7 A. B that crude powder of the fruits of *M.charantia* caused dose dependent inhibition on the post prandial rise in hyperglycaemia from 100 to 500 mg/kg dose. The lowest was being at 100 mg/kg whereas the highest inhibition was at 500 mg/kg dose. The dose dependent inhibition on postprandial rise in hyperglycaemia by *A. marmelos* leaves was little as at 50, 100, 200, 375 and 500 mg/kg dose the percent inhibition were 22.2, 27.5, 29.6, 30.7 and 33.0 %, respectively (Fig. 8 A, B).

The dose dependent inhibition on post prandial rise in hyperglycaemia by *T. foenum-graecum seeds* was found 9.78, 11.0, 14.1, 15.4 and 22.5 %, respectively at 50, 100,200, 375 and 500 mg/kg doses (Fig. 9 A, B.). The crude powder of the seeds of *S. cumini* showed around 24.2, 29.4, 32.4, 33.3 and 48.6 % inhibition on post prandial rise in hyperglycaemia in normoglycaemic rats at the tested doses i.e. at 50, 100, 200, 375 and 500 mg/kg, respectively (Fig. 10 A, B).

The crude powder of *C. longa* rhizome also showed dose dependent inhibition on the postprandial rise in hyperglycaemia in normal rats between 50 to 500 mg/kg doses where the percent inhibition was in between 6.76 to 12.3 % (Fig.11 A, B). The leaves of *C. indica* showed 8.02 to 24.1 % inhibition on postprandial rise in hyperglycaemia when the dose was scaled from 50 to 500 mg/kg (Fig. 12 A, B).

The antihyperglycaemic effects of the dried powders of these six edible vegetable plants in streptozotocin-induced diabetic rats were shown in the Table 1. The leaves of *C. indica* recorded maximum decline in blood glucose levels of streptozotocin-induced diabetic rats primed with sucrose orally. The percent antihyperglycaemic activity was calculated to be around 27.9 and 32.2 % from 5 and 24 h AUC graph, respectively (Fig. 13). Next in this model is the dried powder of *C. longa* rhizome where 11.6 and 15.6 % decline on blood glucose profile was observed in 5 and 24 h AUC graphs (Fig. 14).

The other four powders i.e. of *M. charantia* fruits, *A. marmelos* leaves, *T. foenum-graecum* seeds and *S. cumini* seeds though did not show much decline on the blood glucose profile of the streptozotocin-induced diabetic rats in the first five hours post administration but

Indian Journal of Science and Technology Vol.2 No 4 (Mar. 2009) ISSN: 0974- 6846

did cause appreciable antihyperglycaemic effect at 24 hours post treatment (Fig. 15-18).

The results of the present study indicate antihyperglycaemic activity of the plants studied and strongly support the earlier observations on these six edible vegetable plants. *M. charantia* or karela (Hindi) (Family: Cucurbitaceae) is a slender, climbing annual vine commonly known as 'Bitter gourd' (English) grows in India and other tropical countries. Several earlier and recent studies have indicated the hypoglycaemic activity of various parts of this plant (Karunanayake *et al*., 1990) *S. cumini*. Jamun (Hindi) and Black Berry (English) (Family: Myrtaceae) is widely distributed throughout India. Indian folk medicine mentions its use for the treatment of diabetes mellitus (Chopra *et al*., 1958; Nandkarni *et al*., 1992). Tea prepared from leaves of *S. cumini* (L) skeels (common name is jambolao in Brazil) has been reported to be used by diabetics in Porto Alegre, a southern city of Brazil. Preliminary studies on *S. cumini* seeds have shown hypoglycaemic effects (Mahapatra *et al*., 1985). Aqueous extract of *S. cumini* seeds showed hypoglycaemic and antioxidant activity (Prince *et al*., 1998). Treatment with lyophilized powder of *Eugenia jambolana* also partially restored altered hepatic and skeletal muscle glycogen content and hepatic glucokinase, hexokinase, glucose-6-phosphate and phosphofructokinase levels (Grover *et al*., 2000). *A. marmelos* or Bael or Sriphal (Hindi), wood apple/ holy fruit tree (English) (Family: Rutaceae) is medium sized, armed deciduous tree found wildly, especially in dry forests and is also cultivated throughout India. Oral administration of aqueous extract of *A. marmelos* roots bark showed hypoglycaemic effects in normal fasted rats (Karunanayake *et al*., 1984). Aqueous extract of the leaves significantly controlled blood glucose, urea, body weight, liver glycogen and serum cholesterol of Alloxan-induced diabetic rats as compared to control (Ponnachan *et al*., 1993). The extract was equi-effective in comparison to insulin in restoring blood glucose and body weight to normal levels (Seema *et al*., 1996). Aqueous leaf extract administered orally for 28 days also normalized STZ-induced histopathological alterations in the pancreatic and kidney tissues of rats (Das *et al*., 1996). *C. indica* or kanduri, kudroom (Hindi), and Kovai fruit (English) (Family: Cucurbitaceae) grows wildly in many part of the Indian sub continent and is well known as a hypoglycaemic herb. The hypoglycaemic activity of plant was reported by Khan *et al*. (1980). Hypoglycaemic activity of pectin, isolated from the fruit of *C. indica* was studied in normal rats at a dose of 200 mg/100 g/day upon oral administration and it showed significant reduction in blood glucose and an increase in the liver glycogen level (Kumar *et al*., 1993). Ethanolic leaf extract of *C. indica* (200 mg/kg for 45 days) also produced a modulatory effect on the aortic collagen content of STZ diabetic rats by reducing the accumulation and cross linking of collagen (Venkateswaran *et al*., 2002). The extract also exhibited significant antioxidant activity (Venkateswaran and Pari, 2003b) and hypolipidaemic activity (Pari and Venkateswaran, 2003) in streptozotocin induced diabetic rats. Seeds of *T. foenum-graecum* (Methi in Hindi) and Fenugreek (English) (Family: Fabaceae) are known to exhibit hypoglycaemic activity when taken orally (Shani *et al*., 1974). The hypoglycaemic effect of Trigonella seeds, and their major alkaloids, trigonilline was first described by Fournier (Fournier *et al*., 1948) and by Nadakaris (Nandakarni, 1954). The hypoglycaemic effect of

Effect of dried powder of plant on oral glucose tolerance of normoglycaemic rats

Fig. 1. M. charantia fruits

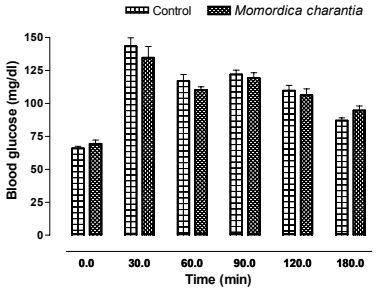


Fig. 2. A. marmelos leaves

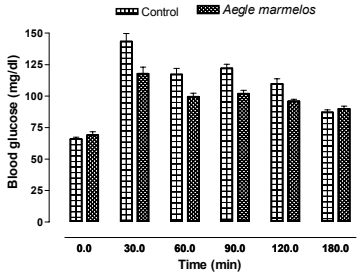


Fig.3. T. foenum-graecum seeds

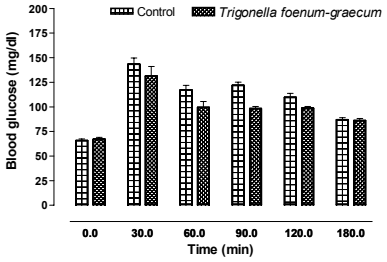


Fig. 4. S. cumini seeds

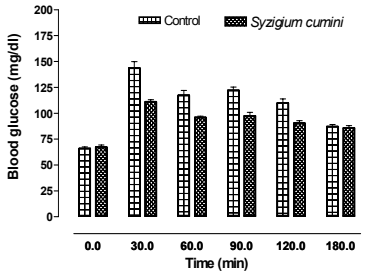


Fig. 5. C. longa rhizomes

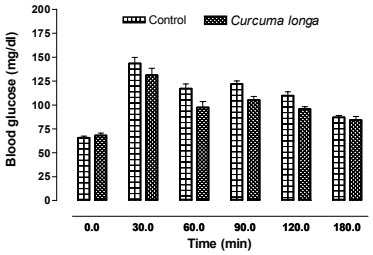
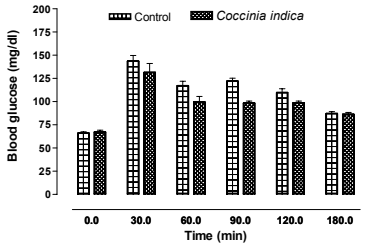


Fig. 6. C. indica leaves



Indian Journal of Science and Technology Vol.2 No 4 (Mar. 2009) ISSN: 0974- 6846

Dose dependent effect of dried plant powder on glucose tolerance of normoglycaemic rat

Fig. 7 A , B. fruits of M. charantia

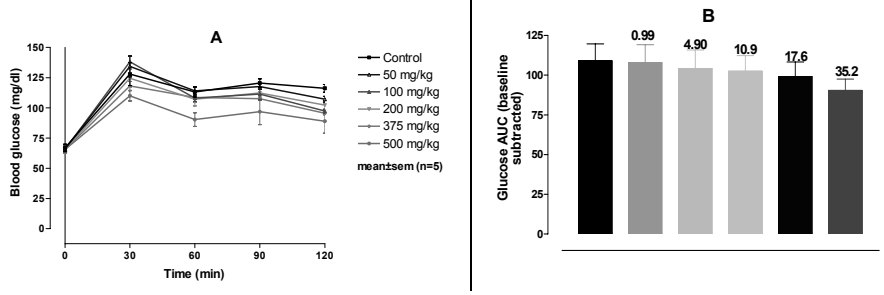


Fig. 8 A, B. Leaves of A. marmelos

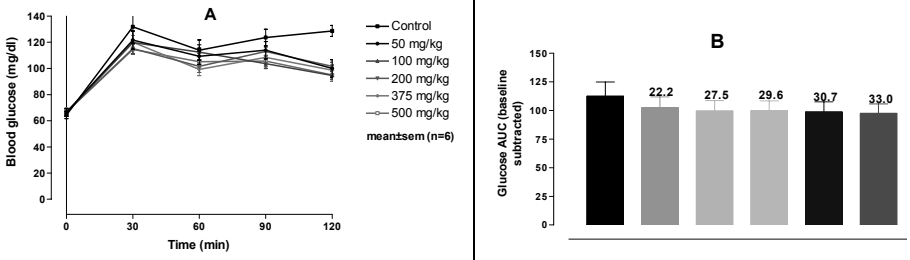
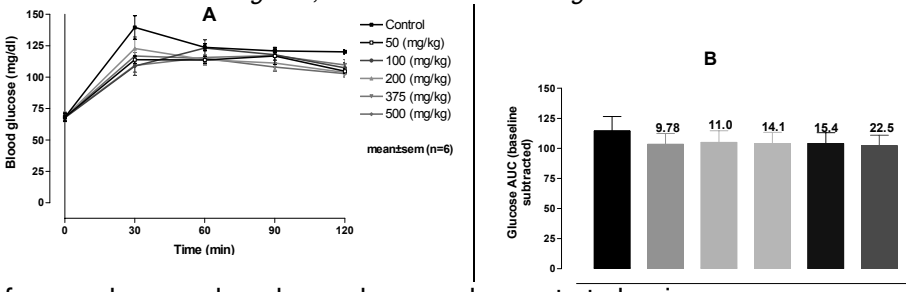


Fig. 9 A, B. Seeds of T. foenum-graecum



fenugreek seeds has been demonstrated in experimentally induced diabetic rats, dogs, mice and healthy volunteers (in both IDDM and NIDDM). The seeds are widely recommended for Non Insulin Dependent Diabetes mellitus patients (Clifford *et al*., 1989). The aqueous and alcoholic extracts of *T. foenum-graecum* leaves were tested for hypoglycaemic activity in normal and Alloxan induced diabetic rats. Graded amounts of the aqueous extracts *T. foenum-graecum* leaf when given to both normal and Alloxan diabetic rats; a significant reduction of blood level concentration was noticed (Jamal Ahmad Abdel-Barry *et al*., 1997). Turmeric (*C. longa* L.) is a medicinal plant extensively used in Ayurveda, Unani and Siddha medicine as home remedy for various diseases (Ammon *et al*., 1991, Eigner & Scholz, 1999). *C. longa* L., botanically related to ginger (Zingiberaceae family), is a perennial plant having a short stem with large oblong leaves and bears ovate, pyriform or oblong rhizomes, which are often branched and brownish-yellow in colour. Turmeric is used as a food additive (spice), preservative and colouring agent in Asian countries, including China and South East Asia. It is also considered as auspicious and is a part of religious rituals. In old Hindu medicine, it is extensively used for the treatment of sprains and swelling caused by injury. In recent times, traditional Indian medicine uses turmeric powder for the treatment of biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis. In China, *C. longa* is used for diseases associated with abdominal pains. The colouring principle of turmeric is the main component of this plant and is responsible for the anti-inflammatory property. Hypoglycaemic and hypolipidaemic effect of *C. longa* constituents has been demonstrated on blood glucose profile and antioxidant properties of STZ-induced diabetic rats (Halim Eshrat M. Ali Hussain, 2002). Curcumin prevents galactose-induced cataract formation at very low doses (Suryanarayana *et al*., 2003). Both turmeric and Curcumin decrease blood sugar level in Alloxan-induced diabetes in rat (Arun & Nalini, 2002). Curcumin also decreases advanced glycation end products induced complications in diabetes mellitus (Sajithlal *et al*., 1998).

In India, number of alternative medicine like Ayurvedic as well as Siddha preparations have attracted great interest in Type-II diabetes management. Several of the ayurvedic formulations are being used for treating diabetes by Ayurvedic practitioners. Diabecon (D-400) is one of such herbal formulation formulated as per ayurvedic principles. The main ingredients are *Eugenia jambolana, Tinospora cordifolia, Pterocarpus marsupium, Ficus glomerulata, Momordica charantia, Ocimum sanctum* and *Gymnema sylvestre* which are well known indigenous oral antidiabetic plants. D-400 treatment caused a significant reduction in blood sugar levels in Alloxan induced diabetes was observed, (Anturlikar *et al*., 1995) an oral glucose tolerance test (OGTT) showed a significant lowering of AUC in streptozotocin induced diabetes in rats (Mitra *et al*., 1996). Diakyur is another ayurvedic polyherbal formulation which contains crude powder of *Cassia javanica* and dried standardized aqueous extracts of *Cassia auriculata, Syzigium jambolana and Terminalia arjuna* (Joshi *et al*., 2007). At the dose of 1600 mg/kg, p.o Diakyur showed a hypoglycaemic effect at varying degree of significance ($p < 0.05$-0.001) in normal as well as alloxan induced diabetic rats and rabbits in comparison with respective control groups. Diakyur treatment in the glucose tolerance test showed the maximum effect at 180th min of glucose administration in both normal and Alloxan diabetic animals. The drug treated alloxan diabetic rats showed significant ($p <$

Indian Journal of Science and Technology Vol.2 No 4 (Mar. 2009) ISSN: 0974- 6846

0.001) reduction in plasma, erythrocyte membrane, liver and kidney lipid peroxide levels after 28 days treatment when compared to untreated alloxan

Dose dependent effect of dried plant powder on glucose tolerance of normoglycaemic rat

Fig. 10 A, B. Seeds of S. cumini

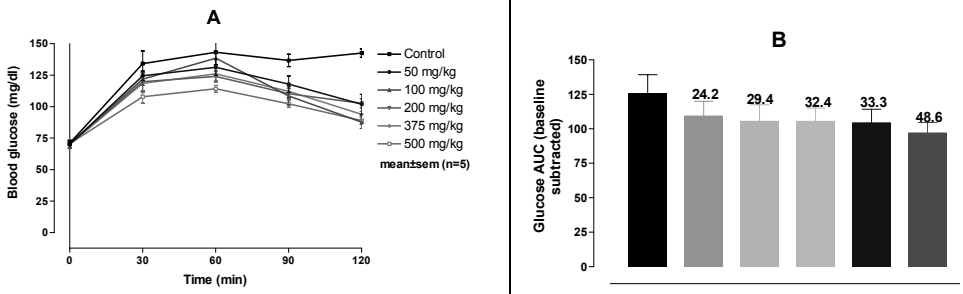


Fig. 11 A, B. Rhizomes of C. longa

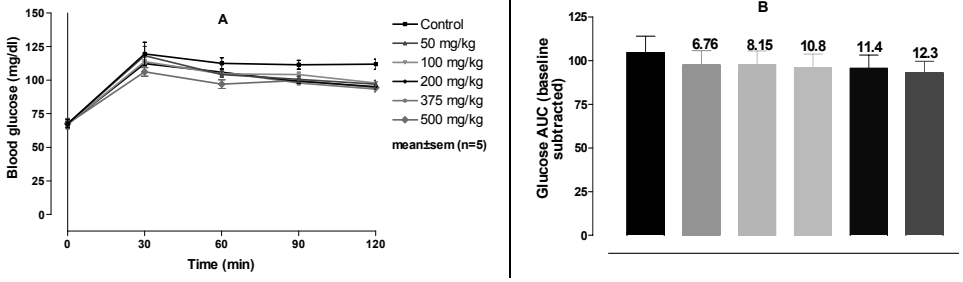
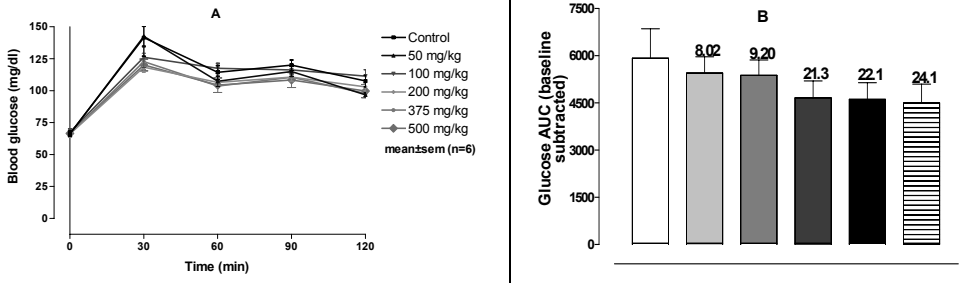


Fig. 12 A, B. Leaves of C. indica



diabetic rats. Dianex, a polyherbal formulation consisting of the aqueous extracts of *Gymnema sylvestre*, *Eugenia jambolana*, *Momordica charantia*, *Azadirachta indica*, *Cassia auriculata*, *Aegle marmelos*, Withania somnifera and *Curcuma longa*, produced significant ($p < 0.05$) hypoglycaemic activity at 250-500 mg/kg doses in both normal and diabetic mice in acute and long term studies. (Mutalik *et al*., 2005).

Further studies are being undertaken for preparing a suitable composition of the crude powders of the parts of these studied edible vegetables and evaluate its effectiveness in lowering blood glucose profile in the animal models of type-II diabetes mellitus.

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Indian Journal of Science and Technology Vol.2 No 4 (Mar. 2009) ISSN: 0974- 6846

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Effect of dried plant powder on blood glucose levels of streptozotocin-induced diabetic rats

Fig.13. M.charantia fruits

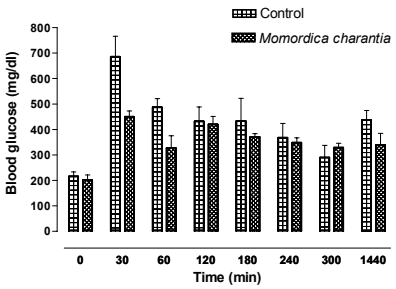

Fig. 14. A. marmelos leaves

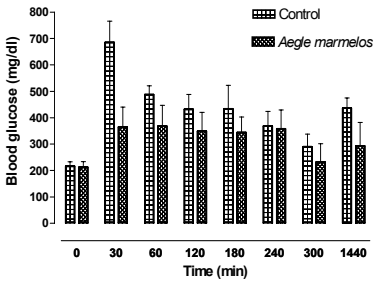

Fig.15. T. foenum-graecum seeds

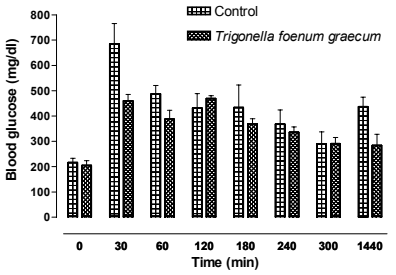

Fig. 16. S. cumini seeds

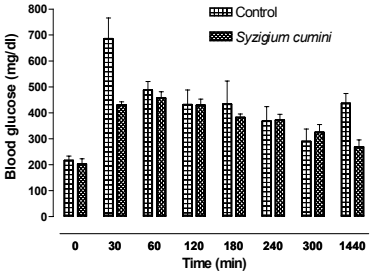

Fig. 17. C. longa roots & rhizomes

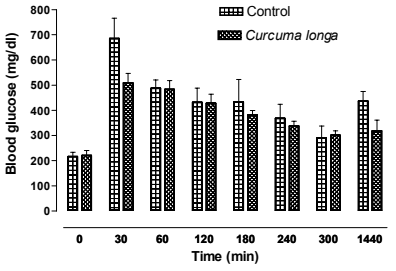

Fig.18. C. indica leaves

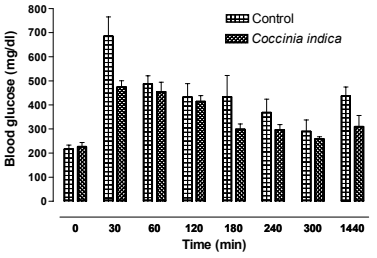

Table 1. Effect of dried powder of the six edible vegetable plants

Group	Test sample (Crude powder)	Dose (mg/kg)	on oral glucose tolerance in normoglycaemic rats (% Improvement on OGTT)	on blood glucose levels of streptozotocin-induced diabetic rats (% Antihyperglycaemic activity)	
				5h AUC	24h AUC
1	*M. charantia* fruits	250	13.0*	9.98	18.4
2	*A. marmelos* leaves	250	15.6	7.99	18.1
3	*T. foenum-graecum* seeds	250	6.80	5.96	23.6
4	*S. cumini* seeds	250	34.9*	3.31	22.3
5	*C. longa* rhizome	250	16.5*	11.6	15.8
6	*C. indica* leaves	250	12.4*	27.9	32.2

*(Significance *p < 0.05)*

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Indian Journal of Science and Technology Vol.2 No 4 (Mar. 2009) ISSN: 0974- 6846

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