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In-vitro screening of cucurbitaceous plants for antidiabetic potential

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Natural products traditionally have played an important role in drug discovery and formed the basis of most early medicines. Medicinal plants and drugs derived from them have been explored extensively for their antidiabetic potential. Extensive literature survey revealed that the family cucurbitaceae of higher plants has contributed a lot in traditional system of medicines for developing antidiabetic formulations. The most discussed *Momordica charantia* and *Cucumis sativus* are some examples. However, many cucurbitaceous taxa are yet to be explored. The objectives of the present study are to gather data from literature on the antidiabetic potential of cucurbitaceous plants with their traditional usage and *in-vitro* screening of different extracts and fractions of collected cucurbitaceous plants for their antidiabetic activity in the glucose utilization assay (GUA) on L6 cell line. Based on literature survey, a list of 32 plant species of cucurbitaceae family was prepared, which have been reported for antidiabetic activity or mentioned in ethnomedicinal and traditional system of medicines for antidiabetic potential. A total of 15 crude extract and their 75 fractions were prepared from 9 collected cucurbitaceous plants and their parts and screened against differentiated rat skeletal (L6) muscle cells in glucose uptake assay. Eight extracts/fractions from 4 plants (*Cucumis callosus* fruit, *Luffa echinata* fruit, *Coccinia indica* fruit and *Cucurbita* species aerial part) were found active in antidiabetic screening. The best antidiabetic activity was found in chloroform fraction of *Luffa echinata* fruit. After bioactivity guided column fractionation of this active fraction, the fraction M010/S/3/5 showed maximum activity in glucose uptake assay. EC_{50} was calculated as 0.59 µg/mL showed potent antidiabetic compound. Present study revealed that there is huge potential in cucurbitaceous plants for developing antidiabetic drug.

Keywords: Antidiabetic activity, Cucurbitaceous plants, Ethnomedicinal use, *In-vitro* screening

Abbreviations: Cpm-counts per minute, KDa-kilodalton, o/n-overnight, ppt-pellet, Sup.-supernatant

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Diabetes mellitus is a group of metabolic disorders in which the body does not produce enough or does not properly use insulin, resulting in hyperglycemia. Type I is the result of the body's failure to produce enough insulin while Type II diabetes is a result of insulin [illegible] generally diagnosed in adult. The International Diabetes Federation estimates that approximately 425 million adults around the world have diabetes. This total is expected to rise to 629 million by the year 2045. Insulin (Humulin, Novolin), Sulfonylureas, Alpha-glucosidase inhibitors, Biguanide class, Meglitinide class, Thiazolidinedione class, Dipeptidyl peptidase-4 inhibitors are the some of the antidiabetic drugs available in market for the treatment of Type II diabetes. Few of these drugs may cause hypoglycemia; patients may become resistant to these drugs, or develop gastrointestinal problems, and hepatotoxicity[2]. Naturally derived antidiabetic drugs such as metformin have the advantage that they do not cause significant side effects and show less toxicity, [illegible]ulfonylurea.

India is rich in plant resources and traditional ayurvedic knowledge. There is a vast potential for natural product based discovery and development of drug candidates with good therapeutic efficacy and low toxicity[3]. Medicinal and aromatic plants have been widely used for treatment of many diseases in a traditional way for several generations. Selection of higher plants as candidates for drug development is based on the information from traditional medicine (ethnomedicine)[4]. Plants and plant derived bioactive compounds have an advantage in this area based on their long-term use by humans, and low human

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toxicity. Chemical diversity of secondary plant metabolites that results from plant evolution may be equal or superior to that found in synthetic combinatorial chemical libraries[3].

A large number of plants used in the traditional medicine have now become a part of the modern world health care system. Natural products offer large structural diversity, and modern techniques for separation, structure elucidation, screening and combinatorial synthesis have led to revitalization of plant products as sources of new drugs[5]. As the Type II diabetes epidemic grows, so does the need for newer, better drugs. There are currently more than 30 diabetes drugs in nine classes in the market. Total 22 drugs were approved by FDA for diabetes during 1995-2008 but none of them is plant based drug[6]. Currently, plant based few compounds are in different stages of clinical trials for diabetes from *Hoodia gordonii*, *Artemisia dracunculus, Berberis aristata & Momordica charantia*[7].

The number of higher plant species is estimated at 250,000. Of these, only about 6% have been screened for biologic activity and a reported 15% have been evaluated phytochemically[4]. About 43,879 species of higher plants have already been reported for their ethnomedicinal, chemical & pharmacologic uses[8]. Most common drug for diabetes Metformin is of plant origin[4]. Berberine which is obtained from *Berberis aristata* has been shown to have antidiabetic properties, although its mode of action is not known. Metabolic effects of berberine have been investigated in two animal models of insulin resistance and in insulin-responsive cell lines. Berberine reduced body weight and caused a significant improvement in glucose tolerance without altering food intake in *db/db* mice[9]. Cucurbitane glycosides, momordicosides Q, R, S, and T and karaviloside XI, were isolated from bitter melon (*Momordica charantia*) and exhibited beneficial effects to diabetes and obesity. Cucurbitane triterpenoids, the characteristic constituents of *M. charantia*, may provide leads as a class of therapeutics for diabetes and obesity[10]. According to a survey based on data from NAPRALERT (Natural Products Alert), about 1200 plants have been studied experimentally or used ethnopharmacologically to treat *diabetes mellitus.* Plant families most commonly represented for antidiabetic activity were Fabaceae, Asteraceae, Lamiaceae, Liliaceae, Poaceae & Euphorbiaceae[11]. The extensive literature survey revealed that the family Cucurbitaceous of higher plants has contributed a lot in traditional Indian system of medicines for developing antidiabetic formulations[12]. The *Momordica charantia*, popularly known as karela is one of the best examples. *M. charantia* was also used in traditional Indian and Chinese medicines to cure diabetes and antigluconeogenic activity of cucurbitacins from *M. charantia* has also been established[12,13]. *Citrullus colocynthis* (Cucurbitaceae) was also described for ethnomedicinal use in diabetes and now well known for antidiabetic effects after pharmacological studies[14].

Online literature search shows that there are at least 32 species of the family Cucurbitaceae that have been reported to possess antidiabetic potential (Table 1) and studied for their antidiabetic activity in pharmacological studies. Table 1 summarizes the details of cucurbitaceous plants evaluated for antidiabetic activity and their ethanomedicinal information. It was also found that alkaloid rich and bitter plants have a maximum possibility to show hypoglycemic effects. A large number of species belonging to family Cucurbitaceae are yet to be explored. Our objective was to screen unexplored plant species from Cucurbitaceae family with a view to identify the promising glucose uptake modulators. In the present study, *in-vitro* screening using glucose utilization bioassay in differentiated L6 myotubes was performed for evaluating antidiabetic activity in 9 species of family Cucurbitaceae.

Methodology

Plant collection and processing

The selection of plant species was carried out on the basis of literature available on ethnomedicinal, ayurvedic and other traditional systems of medicines, online search through various databases and phytochemical works and the patent search on the species of interest for their antidiabetic properties. About 20 selected species that qualified our criteria of selection for further evaluation were targeted for collection. However, depending on the distribution pattern and availability finally 9 taxa from family Cucurbitaceae were collected from the State of Maharashtra, India. A total of 15 plant parts weighing 3-4 kg of fresh material of each were collected from the forests of Thane and different localities in Mumbai and surrounding areas (Table 2). The plant parts were dried separately in shade using dehumidifier. Taxonomically identified voucher

Table 1 — Ethnomedicinal use of cucurbitaceous plants and their evaluation for antidiabetic activity

S. No.	Plant	Parts used	Extracts/ Active constituents	Activity	Ethnomedicinal use
1.	***Benincasa hispida***	Stem Fruit Stem	Chloroform extract Ethanol extract Aqueous extract	Hypoglycemic activity in normal male Wistar rats[28] Decrease in glucose, triglyceride and insulin levels in plasma on dexamethasone induced insulin resistance in mice[29] Significant reduction in the blood glucose levels in alloxan-induced diabetic rabbits[30]	Asthma, cough, hemorrhages, peptic ulcer, diabetes, epilepsy and nervous system disorder[16]; Respiratory disease, heart diseases, diabetes mellitus, urinary diseases and gastrointestinal problems[31]; Fruits are used as a laxative, diuretic, tonic, aphrodisiac, cardiotonic, urinary calculi, blood disease, insanity, epilepsy, schizophrenia and other psychologic disorders[31]; Main ingredient in kusmanda lehyam, in Ayurvedic system of medicine, dyspepsia, vermifuge, burning sensation, heart disease, and urinary disease[30].
2.	***Bryonia alba***	Root Root	Trihydroxyoctadec-adienoic acids Ethanol extract	Restores the disordered lipid metabolism of alloxan-diabetic rats[32] Hypoglycaemic activity in alloxan-induced diabetes in rats[33]	Constipation, stiffness of joints due to rheumatism, headache, bronchitis, pneumonia, measles, synovial inflammation and pneumonia[34].
3.	***Citrullus colocynthis***	Fruit Fruit Fruit Seed	Petroleum ether extract Ethanol extract Aqueous extract Aqueous extract	Reduction in blood glucose levels in streptozotocin induced diabetic rats[35] Decrease in the levels of total cholesterol, triglycerides, free fatty acids and phospholipids in serum and liver of treated diabetic rats[36] Decrease of blood glucose from 132 to 93 mg/100 mL after 24 h of normoglycaemic rabbits[37] Reduction in plasma level of AST (aspartate dehydrogenase) and LDH (lactic dehydrogenase) significantly in streptozotocin induced diabetic rats[38]	Asthma, bronchitis, ascites, ulcers, leucoderma, constipation, tumors and hypoglycemia, fruits are cooling, carminative, carthartic, antipyretic and anthelmintic[16]; Diabetes, constipation, asthma, bronchitis, leprosy, jaundice, joint pain, cancer, mastitis, indigestion, dysentery, gastroenteritis and colic pain , common cold, cough, toothache, wounds, hypertension, hepatoprotective, leaves for the treatment of jaundice and asthma[14]
4.	***Citrullus lanatus***	Seed	Globulins	Significant anti-hyperglycaemic activity in male Wistar rats by the oral glucose tolerance test[39]	Ripe fruits as cooling, strengthening, diuretic, stomachic, purifies the blood, aphrodisiac, astringent, biliousness, sore eyes, scabies and itching, fruit juice as an antiseptic in typhus fever and purgative, seeds are tonic to the brain[40].
5.	***Coccinia grandis***	Leaf Leaf	Aqueous extract Methanol extract	Antihyperglycemic effect in alloxan induced diabetic Wistar rats[41] Significant antihyperglycemic activity in Swiss albino mice on oral glucose tolerance tests[42]	Fresh root extract as antidiabetic[12]; Fruits in diabetes, aphrodisiac, biliousness and disease of the blood. Juice of whole plant is used in diabetes, anorexia, asthma, fever, dropsy, catarrh, epilepsy and gonorrhea, whole plant in diabetes mellitus. Fruit and leaves are prescribed in the treatment of snake-bite[40]

(*Contd.*)

Table 1 — Ethnomedicinal use of cucurbitaceous plants and their evaluation for antidiabetic activity (*Contd*.)

S. No.	Plant	Parts used	Extracts/ Active constituents	Activity	Ethnomedicinal use
6.	***Coccinia indica*** (Synonym: ***Coccinia grandis***, ***Coccinia cordifolia***)	Aerial parts Leaf Aerial parts	95% ethanolic extracts 60% Ethanolic extracts Ethanol extract Dried extract	Blood glucose lowering effect in alloxan diabetic albino rats[19] Decreased level of blood glucose and fatty acid in streptozotocin (SZT) induced diabetic rats[43] Antihyperglycemic effects in STZ induced diabetes in Sprague–Dawley rats[17] In a clinical study, restored the raised activity of lipoprotein lipase and the levels of G-6 phosphotase and LDH in diabetic patients[44]	Antidiabetic property, used for treating diabetes mellitus in Ayurveda[17]; Leaf extract and aerial parts have hypoglycemic and antihyperglycemic effect [17,45]; Ayurveda and Unani system of medicine for treatment of diabetes, skin eruptions, tongues sore, earache, etc[46]
7.	***Cucumis callosus***	Fruit	Ethanol extract	Antihyperglycemic effect in alloxan induced diabetic rat[47]	Prevent insanity, seeds are cooling and astringent and useful in bilious disorder[40]; *Cucumis callosus* is a wild relative of *Cucumis melo*[48].
8.	***Cucumis melo***	Leaf	Methanol and aqueous extract	Anti-hyperglycemic activity in streptozotocin induced hyperglycemia model[49]	Leaves are used in flatulence, fever, cough, anemia, jaundice, leprosy, diabetes, antiobesity, constipation, ascites, bronchitis and amentia; Fruit pulp is liver tonic, cardio tonic, appetizer, anthelmintic, thermogenic, expectorant and intellect promoting; Roots are used as emetic and purgative[49]; Seed powder for diabetes[50].
9.	***Cucumis metuliferous***	Fruit Fruit	Fruit pulp extract Glycoside fraction	Decrease in the blood glucose concentration in alloxan induced hyperglycemic rats[51] Significant dose-dependent reductions in blood glucose concentration in albino rats with alloxan-induced diabetes[52]	Roots are used to treat Appendicitis; Stomach ache[53].
10.	***Cucumis prophetarum***	Fruit Fruit	Aqueous extract N-Trisaccharide	Effective antidiabetic activity in α -amylase assay and α -glucosidase assay[54] Antihyperglycemic activity in streptozotocin(STZ)–nicotinamide (NA) induced type 2 diabetic rats[55]	Inflammatory-related problems[54].
11.	***Cucumis sativus***	Fruit peel Fruit Fruit	Ethanolic extract Aqueous extract Ethanolic extract	Antidiabetic activity in alloxan induced diabetes mellitus in male mice[20] Anti-hyperglycemic effect by subcutaneous glucose tolerance tests on 27 healthy rabbits[56] Hypoglycemic effects on alloxan induced diabetic rats[57]	Constipation, indigestion, seeds are tonic, anthelmintic and diuretic[16]; Skin problems, anti-diarrheal, detoxicant and anti-gonorrheal agents[18]; Fruit is direct used in demulcent. Fried seeds are used in cooling tonic, diuretic and anthelmintic. Leaves along with cumin seeds administrated in throat affections[40].
12.	***Cucumis trigonus***	Fruit	Aqueous extract	Beneficial effects in reducing the elevated blood glucose level and lipid profile of STZ-induced-diabetic rats[58]	Leprosy, fever, jaundice, diabetes, cough, bronchitis, anaemia, constipation and other abdominal disorders[58]; Fruit juice for treating diabetes[50].

(*Contd*.)

Table 1 — Ethnomedicinal use of cucurbitaceous plants and their evaluation for antidiabetic activity (*Contd*.)

S. No.	Plant	Parts used	Extracts/ Active constituents	Activity	Ethnomedicinal use
13.	***Cucurbita ficifolia***	Fruit Fruit	Aqueous extract Traditional preparations Methanol extract	Anti-hyperglycemic effect by subcutaneous glucose tolerance tests on 27 healthy rabbits[56] Hypoglycaemic effect similar to that of tolbutamide in healthy and mildly diabetic rabbits[59] Antihyperglycemic activity in streptozotocin-induced experimental diabetes in rats[60]	Hemorrhoids, fever and wound cure[16]
14.	***Cucurbita maxima***	Aerial parts Fruit powder	Methanol extract	Antidiabetic activity in Wistar albino rats against streptozotocin[61] Reduce blood glucose levels significantly in the 20 NIDDM diabetics patients[62]	Antitumor, antidiabetic, antihypertensive, antibacterial, anti-inflammatory and immunomodulatory effects[61]; Fruit is used in diuretic, tonic, inflammations and boils. Fried seeds are used in anthelmintic, diuretic and tonic[40].
15.	***Cucurbita moschata***	Seeds Stem	Globulins Crude extract	Significant anti-hyperglycaemic activity in male Wistar rats by the oral glucose tolerance test[39] Hypoglycaemic effect *in-vivo* in streptozotocin-induced diabetic mice[63]	Folk medicine for measles, jaundice, insomnia, colic, and treatment of amoebas[64]; Leaf paste is used in biliousness and burning sensation, fruit is cooling, astringent to the bowels, laxative, good for teeth, throat, eyes, seeds are diuretic, tonic, bronchitis, fever, good for the kidney and the brains[40].
16.	***Cucurbita pepo***	Fruit peel Fruit	Ethanolic extract Fruit powder	Antidiabetic activity in alloxan induced diabetes mellitus in male mice[20] Hypoglycaemic effects in alloxan-induced diabetic rats[65]	Astringent, blood purification, leprosy, sore chests, bronchitis, hemoptysis and fever[16]; Fruit is cooling, astringent to the bowels, laxative, and good for teeth, throat and eyes. Leaf paste is used in biliousness and burning sensation. Seeds are diuretic, tonic, bronchitis, fever, good for the kidney and brains[40].
17.	***Ibervillea sonorae***	Root Root	Traditional preparations (freeze-dried decoction) Aqueous extract	Significantly lowered the glycemia of mild alloxan-diabetic mice and rats, but did not in severe alloxan-diabetic rats[66] Antidiabetic properties by stimulating the glucose uptake in human preadipocytes by a PI3K-independant pathway[67]	Treatment of type 2 diabetes in México[67]; Roots are widely used as a topical antibiotic, cathartic, antirheumatic, and hypoglycaemic[68].
18.	***Lagenaria siceraria***	Fruit Aerial parts Fruit	Ethanol extract Methanol extract Methanol extract	Antihyperglycemic activity in induced in alloxan-induced diabetic rats [69] Antihyperglycemic activity on streptozotocin induced diabetes in rats[70] α-Glucosidase inhibitory activity[22]	Cardiotonic, general tonic and diuretic properties, diabetes mellitus[70]; General tonic in Ayurveda, cardiotonic[16]; Ulcers, pain, fever, asthma, bronchial disorders, fruit is traditionally used for its cardioprotective, cardiotonic, general tonic, aphrodisiac, purgative, diuretic properties[71].

(*Contd*.)

Table 1 — Ethnomedicinal use of cucurbitaceous plants and their evaluation for antidiabetic activity (*Contd*.)

S. No.	Plant	Parts used	Extracts/ Active constituents	Activity	Ethnomedicinal use
19.	***Luffa acutangula***	Fruit Fruit Fruit Fruit	Chloroform and Ethyl acetate extract Methanol extract Methanol and aqueous extract Ether, chloroform, ethanol and aqueous extracts	α-Glucosidase inhibitory activity[22] Increased mucosal glycoprotein and antioxidant enzyme level in gastric mucosa of streptozotocin (STZ) induced diabetic rats[24] Antidiabetic activity in STZ induced diabetic rats[72] Antidiabetic activity[73]	Jaundice, splenic enlargement and laxative[72]; Jaundice, insect bites, fruit powder for swollen hemorrhoids, seeds is used for dysentery while the juice of roasted young fruit is used to cure headache; diuretic properties, expectorant, laxative, and purgative; hypoglycemic agent, bitter tonic; used in the enlargement of spleen. Roots for kidney stones, swelling of the lymph glands. Leaves are useful in dysentery, inflammation of spleen, ringworms, piles and leprosy[74]
20.	***Luffa aegyptica*** Syn: ***Luffa cylindrica***	Leaf Seeds	Aqueous and Ethanol extract Ethanol extract	Significant antidiabetic activity in alloxan induced diabetic rats[75] Decreased blood glucose level with a potency similar to that of the biguanide, metformin in STZ diabetic rats[76]	Leaf juice cures conjunctivitis[77]; Fruit in jaundice[78].
21.	***Luffa tuberosa***	Fruit	Aqueous extract	Antidiabetic property in streptozotocin (STZ) induced diabetic rats[79]	Used for the treatment of diabetes mellitus[79]; Abortifacient[80]
22.	***Momordica balsamina***	Seeds Fruit Various plant parts	Aqueous extract Fruit pulp powder and aqueous methanolic extract (90%) Aqueous and Organic extract	Significant antihyperglycemic potential in STZ-induced diabetes models in rats[81] Antidiabetic activity in streptozotocin (STZ) induced diabetic Wistar rats[82] Antidiabetic activity in *in vitro* studies using glucose utilisation method[1]	Snake bite[83]; Purgative, vermifuge and fruit is used in diabetes[82].
23.	***Momordica charantia***	Fruit Fruit Fruit Seed Fruit juice	95% ethanolic extracts Ethanolic extract, 21 cucurbitane compounds Ethyl acetate extract Acetone extract ----	Blood glucose lowering activity in alloxan diabetic albino rats[19] Compounds 1, 10, 11, and 12 (at 25–100 μM) showed concentration-dependent inhibition on glucose production from liver cells; compounds 11 and 12 (at 100 μM) showed around 20–30% inhibition on PEPCK activity[13] α-Glucosidase inhibitory activity[22] Antilipolytic activity in isolated rat adipocytes[84] In a clinical study, administration of 100 mL of fruit juice improved glucose tolerance in 73% of test subjects following an oral glucose tolerance test[85]	Anthelmintic, carminative, purgative, antiemetic, anaemia, jaundice, cholera, malaria and unripe fruit for diabetes[16]; Fruit extract as antidiabetic[12]; Stem and root are used to treat toothaches, diarrhea, furuncle, and diabetes. Fruit is used to cure diarrhea, furuncle, heat stroke, and diabetes and seeds are used to remedy asynodia[13]

(*Contd*.)

Table 1 — Ethnomedicinal use of cucurbitaceous plants and their evaluation for antidiabetic activity (*Contd*.)

S. No.	Plant	Parts used	Extracts/ Active constituents	Activity	Ethnomedicinal use
24.	***Momordica cymbalaria***	Fruit powder Fruit	Aqueous extract	Significant blood glucose lowering effect in alloxan-induced diabetic rats and reduced the level of cholesterol and triglycerides in diabetic rats[86] Significant antihyperglycemic as well as antihyperlipidemic effects in the alloxan-induced diabetic rats[87]	Fruits for gastric ulcer, roots have been used by the natives of north Karnataka and Andhra Pradesh to treat gynecological ailments and also to induce abortions[88]
25.	***Momordica dioica***	Fruit Fruit Fruit	Ethyl acetate and alcoholic extracts Aqueous extract Aqueous, hexane, chloroform, and ethanol extract	Antidiabetic activity in alloxan induced diabetic rats[89] Oral hypoglycemic effect in rat model[90] Fall in fasting blood glucose in glucose tolerance test in normal healthy rats[91]	Antiseptic, anthelmintic, astringent, febrifuge and spermicidal[92]; Fresh fruit juice is prescribed for hypertension and fruit cooked in oil is used for treating diabetes[92, 93]; Fruits have diuretic, laxative, hepatoprotective, antivenomous, antihypertensive, anti-inflammatory, antiasthmatic, antipyretic, antileprosy, antidiabetic, and antidepressant properties. Leaves have antihelminthic, aphrodisiac, antihemorroidal, hepatoprotective, antibronchitic, antipyretic, antiasthmatic, and analgesic properties[93]
26.	***Momordica foetida***	Various plant parts	Aqueous and Organic Extracts Foetidin	Antidiabetic activity in *in vitro* studies using glucose utilisation method[1] Lowered blood glucose levels in normal but not in diabetic rats[94]	Diabetes, piles, haemorrhoid, gastroenteritis, snake bites, pregnancy, small pox, stomach ache, dropsy, fever, ear ache, anthelmintic, tumours[95]
27.	***Mukia madaraspatana*** (Synonym: ***Melothria Maderaspatana***)	Entire plant Stem Roots Aerial parts	Ethanol extract Ethanol and aqueous extracts Methanol extract Ethanol extract	Blood glucose level decreased in alloxan induced male Wistar albino rats[96] Hypoglycemic activity by increase in glucose uptake in L-6 skeletal muscle cells in vitro[97] Normal blood glucose was achieved in alloxan induced diabetic rats[98] Antihyperglycemic effects in STZ induced diabetes in Sprague–Dawley rats[17]	Diuretic, antipyretic, stomachic gentle aperients and antiflatulent, antiasthmatic, anti-inflammatory, antidiabetic and antibronchitis, tooth-ache, vertigo and biliousness[99, 100]. Inflammatory diseases[101]; Seeds, roots and leaf juice were used to treat diabetes[102]
28.	***Praecitrullus fistulosus***	Fruit peel	Ethanol extract	Antidiabetic activity in alloxan induced diabetes mellitus in male mice[20]	Leaves are used in blood pressure[103]
29.	***Sechium edule***	Fruit	Ethyl acetate extract	α-Glucosidase inhibitory activity[22]	Kidneys, circulatory systems and inflammatory diseases[16].
30.	***Telfairia occidentalis***	Seed Leaf Seed	Ethanol extract Ethanol extract Globulins	Hypoglycemic effects in alloxan diabetic rats[104] Significant reduction in blood glucose level in alloxan-induced diabetic rats[105] Anti-hyperglycaemic activity in male Wistar rats by the oral glucose tolerance test[39]	Cholesterolemia, liver problems and impaired immune system[105]

(*Contd*.)

Table 1 — Ethnomedicinal use of cucurbitaceous plants and their evaluation for antidiabetic activity (*Contd*.)

S. No.	Plant	Parts used	Extracts/ Active constituents	Activity	Ethnomedicinal use
31.	***Trichosanthes cucumerina***	Seeds Whole plant Aerial parts Fruit	95% Ethanolic extracts; Aqueous extract; Hot water extract Ethyl acetate extract	Blood glucose lowering activity in alloxan diabetic albino rats[19] Improved glucose tolerance and tissue glycogen in non insulin dependent diabetes mellitus induced rats[106] Improvement in glucose tolerance and increase in liver glycogen and adipose tissue triglyceride levels in normal and streptozotocin–induced diabetic rats[107] α-Glucosidase inhibitory activity[22]	Hepatoprotective, antidiabetic, cytotoxic, anti inflammatory and larvicidal effects[108]; stem decoction, aerial parts and leaves were used in the treatment of diabetes and inflammatory diseases[106]; Anthelmintic, bronchitis, cathartic, headache and boils, seeds are antifebrile, anthelmintic and useful for stomach disorder[16]
32.	***Trichosanthes dioica***	Leaf Leaf	Aqueous extract Aqueous extract	Reduced blood glucose significantly in streptozotocin induced hyperglycemic rats[109] Hypoglycemic effects in streptozotocin (STZ)-induced sub- and mild-diabetic rats[110]	Epilepsy, alopecia, skin disease and diabetes mellitus[109]; Fresh fruit juice is used as cooling and laxative. Fruit is also used in spermatorrhoea. Leaves are aperients, tonic and febrifuge; used in the cases of enlarge liver and spleen. Fruit is febrifuge, laxative, antibilious[40]

Table 2 — Extraction of collected cucurbitaceous plants and their extracted yield

S. No.	Plant Name	Plant Part	Dry weight (g)	Extracts	Extract Yield (g)
1.	*Trichoanthes cucumerina*	Aerial	250	M001/A	10.940
2.	*Mukia maderaspatana*	Aerial	50	M002/A	3.794
3.	*Momordica dioica*	Aerial	150	M003/A	8.984
4.	*Trichoanthes cucumerina*	fruits	100	M004/A	17.027
5.	*Benincasa hispida*	Aerial	250	M005/A	9.641
6.	*Cucumis callous*	Aerial	115	M006/A	4.411
7.	*Cucumis callous*	fruits	20	M007/A	2.871
8.	*Lagenaria siceraria*	Aerial	250	M008/A	11.433
9.	*Luffa echinata*	Aerial	300	M009/A	4.541
10.	*Luffa echinata*	fruits	60	M010/A	9.100
11.	*Coccinia indica*	Aerial	345	M011/A	15.686
12.	*Coccinia indica*	fruits	25	M012/A	2.294
13.	*Cucurbita sp.*	Aerial	235	M013/A	9.376
14.	*Cucurbita sp.*	fruits	25	M014/A	2.499
15.	*Trichoanthes cucumerina*	(whole plant)	100	M015/A	28.155

specimens were deposited in the herbarium of Natural Products Botany Department, Piramal Life Sciences Ltd, Mumbai.

Extraction and fractionation

Dried plant materials were pulverized to a course powder. The pulverized material was taken for extraction. The dried coarse powder (100 g) was soaked in 1 L DCM (dichloro methane): MeOH (Methanol) (1:1) in a flask for 8 h at room temprature. The extract is filtered with Whatman filter paper and the filtrate-1 was collected. The same extraction procedure was repeated one more time with remaining residue and filtrate-2 was collected. The filtrate-1 & filtrate-2 were pooled and the organic crude extracts (A) were concentrated by using rotary vacuum evaporator (BUCHI, Switzerland) at 40^0C & further dried in speed vac (Savant, Germany) at an ambient temperature for overnight. The plant marc was re-extracted sequentially with water and was frozen dried (H). All the dried extracts were stored at room temprature. (22–24^0C). The crude DCM: MeOH extract (A) (1 g) was dissolved in 25 mL of water: methanol (9:1). The sequential fractionation was

performed in separatory funnel using different organic solvents viz. petroleum ether (B), chloroform (S) and ethyl acetate (C) (4 X 25 mL) with a view to separate the range of highly polar to non-polar compounds. Solvent fractions were concentrated by using rotary vacuum evaporator at 40^0C and aqueous alcoholic fraction (D) was lyophilized using Freeze dryer (Edwards, Germany). All the crude extracts (A) and their fractions (B, S, C, D & H) were dissolved in DMSO (dimethyl sulfoxide) (20 mg/mL) and taken for screening for antidiabetic activity in glucose utilization assay (GUA). All the organic solvents used for extraction and fractionation were of analytical grade and supplied by Merck, Mumbai.

Cell culture and glucose uptake assay

L6, rat skeletal muscle (myoblast) cells were obtained from ATCC (American type culture collection) and used for screening of antidiabetic compounds in GUA. L6 cells are adherent in property and fuse in culture to form multinucleated myotubes and striated fibres. Growth medium used for L6 cell line was MEM-α (minimum essential medium α modification) (HyClone), with 10% FBS (fetal bovine serum). Trypsin- EDTA treatment was performed to disrupt the cell monolayers at confluency. Cells were incubated with layer of Trypsin-EDTA at 37^0C for 30 s and resuspended in 10 mL of fresh growth media. Number of cells were counted using haemocytometer and quantity of cells were calculated to add to new T-175 flask (Nunc, Denmark) or 24 well culture plates (Nunc, Denmark). Cultures were incubated at 37°C in 5% CO_2 environment.

L6 cells were seeded into 24 well culture plates at the density of 25 x 10^4 cells /well in MEM-α with 10% serum & 0.7% antibiotic (penicillin-streptomycin), and were cultured for 48 h in 5% CO_2 at 37^0C. For differentiation, L6 myoblasts were cultured in MEM-α containing 2% FBS for 4 days to promote the fusion into myotubes and about 80-90% of the myoblasts were fused into myotubes[15]. Differentiated myotubes were serum starved for 4 h and then incubated with the plant extracts and fractions for overnight. Sample treatment was done by adding 2.5 µL of extracts and fractions or rosiglitazone (positive control) to the medium in the respective wells. After 18 h of plant extract treatment, 200 nM insulin was added after aspiration of media from plates and incubated for 25 min at 37^0C. Then 22 µL per well radioactive glucose solution (2-Deoxy-D-[1-^{14}C] Glucose from Amersham, UK) was added. Mixed the content by gentle tapping from the sides and incubated for 15 min at 37^0C. Thereafter, wells were washed twice with cold KRPH (Krebs-Ringer Phosphate Hepes) buffer after aspiration of the solution from the well. Then 0.1% SDS was added in each well and allowed 15 min for lysis. Each well was scrapped & transferred in scintillation vial with scintillation fluid and scintillation counting was performed. Cpm was measured using Packard Tri-Carb Liquid Scintillation Counter. The compounds that promoted the glucose consumption more than 2-fold relative to 200 nM insulin were considered as active compounds.

Bioactivity guided fractionation

HPTLC (high performance thin layer chromatography) analysis was performed for active extracts to optimize the best solvent system for chromatographic separation on TLC Silica gel 60 F_{254} plates (Merck, Germany). 10% Methanol in chloroform, 5% methanol in chloroform and 20% ethyl acetate in petroleum ether solvent systems were used for better resolution of compounds. Resolved components were visualized under UV light and also on exposure to vanillin sulphuric acid spray reagent. Column chromatography was employed for the purification of active solvent fraction of plant crude extract. Combi Flash Sq 16 X (Isco) with RediSep 12 g Flash column was used for chromatography. Extract was dissolved in MeOH & $CHCl_3$ and adsorbed with equal amount of silica gel with 200-400 mesh size. Dried it on rotavapor and loaded in column of combi flash. Elution was performed with the concomitant increase in concentration of methanol and all the eluted fractions were subjected to TLC (Thin Layer Chromatography) analysis. Bioassay guided fractionation was performed for assessing the antidiabetic activity of each fraction and then next round of separation was done for each active fraction. A fractionation process was performed several times and many sub-fractions were obtained. GUA was performed for each sub fraction eluted and grouped according to their chemical profiles analyzed by TLC.

Statistical analysis

Data collection, tabulation and initial analysis were performed by using Microsoft Excel 2007 and GraphPad Prism 4.0 was utilized for analysis of results, graph preparations and calculation of $EC_{50.}$

Results

Plant extracts and fractions

The 15 plant parts from 9 plant species of family Cucurbitaceae produced a total of 15 crude extracts (Table 2) and 75 fractions using different organic solvents (Table 3). Extraction from *Trichosanthes cucumerina* whole plant produced maximum crude extract yield of about 28.15 g from 100 g of plant material while minimum crude extract yield was obtained from *Luffa echinata* aerial part of about 4.54 g from 300 g of plant material. One gram crude extract of each plant sample was taken for fractionation and the yield of each fraction along with solvent used is listed in Table 3. All the crude extracts and their fractions (total 90 samples)

Table 3 — Fractionation of plant extracts and yield

S. No.	Fractions	Solvent used	Yield (mg)
1	M001/B	Petroleum ether	253
2	M001/S	Chloroform	208
3	M001/C	Ethyl acetate	52
4	M001/D	Aqueous alcoholic	354
5	M001/H	DCM-MeOH sequential water	653
6	M002/B	Petroleum ether	207
7	M002/S	Chloroform	195
8	M002/C	Ethyl acetate	61
9	M002/D	Aqueous alcoholic	249
10	M002/H	DCM-MeOH sequential water	3436
11	M003/B	Petroleum ether	110
12	M003/S	Chloroform	126
13	M003/C	Ethyl acetate	150
14	M003/D	Aqueous alcoholic	395
15	M003/H	DCM-MeOH sequential water	3416
16	M004/B	Petroleum ether	673
17	M004/S	Chloroform	73
18	M004/C	Ethyl acetate	39
19	M004/D	Aqueous alcoholic	5
20	M004/H	DCM-MeOH sequential water	11591
21	M005/B	Petroleum ether	269
22	M005/S	Chloroform	125
23	M005/C	Ethyl acetate	56
24	M005/D	Aqueous alcoholic	213
25	M005/H	DCM-MeOH sequential water	3240
26	M006/B	Petroleum ether	266
27	M006/S	Chloroform	88
28	M006/C	Ethyl acetate	72
29	M006/D	Aqueous alcoholic	14
30	M006/H	DCM-MeOH sequential water	4086
31	M007/B	Petroleum ether	183
32	M007/S	Chloroform	231
33	M007/C	Ethyl acetate	35
34	M007/D	Aqueous alcoholic	403
35	M007/H	DCM-MeOH sequential water	2535
36	M008/B	Petroleum ether	188

(*Contd.*)

Table 3 — Fractionation of plant extracts and yield (*Contd.*)

S. No.	Fractions	Solvent used	Yield (mg)
37	M008/S	Chloroform	86
38	M008/C	Ethyl acetate	62
39	M008/D	Aqueous alcoholic	346
40	M008/H	DCM-MeOH sequential water	2485
41	M009/B	Petroleum ether	157
42	M009/S	Chloroform	54
43	M009/C	Ethyl acetate	49
44	M009/D	Aqueous alcoholic	220
45	M009/H	DCM-MeOH sequential water	4024
46	M010/B	Petroleum ether	77
47	M010/S	Chloroform	219
48	M010/C	Ethyl acetate	248
49	M010/D	Aqueous alcoholic	225
50	M010/H	DCM-MeOH sequential water	4503
51	M011/B	Petroleum ether	453
52	M011/S	Chloroform	59
53	M011/C	Ethyl acetate	38
54	M011/D	Aqueous alcoholic	446
55	M011/H	DCM-MeOH sequential water	3738
56	M012/B	Petroleum ether	191
57	M012/S	Chloroform	4
58	M012/C	Ethyl acetate	15
59	M012/D	Aqueous alcoholic	21
60	M012/H	DCM-MeOH sequential water	2502
61	M013/B	Petroleum ether	289
62	M013/S	Chloroform	60
63	M013/C	Ethyl acetate	67
64	M013/D	Aqueous alcoholic	312
65	M013/H	DCM-MeOH sequential water	3939
66	M014/B	Petroleum ether	217
67	M014/S	Chloroform	83
68	M014/C	Ethyl acetate	48
69	M014/D	Aqueous alcoholic	16
70	M014/H	DCM-MeOH sequential water	3328
71	M015/B	Petroleum ether	406
72	M015/S	Chloroform	35
73	M015/C	Ethyl acetate	35
74	M015/D	Aqueous alcoholic	182
75	M015/H	DCM-MeOH sequential water	3716

were taken for primary screening in GUA for antidiabetic activity.

***In-vitro* screening**

All the 90 plant extracts and their fractions were evaluated with GUA in differentiated L6 myotubes for antidiabetic activity. Samples were dissolved in DMSO at the concentration of 20 mg/mL before primary screening. Out of 90 extracts screened, 8 extracts from 4 plant species i.e., *Cucumis callosus* fruit, *Luffa echinata* fruit, *Coccinia indica* fruit and *Cucurbita* species aerial part were found active in primary screening in glucose uptake assay for antidiabetic activity (Fig. 1). All 8 active extracts in preliminary screening (M007/S, M010/A, M010/S, M010/C, M012/A, M012/S, M012/C & M013/S) were taken for repeat screening or secondary screening in dose dependent manner at concentrations 30, 10, 3 and 1 µg/mL. All of these 8 extracts from 4 plant species showed antidiabetic activity at 30 and 10 µg/mL conc and 3 extracts (M010/A, M010/S & M012/C) from 2 plant species were found active at 3 µg/mL conc (Fig. 2). These screening results indicate that chloroform fraction of *Cucumis callosus* fruit (M007/S), chloroform and ethyl acetate fraction of *Luffa echinata* fruit (M010/S & M010/C), chloroform and ethyl acetate fraction of *Coccinia indica* fruit (M012/S & M012/C) and chloroform fraction of *Cucurbita* sp. aerial part (M013/S) exhibited activity in GUA. Almost all the fractions of *Luffa echinata* fruit extract (M010) demonstrated higher antidiabetic activity in GUA.

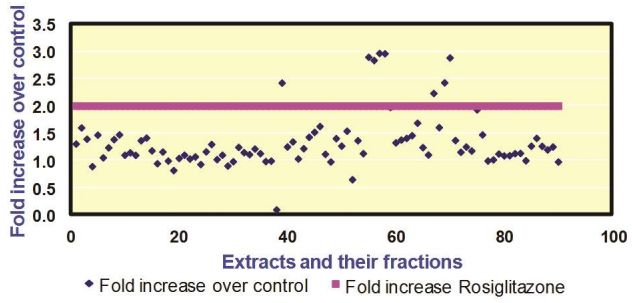

Fig. 1 — Active plant extracts and their fractions in primary antidiabetic screening in glucose uptake assay (GUA)

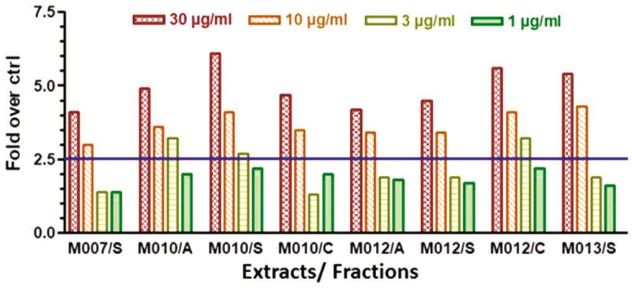

Fig. 2 — Dose dependent repeat analysis of extracts and fractions active in primary screening in GUA

Antidiabetic activity after bioassay guided fractionation

Sequential fractionation was performed with different solvents and analyzed for antidiabetic activity at each step. The most active chloroform fraction of *Luffa echinata* fruit extract (M010/S) was taken for column fractionation and flash chromatography was carried out using combi flash Sq 16x. Total 7 pooled fractions (M010/S/1, M010/S/2, M010/S/3, M010/S/4, M010/S/5, M010/S/6 & M010/S/7) after chromatography were screened again for antidiabetic activity and fractions 3 (M010/S/3) & 4 (M010/S/4) were shown activity at 10 & 1 µg/mL conc in GUA (Fig. 3). Both the fractions (M010/S/3 & M010/S/4) exhibited significant increase in bioactivity at 10 µg/mL conc. Most active sub-fraction M010/S/3 was taken for fractionation again using flash chromatography to get pure compound. Collected 39 tubes were pooled into 5 fractions (M010/S/3/1, M010/S/3/2, M010/S/3/3, M010/S/3/4 & M010/S/3/5) after TLC analysis. Of these 5 fractions, fraction 5 (M010/S/3/5) has shown maximum antidiabetic activity in GUA at 10 and 1 µg/mL conc (Table 4). Bioassay guided column fractionation of active extract lead to the purification and isolation of fraction 4 (M010/S/3/4) & fraction 5 (M010/S/3/5). Fraction 5 (M010/S/3/5) showed maximum glucose uptake in GUA and was comparable with insulin and rosiglita zone.

EC_{50} of most active fraction M010/S/3/5

Most active fraction M010/S/3/5 was taken again for measuring activity in GUA at 8-point dilutions for

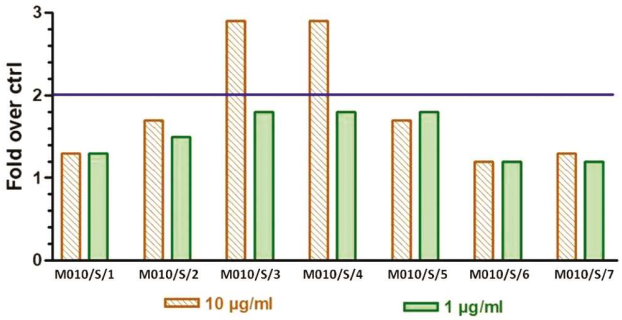

Fig. 3 — Antidiabetic activity in GUA after CombiFlash fractionation of most active extract M010/S (chloroform fraction of *Luffa echinata* fruit)

Table 4 — Fractionation and antidiabetic activity of most active fraction 3 of M010/S (chloroform fraction of *Luffa echinata* fruit)

S. No.	Fractions	Solvent Used	Conc (µg/ml)	Fold increase over ctrl	Rosiglitazone, fold increase at 30 µM	Antidiabetic Activity
1	M010/S/3/1	CombiFlash Fr. CHCl3:MeOH	10	1.4	2.1	Not active
		CombiFlash Fr. CHCl3:MeOH	1	1.1	2.1	Not active
2	M010/S/3/2	CombiFlash Fr. CHCl3:MeOH	10	3.4	2.1	Active
		CombiFlash Fr. CHCl3:MeOH	1	2.7	2.1	Active
3	M010/S/3/3	CombiFlash Fr. CHCl3:MeOH	10	3	2.1	Active
		CombiFlash Fr. CHCl3:MeOH	1	2.5	2.1	Active
4	M010/S/3/4	CombiFlash Fr. CHCl3:MeOH	10	2.7	2.1	Active
		CombiFlash Fr. CHCl3:MeOH	1	2.8	2.1	Active
5	**M010/S/3/5**	CombiFlash Fr. CHCl3:MeOH	10	**3.4**	2.1	Active
		CombiFlash Fr. CHCl3:MeOH	1	**2.8**	2.1	Active
	Insulin ctrl				1.3	

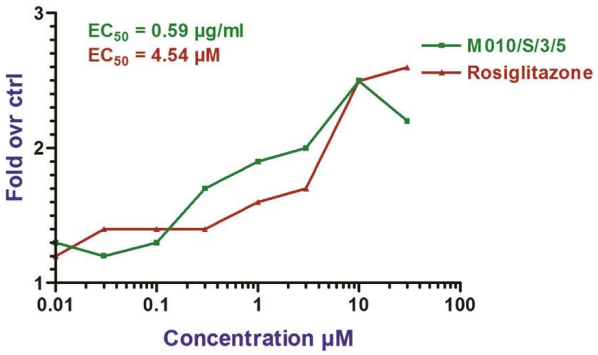

Fig. 4 — EC_{50} of the most active fraction M010/S/3/5 of *Luffa echinata* fruit

calculating EC_{50}. Fraction M010/S/3/5 has shown higher antidiabetic activity at 10, 3, 1 & 0.3 µg/mL conc on comparison to rosiglitazone (Fig. 4). Purified fraction 5 (M010/S/3/5) demonstrated significantly increased antidiabetic activity in GUA on comparison to positive control rosiglitazone. EC_{50} was calculated for the most active fraction M010/S/3/5 and found to be as 0.59 µg/mL (Fig. 4). EC_{50} value has shown that the fraction M010/S/3/5 could become more potent antidiabetic compound than the rosiglitazone. Purified and most active fraction M010/S/3/5 (chloroform fraction of *Luffa echinata* fruit extract) could be further purified and isolated using HPLC (High Performance Liquid Chromatography) and taken for structure elucidation using NMR (Nuclear Magnetic Resonance Spectroscopy) and MS (Mass Spectroscopy).

Discussion and Conclusion

The family cucurbitaceae of higher plants have about 130 genera and about 800 species and contains many plants which have medicinal importance. Dhiman et al., 2012 reviewed extensively about medicinal value of the family cucurbitaceae for their use in traditional medicine and pharmacological studies. *Momordica charantia*, *Cucurbita ficifolia*, *Citrullus colocynthis*, *Lagenaria siceraria*, *Benincasa hispida* and *Trichosanthes cucumerina* plants from family Cucurbitaceae have been mentioned for the treatment for diabetes in his review[16]. Apart from this many other literature and some patents are available for antidiabetic activity of Cucurbitaceous plants. A comprehensive list of 32 plant species of Cucurbitaceae family has been tabulated based on ethnomedicinal use and their evaluation for antidiabetic activity (Table 1). *Cucumis sativus*, *Coccinia indica* and *Momordica charantia* are some of the plants from cucurbitaceae family are mentioned extensively in Ayurvedic system of medicine for their antidiabetic properties and also reported in many other literatures including Pub Med and USPTO. Medicinal plants have been used extensively by native population for cure of various diseases and formed the principal constituent for Indian traditional medicine system. Herbal formulations of *Momordica charantia* and *Coccinia grandis* were used by tribal people of Sikkim and Darjeeling Himalayas for treating diabetes[12]. A wide range of plant- derived compounds have been demonstrated for their possible use in the treatment of Type II diabetes.

There are immense examples of cucurbitaceous plants known for their antidiabetic properties and used in traditional medicinal system in many countries. Present study also emphasized the importance of cucurbitaeous plants for the treatment of Type II diabetes. *Cucumis callosus* fruit, *Luffa echinata* fruit, *Coccinia indica* fruit and *Cucurbita species* aerial part

were found beneficial for antihyperglycemic activity in *in-vitro* studies on L6 myotubes in GUA. First time we are reporting about antidiabetic activity of chloroform fractions of *Luffa echinata* and *Cucumis callosus* fruit in *in-vitro* studies. *Coccinia indica*[17] and *Cucumis sativus*[18] have been accounted earlier by many researchers for their antihyperglycemic activity and our results also showed that the fruit of *Coccinia indica* and *Cucumis callosus* have antidiabetic activity in GUA. Hypoglycemic effects of *Coccinia indica* in alloxan diabetic albino rats have also been reported[19]. Some herbal formulations are also available for Type II diabetes using *Coccinia indica* extract. Several species of *Cucurbita* such as *C. pepo*[20], *C. maxima* and *C. moschata*[21] were mentioned for antidiabetic property in ethnomedicine or tested therapeutically for antidiabetic activity in pharmacological studies. Cucurbit fruits of the plants *Luffa acutangula*, *Momordica charantia*, *Lagenaria siceraria*, *Sechium edule* and *Trichosanthes cucumerina* from the family Cucurbitaceae have been reported for α-glucosidase inhibitory activity[22]. Marles and Farnsworth, 1995 have presented a comprehensive literature review on antidiabetic plants and constituents from NAPRALERT database up to 1995. They have reported about 1200 plant species used for the treatment of diabetes and/ or investigated for antidiabetic activity. This list of antidiabetic plants also include about 30 plant species from Cucurbitaceae family[21] and some these plant species are also evaluated in our studies.

Numerous species of *Luffa* is used by traditional native practitioners for treatment of various diseases and also reported by many researchers. Methanolic extract of *Luffa echinata* seeds showed antioxidant activity, anti-inflammatory and analgesic effect in *in-vivo* model[23] whereas methanolic extract of *Luffa acutangula* has been reported to be effective in treatment of gastric ulcers in diabetic rats[24]. *Luffa acutangula* fruit extract has also been demonstrated antidiabetic and hepatoprotective activity in *in-vitro* and histopathological studies[25]. Here, first time we reported the antidiabetic activity of chloroform extract of *Luffa echinata* fruit in *in-vitro* studies, whereas aqueous and alcoholic extract of *Luffa echinata* fruits are also described for antiarthritic activity on Freund's adjuvant induced arthritic rats[26]. Cucurbitaceae family have enormous medicinal value and reported for anxiolytic, carminative, antioxidant, anthelmintic, laxative, purgative and antidiabetic activity in various literature[27]. Our studies also uphold this view that members of family Cucurbitaceae have many therapeutically important chemical constituents and could be explored extensively for their antidiabetic properties. It will also be of interest to evaluate further about antidiabetic activity of *Luffa echinata* fruit which could lead to the development of novel plant based compound for the treatment of Type II diabetes. After taking hint from traditional knowledge or folk medicine if we perform targeted screening of some specific group of plants then it will be more fruitful and rapid for identification of new leads and definitely better than random screening for all plants. Interestingly we have many plants reported for diabetes in Indian literature. The present study was a step towards selecting few plant species from a family known to have antidiabetic potential in traditional medical literature and study those using modern scientific tools. The study demonstrated that there is a huge potential in the family Cucurbitaceae as far as its antidiabetic potential is concerned. The promising results on the 4 species i.e. *Cucumis callosus* fruit, *Luffa echinata* fruit, *Coccinia indica* fruit and *Cucurbita* species aerial part, out of 9 selected in glucose uptake assay have proved this. One species *Luffa echinata* fruit, which showed remarkably high antidiabetic activity in our study is to be investigated further and might be interesting one. The study supported the view that the natural products continue to play dominant role in the discovery of leads for the development of drugs for alleviating human diseases. We believe that a target based approach for screening bioactivity of compounds from medicinal plants will expedite the drug discovery process and might contribute towards identification of interesting/novel chemical scaffolds with antidiabetic activity.

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