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Antidiabetic potential of *Coccinia grandis* (L) voigt: A review

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Abstract
Traditional medicine houses wealth of knowledge for curing various ailments by plants. *Coccinia grandis* (L) Voigt is one such traditionally used plant for relief from diabetes related complications. The leaves and unripe fruits of *Coccinia grandis* are extensively used by the people in the Indian Sub-continent as vegetable. Its leaves, roots, stem and fruits do exhibit antidiabetic potential. The antidiabetic potential of *Coccinia grandis* is mainly because of its insulin mimetic, anti-hyperglycemic, β-cell restoration, antioxidant and antihyperlipidemic activity. Moreover, it is found to be safe *in vivo* in toxicological studies making it suitable candidate for development of prospective neutraceuticals for management of type 2 diabetes.

Keywords: *Coccinia indica*, antidiabetic, antihyperglycemic, normal and diabetic rats

Introduction

Diabetes mellitus is a disorder of endocrine system causing chronic hyperglycemia. In addition, it causes disruption in metabolism of fats, carbohydrates, and proteins. It results from decreased insulin secretion by beta cells in islet of langerhans, or decreased insulin action or both (Ghadge 2017) [17]. In 2019, about 463 million people which is about 9.3% of total adult population of were anticipated to have diabetes problem. The number is likely to grow to 578 million i.e.10.9%of total adult population by 2030 and 700 million by 2045. In India also, the number is expected to soar from 77 million to 134 million by 2045. Seeing that about half a billion of population at present is diabetic, there is dire need to develop and look for a parallel complementary system of medicine (Saeda, *et al*.2019).

Herbs and herbal medicines have made their way as complementary medicine because of their beneficial effect on glycemic index and its related complications (Waisundra, 2015, Jacob *et al* 2016).Since, co morbidities are the major reason behind mortality in diabetes, an integration of traditional phytotherapies can be of help to manage glycemic index to prevent secondary complications. (Marles and Farnsworth, 1996).Charak Samhita and Susruta Samhita (1500-1000 BC), the classical Ayurvedic texts have described 700 herbs with their specific curative properties and scientific methods of drug development (Patwardhan *et al*.) *Coccinia grandis* is one such traditionally used plant for culinary as well medicinal uses (Jamwal and Kumar 2015). Thrust on exploring new lead molecules from plant origin impelled us to compile studies done to assess antidiabetic potential of *Coccinia grandis*. Present review intends to validate the traditional use of *C. grandis* for management of diabetes systematically justified with isolation of bioactive compounds responsible for antihyperglycemic, antioxidant and antihyperlipidemic activities.

The available information about traditional anti-diabetic uses of *Coccinia grandis* and studies on *in vivo* and *in vitro* assessment of the same carried after 2000 were collected from various search engines like SciFinder, Pub med, Elsevier, Science Direct, Springer, Scopus, Web of Science and Google Scholar.

Botany: *Coccinia grandis* (L) Voigt. is a perennial dioecious plant which is usually climber or creeper. The stem of the plant range upto 5 m, and is smooth. However, stem of, older plants is quite often white pustulate. The petioles areglabrous with size ranging from 0.5–5.4cm, and have trichomes on its adaxial side. The leaves are of size 3.11 × 3.13 cm and the shape is either cordate to 3-lobed or 5-edged to 5-lobed and quiet often are lobulate also. The lobes of the leaves are usually triangulate, oblong to obovoid or ovoid. The margin of leaves is dentate and is rarely found to have short whitish trichomes (< 1 mm) and the color of teeth is usually yellowish red to brownish gland, which changes to black when the leaves are dried. The apex of leaves is obtuse to acute and is linked to final tooth. The leaf surface on upper side is glabrous and is dense hyaline to white pustulate. The leaf surface on lower side is glabrous and possesses glands, which are generally of lighter color between major nerves which are occasionally associated with white pustules. The protracts are either missing or less than 1.5 mm. The tendrils of plant are simple.

Male flowers: The male flowers 1(–3) are solitary, and the flowers possess rarely, the short racemes. Both Peduncles and pedicels of flowers are glabrous. The Peduncles of the flowers ranges from 0.3–1.5 cm. The pedicels of the flowers in racemes grow up to size of 3.2 cm. However, the solitary flowers pedicels grow up to size of 4.5 cm. Bracts are either inconspicuous (< 1 mm), or mostly absent. The Perianth tubes of the flowers are also glabrous. Calyx lobes are quite often associated with reddish to brownish glands on lower side at the acute tip and are1.2–3.5 mm long, lineal, spreading to reflexed. The Corolla is 1.7–4 cm long. It is yellowish buff for those found in Africa and snow-white especially outside Africa. The lobes of Corolla are of the

size 0.7–1.7 cm. The filament column and anther head is pale greenish, whereas pollen sacs are yellow.

Female flowers: The female flowers are generally solitary. The Pedicels, Hypanthium, Ovary and fruits are glabrous. Pedicel up to 1 cm.

Hypanthium of female flowers is like calyx and corolla as found in male flowers. Columnar style, usually yellowish green in color. The stigmas of flowers possess two lobes and are greenish.

Fruits of the flower range from 3–4.5 × 1.5 cm and are globose to ellipsoid, cultivated and cylindrical. The unripe fruits are greenish and are having few pale spots or lines or both. The ripe ones are scarlet red. The size of seeds is5–7 × 2.5–3.5 × 1.2 mm (Length/Width/Height) and are asymmetrically obovate, face flat. (Norbert, *et al*. 2015)

Flowering time: Mostly all over year except end of dry or cold season, 10 hrs of light period for flower induction.

Geographical Distribution: The plant is found extensively distributed in countries and regions like Cameroon, S Chad, Djibouti, Ethiopia, Eritrea, Kenya, S Mauritania, Mali, Niger, Somalia, Senegal,Tanzania (Morogoro, Arusha, Dares Salaam, Mwanza, Manyara, Pwani, Zanzibar, Tanga,),South Sudan, S and E Sudan, Uganda, subtropical and tropical parts of India, Pakistan, Sri Lanka, subtropical Nepal, southern and western Arabian Peninsula, South East Asia, S China.

(Norbert, 2015) Recent introduction of plant in countries and territories like Republic of China, Australia (Western Australia**,** Queensland, Northern Territory), Mozambique**,,**Maldives, Mauritius, USA (Wake Island, Guam, Florida, Hawaii), Caribbean area, Central and tropical South America and in many tropical Pacific islands, has been reported.

Synonyms: The plant is also known by *Coccinia cordifolia, Bryonia grandis, Calabaza hiedra, Coccinia indica, Calabacita, Cephalandra indica, Coccinia grandis, Cephalandra grandis (* Norbert, *et al*. 2015)

Table 1

Language	Name
English	Scarlet-fruited gourd
Chinese	Hong gua
Hindi	tindora, kovai fruit, kundru
Japanese	Yasaikarasuuri
Malayalam	Papasan, Pepasan, kovakka, kovai
Ayurveda	Kunduru, Piluparni, Bimbi, Raktaphala
Various Indian Languages	Oriya: Kundru, Parwal, Tondi; Marathi: Tindora, Tindori,; Tamil: Kovakka; Kannada: Tondekayi; Telugu: Dondakaya; Malayalam: Tendli (Konkani), Ghiloda, Kundri, Kowai, Kovai, Kovakkai

Chemical Constituent of Different Parts of *Coccinia grandis*: (Allanger *et al*.2014, Deokate&Khadabadi, 2012, Ajithabai, *et al*.2011)

Whole Plant (Rahman *et al*., 1990): The chemical compounds reported in whole plant (Figure 1)includes amino acids like Aspartic acid (compound 1), Asparagine (compound 2),,Glutamic Acid (compound 3), Arginine (compound 4), Tyrosine (compound 5), Threonine (compound 6), Histidine (compound 7), Phenylalanine (compound 8), Valine(compound 9).

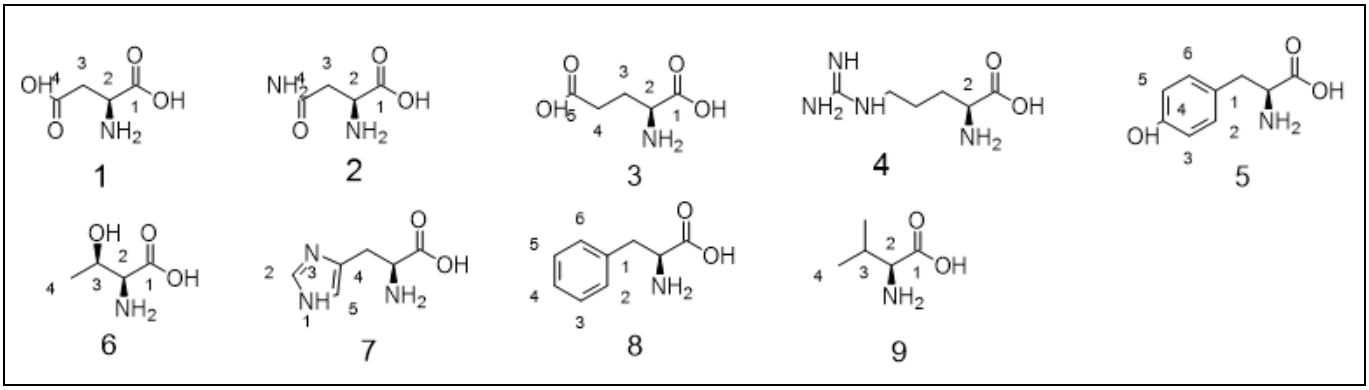

Fig 1: Chemical constituents of whole plant

Root: The chemical compounds (Figure 2) reported in root includes Triterpenoid, saponin: Coccinioside-K (compound 10), Flavonoids (3-O-beta-(alpha-Ñ-L-arabinopyranosyl)-(1 → 2)-beta-D-glucopyranosyl-(1 → 3)-beta-hydroxylup-20 (29)-en-28-oic acid) (compound 11), Lupeol (compound 12),β-amyrin (compound 13),,, and β- sitosterol stigmast-7-en-3-one (compound 14),Methyl chlorogenic acid (compound 15)and Octenyl phenylpropionate (compound 16).

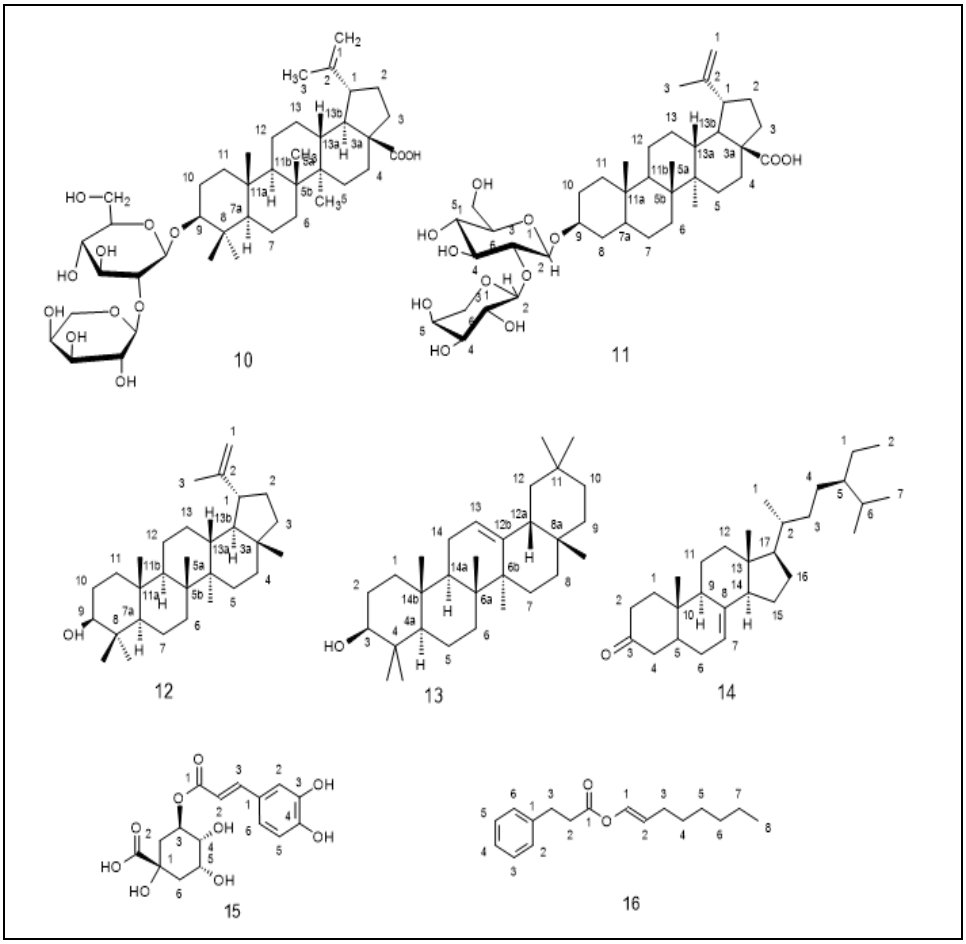

Fig 2: The chemical compounds found in roots

Leaves: The chemical compounds (Figure 3) reported in leaves includes Betulin (compound 17),Heptacosane (compound 18),Tritriacontane (compound 19)**,**β-sitosterolalkaloids (compound 20)Cephalandrine-aandb, Quercetin (compound 20), Cephalandrol.

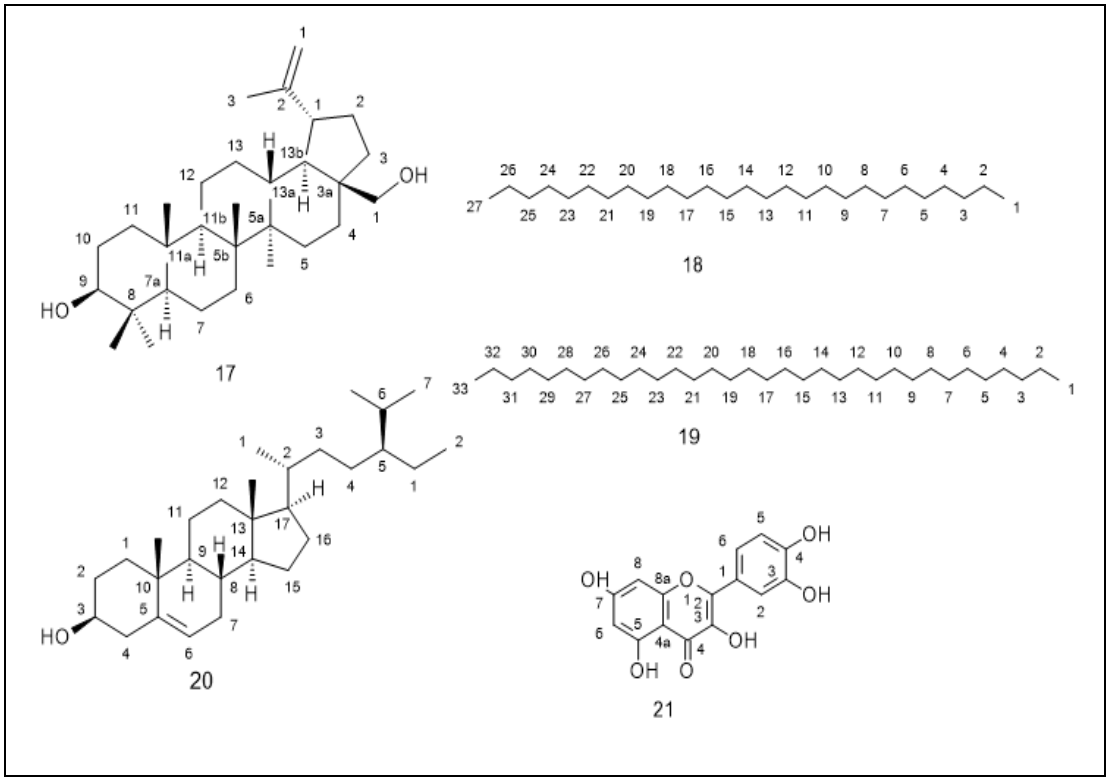

Fig 3: Chemical compounds found in leaves

Fruits: The chemical constituents of fruits includes Taraxerol (compound 22)**,** Taraxerone (compound 23), and (24R)-24-ethylcholest-5-en-3β-olglucoside (compound 24), β-carotene (compound 25), lycopene (compound 26), cryptoxanthin (compound 27), apo-6'-lycopenal (compound 28) and β-sitosterol (compound 29).

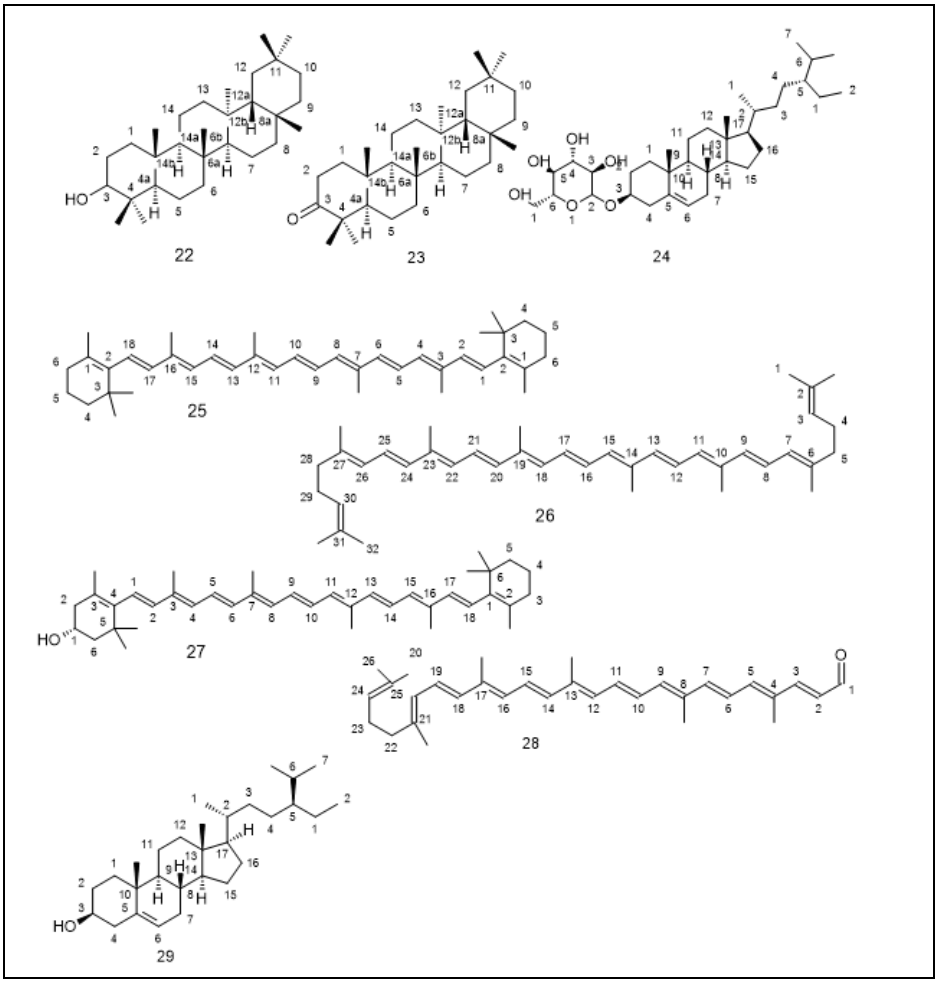

Fig 4: The chemical compounds found in Fruits

Table 2: Abbreviations

S.No.	Abbreviation	Name
1.	AIDR	Alloxan induced diabetic rat
2.	STZ	Streptozotocin induced diabetic rats
3.	ALT	Alanine Aminotransferase
4.	AST	Aspartate Aminotransferase
5.	AIN-76	American Institute of Nutrition Diet
6.	Clet	Coccinia indica leaf extract
7.	STZ	Streptozotocin induced Diabetic Rats
8.	BG	Blood Glucose
9.	FBG	Fasting Blood Glucose
10.	GK	Glucokinase
11.	GLUT4	Glucosetransporter type4
12.	GPR	G-proteincoupledreceptor
13.	GLUT1	pGL3-glucose transporter 1
14.	GSH	Glutathione
15.	G6Pase	Glucose-6-phosphatase
16.	HDL	High-density lipoprotein
17.	LDL	Low-densitylipoprotein
18.	MDA	Malondialdehyde
19.	TC	Total Cholesterol
20.	TG	Triglycerides

In-vivo studies on Coccinia grandis

Venkateswaran and Pari (2002) [53] reported that administration of ethanolic fraction of *Coccinia indica* leaves at dose of 200 mg/kg, of the body weight in STZ induced diabetic rats for 45 days showed hypoglycaemic effect and diminished the related biochemical complications. Substantial suppression in level of the blood glucose and glucose bound hemoglobin i.e. Glycosylated hemoglobin was reported. The increase of insulin level in Plasma was also observed. Significant hypoglycemic effect recorded in normal animals. Similarly ethanolic extract and glibenclamide separately were given to normal and diabetic rats and effect on level of hepatic enzymes like G6Pase, hexokinase, fructose-1,6 bisphosphates and one lipogenic enzyme i.e. glucose-6-phosphate dehydrogenase was assessed. The ethanolic extract of *C. indica* as well as reference drug glibenclamide restored the changed enzyme level to nearly control levels. In addition, decrease in lipogenic enzymes and increase in glucose enzymes was also observed. The effect of CLEt was significantly more than the glibenclamide.

Niedzielski (2002) [38] administrated 400 mg/kg and 200 mg/kg of *Coccinia indica* root extract to diabetic rats using Tolbutamide as reference drug. Both *Coccinia indica* and Tolbutamide decreased levels of glucose in moderately AIDRs by 77.17%and 61.05 %, whereas in mice with severe hyperglycemia, the decrease was 21.7 and 47.9 percent respectively. The percent mean changes in BG levels for the moderately and severely diabetic mice at 2hrs and 4 hrs was not substantial ($p>0.05$), hence *Coccinia indica* had the

same capability to decrease glucose levels as that of reference drug Tolbutamide.

Venkateswaran and Pari (2003) [52] administered ethanolic extract of *Coccinia indica* leaves(CLEt) (200 mg/kg, of b.w.) to STZ diabetic rats where CLEt exhibited higher antioxidant potential than glibenclamide. A reduction in level of reactive oxidative substances, thiobarbituric acid and hydro peroxides after 45 days was detected. Antioxidant property was further confirmed with decrease in levels of oxidizing enzymes of both liver and kidney.

Eshrat (2003) [8] studied the effect of aqueous extract from powdered dried roots of *Abroma augusta* and leaves of *Coccinia indica*. 300mg of water extract containing equal proportions of the roots of the two plants was daily administered for 8 weeks. Restoration of FBG was observed with improved glucose tolerance. In addition, the lipid profile also improved in STZ induced albino diabetic rats.

Dhanabal *et al* (2004) [7] performed a study to find out most active fraction in *Coccinia indica* effective against hyperglycemia. The researchers used a variety of fractions of alcoholic extract of *Coccinia indica* which were further extracted with Toluene, n-butanol, chloroform and ethyl acetate.The different fractions so obtained were then administered to 07 groups of rats. Phenformin (30 mg/kg, b.w.) was given to the positive control group. Out of all, the toluene sub-fraction was most effective in lowering level of blood sugar. In addition, it significantly reduced lipid profile (*P<0.001*) as compared to control diabetic rats. The restoration in levels of AST and ALT to their normal levels was also observed with toluene fraction which was suggestive of insulin revival. The active ingredients of the toluene fraction were triterpenes which possessed property to restore functions of the beta cells and hence, rectified the changed metabolic functions. The activity may be due to healing of beta cells which were damaged by alloxan.

Paliwal*et al.* (2006) evaluated the antihyperglycemic ability of *Coccinia indica* by administering glibenclamide and ethanolic extract of leaves in combination with alpha lipoic acid (ALA) extracts to diabetic rats (alloxan induced)for fifteen days persistently. There was notable repression in level of the blood glucose and change in MDA levels was also noticed.

Purintrapiban *et al* (2006) [41] investigated the effect of water extract (WE) of *Coccinia indica* stem in their study and reported that aqueous fraction induces uptake of 2-deoxyglucose in rat L8 myotubes in dose dependent manner. An increase of three-fold in 2-deoxyglucose transport was noticed in 16 hours therapy, which was maximum as compared to the control. It was stronger than 1 mM metformin. There was noticeable increased manifestation of GLUT1 protein with administration of Water Extract. The relocation of GLUT4 on plasma membrane was also observed.

Mallick *et al.* (2007) [29, 30] examined the impact of 40:60 aqueous-methanolic fraction of roots of *Musa paradisiaca* and leaves of *Coccinia indica*. The effect of these two extracts was investigated separately and in combination on STZ induced diabetic rats.

Studies revealed that when the animals are administered with two plant extracts, the one in combination proved to be much more potent than separate extracts. It markedly enhanced the serum insulin level in streptozotocin-induced diabetic rat. Thus, studies reveled that administration of composite extract treatment is more potent as compared to single plant extract. Researchers observed no metabolic toxicity.

Akhter, *et al.* (2007) investigated and compared the effects of *Coccinia cordifolia* and *Catharanthus roseus (C. roseus)* leaves on the level of blood sugar and lipid in diabetic rats. Diabetes was induced by administering rats with alloxan (AIDR). The researchers administered diabetic rats intra-peritoneally with leaf extracts of *C. cordifolia* with dosage of 300 mg/kg and *C. roseus* with dosage of 150 mg/kg. The level of FBG, TGs and TC in blood serum were measured on 0 days, 7 days and 14 days in AIDRs.On 7th day, thedecreaseinblood glucose levelwas 47.4 and 37.1 % ($P < 0.01$) whereas on 14th day the decrease was by 59.7 and 48.5 %. The administration of one dose of the extracts of leaves of *C. cordifolia*at a dosage of 300 mg/kg, of b.w and of *C. roseus* 150 mg/kg of b.w. caused a considerable decline ($P < 0.01$) by 31.7% and 43.3 % in serum TCon 14th day. Similarly, the decrease in serum TGs was by 45.5% and 39.4 %. Furthermore, 300 mg/kg of *C. roseus* extract displayed high toxicity. The results revealed that *C. cordifolia* was better in lowering the level of blood glucose as well as serum TGs than *C. roseus*.The extracts of both the plants, thus exhibited almost same hypoglycemic and hypolipidemic effect as compared with standard drugs glibenclamide with dosage of 0.05 mg/kg and metformin hydrochloride with dosage of 100 mg/kg of body weight.

Das *et al.* (2008) studied the antidiabetic potential of the seed extracts of *Trigonella foenum-graecum* and leaves of *Coccinia indica* in comparison to the effectiveness of Glimepiride. The researchers orally administered the diabetic rats with Telakucha leaves and Methi seedsin a graded dose (250mg, 500mg, 750mg) and Glimepiride at 800µg/kg of body weight for14 days daily once a day. The researchers observed that there was substantial lowering of blood glucose levels ($P<0$) concomitant with substantial increase in the body weight of animals ($P<0.05$) by 2.3%, 3.9%, 4.8% and 10.4%, respectively. The reduction in concentration of blood glucose with increase in body weight is clear validation of traditionally reported antidiabetic activity in Ayurvedic herbal extracts of both *Trigonella foenum-graecum* and *Coccinia indica.*

Manjula, *et al.*(2007)reported in their study that giving dosage of theaqueous leaf extract of *Coccinia indica* for twenty one days to AIDRs inhibited the elevation of the serum lipid levels indicating usage of the plant to inhibit diabetic complications. Kumar and Verma *(2011)* examined theeffect of mixed aqueous fruit extracts of *Morinda citrifolia* and *Coccinia indica* on glucose level of diabetic rats with diabetes induced by alloxan. It was observed that, giving dosage of combined aqueous fruit extract of these two plants (300 mg/kg of b.w.) to AIDRs for 7days,15days and 30 days led to reversal of glucose levels to normal. In addition, there was considerable reduction in antihyperlipidemic activity with significant improvement in level of triglycerides (TG), serum cholesterol, and LDL and HDL cholesterols. Umamaheshwari, *et al.* (2008) examined numerous fractions of aqueous-methanolic extract of the *Coccinia grandis* leaves for their antioxidant potential. The studies showed that, the various fractions of leaf extract exhibited free radical decomposition activity, H-donor activity, reducing potential, metal chelating capability and β-carotene bleaching inhibition activity. The antioxidant potential was due to presence of phenolics and flavinoids in the extract of leaves of the plants.

Doss *et al.(*2008)examined antihyperglycemic effects of *C. grandis* leaves water decoction. The researchers administered the decoction to diabetic and normal rats for ten days. Repression ($p < 0.05$) in level of FBG was seen in both groups of animals. However, serum insulin levels remained unchanged.

Shakya(2008) studied effect of n-hexane extracts of *Coccinia indica* on glucose levels in STZ induced diabetic rats.Extracts at a dose of 200 mg/kg of body weight were given orally for 30 days. The effect of the compound was 206 ± 23.54 mg/dl of blood, after the extract was given to the diabetic rats thus, revealing synergistic effect of extract upon lowering glucose levels.

Graidist, *et al*(2009)probed the mechanism behind hypoglycemic effect of *Coccinia indica*.GLUT1 promoter was generated to observe molecular response of aqueous extract of *C. indica* stem (CI extract). The 0.15 mg of *Coccinia indica* extract significantly increased transcription by 5.71 fold of the basal value in normal glucose level of 5mM and more than 2 mM metformin. At 15mM glucose, 1.63 fold increase from the basal value with administration of 0.50 mg of extract. At 5 mM and 15 mM glucose, an increase in the 2-deoxyglucose (2-DG) uptake in L6 myocytes was recorded in manner dependent on dose. An enhancement of 2.12 fold seen in the activity of the GLUT1 promoter (-273 to +134) from the basal value indicated that the hypoglycemic activity of *C. indica* may be controlled via stimulation of GLUT1 promoter causing a rise of the GLUT1 protein expression.

Rafiq, (2009)observed substantial reduction($p < 0.001$) in level of blood sugar in diabetic rats upon administration of aqueous extracts (freshly prepared) of *Psidium guajava*, *Coccinia indica*, *Momordica. charantia* leaves. Hypoglycemic action of the extracts was more pronounced in combination treatment than when treated individually with the extracts ($p < 0.01$). There was also enhancement in level of glucose tolerance when taken orally ($p < 0.001$). Treatment with both combination and individual extracts ($p < 0.02$) lessened loss of body weight. There was substantial improvement in tactile allodynia, in diabetic rats when treated with freshly prepared water extract of the leaves,which was otherwise greater in combination treatment. Hence, data suggests that combination of *M. charantia, P. guajava,* and *C. indica* leaf extract is more effective in treating hyperglycemia and neuropathy of STZ-induced diabetic rats.

Ajay (2009) [1] studied effect of alcoholic extract of the leaves of *Coccinia indica* on STZ induced diabetic rats. Four groups *viz*; Group-I of normal rats were treated with normal saline solution, group-II of control group of diabetic rats, group III was of diabetic rats administered with glibenclamide (5mg/kg body weight by the oral dose) and group–IV of diabetic rats administered with alcoholic extract of *Coccinia indica* leaves (250 mg/kg b.w. by the oral dose). The results revealed that there was notable fall in glucose level in STZ induced diabetic rats administered with alcoholic extract of *Coccinia indica* as compared to reference anti-diabetic drug glibenclamide.

Balaraman, *etal (*2010) examined the effect of ethanolic extract of the aerial parts of *Melothria maderaspatana* and *Coccinia indica* in STZ induced diabetes Dawley rats.The administration of ethanolic extracts of *M.spatana* and *C.indica* caused remarkable antihyperglycemic and hypolipidemic effects ($p < 0.001$) after 5 days. The effect was equivalent to reference drug Glibenclamide at dosage of 0.5 mg/kg body weight. The extract of the plants were also quite successful ($p < 0.001$; $p < 0.05$) in reversing the altered biochemical changes caused by diabetes. In addition, the reduction in the body weight of treated animals was also recorded.

Gunjan, M. *et al (*2010) administered fruit extracts(200mg/kg) of *Coccinia grandis* for 14 days to hyperglycemic animals and recorded substantial lowering in blood glucose at 7thday[$p<0.01$] and 14th day [$p<0.001$] of the induced diabetes, which thus demonstrated anti-hyperglycemic effect of the fruit extract. The activity was similar standard antidiabetic drug, Glibenclamide.

Mishra,*et al*.(2009)evaluated antidiabetic potential of six edible plants in STZ induced diabetic rats.The dried powder of fruit and leaves of *Coccinia indica*, dried powder of seeds of *Syzigium cumini*, dried powder of fruits of *Momordica charantia*, seed oil of *Aegle marmelos*, dried powder *Curcuma longa*'s roots and rhizomes and *Trigonella foenum-graecum's* seeds were assessed for their antihyperglycemic activity in diabetic rats along with normal animals. The leaves of *C. indica*were found most efficient in lowering the level of blood glucose inSTZ induced diabetic rats.The antihyperglycemic activity of *C. indica* calculated graphically from 5 h and 24 h AUC graph was around 27.9 and 32.2 % respectively followed by *C. longa* rhizome which exhibited 11.6 and 15.6 % reduction in BG levels in 5 h and 24 h AUC graphs. The study thus, establishes the traditional claim that these edible plants possess antihyperglycemic activity.

Jose, *et al*. (2010) observed the effect of ethanolic extract of *C. indica* leaves (200 mg/kg of body weight) and glibenclamide (0.25 mg/kg of body weight) in AIDRs (Sprague-Dawley strain) for 45 days. The researchers observed remarkable ($p<0.05$) lowering of BG level, TGs**,** serum cholesterol and lipid peroxides besides rise in the level of reduced GSH and liver glycogen in group of diabetic rats treated with *C. indica*. The ethanolic extract of leaves of *C. indica* was also evaluated for acute and subacute toxicity besides bioactive principle, wherein it showed no toxicity.

Islam, *et al. (*2011) investigated the effect of ethyl acetate, petroleum-ether, and chloroform fractions of ethanolic extract of the leaves of *C. cordifolia* extracts (150 mg/kg of b.w.) The extracts were given to both STZ induced diabetic rats and normal rats for 24 hours once a day. The levels of FBG, serum TGs and serum total cholesterol at 0th, 1st, 2nd, 3rd, 6th, 10th, 16th, and 24th hours, were recorded in both groups of animals. The evaluation results revealed that petroleum ether and ethyl acetate fractions were most effective in lowering the concentration of blood glucose. The decrease was significant, 39.66% at 16 h and 40.68% at 24th hour in normal rats. Where in STZ-induced diabetic rats, petroleum ether and ethyl acetate fractions lowered the level of blood glucose by 50.39% at 10th h and 50% at 24th h. The ethyl acetate fraction was most potent as it lowered the TC level by 31.04% in normal and 36.69% and STZ-induced diabetic rats. TGs levels were lowered by 43.82% and 42.01% in normal and STZ-diabetic rats. Thus, petroleum ether fraction of *C. cordifolia* can have potential against hyperglycemia and ethyl acetate fractionhas potential against hyperlipidemia.

Sutradhar *etal* (2011) [50] screened *Coccinia grandis* for its two folklore medicinal values *viz*; the antidiabetic and

antinociceptive effects. Leaf methanolic extract of the plant was given to mice at doses of 50, 100, 200 and 400 mg per kg of body weight. The results showed blood glucose lowering potential. The highest-level reduction in serum glucose (56.3%) was noticed with dosage of 400 mg/kg (b.w.). Glibenclamide, on the other hand lowered serum glucose level in rats at a dose of 10 mg per/kg by 55.5%, thus indicating that extract of leaves possesses significant antihyperglycemic activity. The methanolic extract also showed antinociceptive activity. The number of writhings also decreased by 36.4% and 47.5% with extract of 100 mg/kg &400 mg/kg extract respectively. It was higher than that observed with aspirin. Thus, this study validated the ancient use of the plant for two folklore medicinal values i.e. diabetes and pain.

Ramakrishnan *et al. (*2011) [43] studied the efficacy of administration of 250mg/kg of body weight aqueous, ethanolic and chloroform extracts of fruits of *Coccinia indica* to AIDRs. Ethanol extract exhibited most potent anti-hyperglycemic activity as it lowered 8.2% ($p < 0.005$) and 10.06% ($p < 0.01$) FBG levels, upon 5th and 7th hour of administration.

Shibib, *et al* (2012) [48] studied the anti-hyperglycemic and anti-ureogenic efficacy of *Coccinia grandis*. A decrease in the level of glucoseby23% ($p < 0.01$) and 28% ($p < 0.001$was observed in diabetic rats and normal rats. Free fatty acid fell by 15% ($p < 0.01$) and 25% ($p < 0.001$) respectively was also seen in these two group of animals. Besides this, lowering of activity of hepatic arginase by 14% ($p < 0.05$) and 22% ($p < 0.02$) was observed in the normal and diabetic rats. So this study showed that *C. indica* extract is effective in lowering level of blood glucose and free fatty acid and also lowered hepatic arginase activity.

Saklani *et al* (2012) [46] studied the anti-hyperglycemic potential of leaf extract of *Coccinia indica* and *Salvadora oleoides* in diabetic rats (alloxan induced). Methanolic extract of *C.indica* and *S.oleoides* at 150 mg/Kg of b.w. considerably lowered ($p<0.01$) level of glucose in blood of diabetic rats. The activity was comparable to Glipizide (5 mg/kg of body weight), a standard drug. Methanolic extract also exhibited substantial ($p<0.01$) effect on ALT and AST activity, lipid profile, serum creatinine and urea levels.

Gurukar, *et al* (2013) examined the efficacy of fruits and leaves of *Coccinia indica* on diabetic nephropathy by including them in diet. The *f*ruits and leaves of *Coccinia indica* were substituted into the diet AIN-76 of rodent sat 10% and 5% levels in place of starch respectively.AIN-76 diet augmented with *C. indica* fruits and leaves was administered individually for a period of 2 months to control and diabetic animals. The consumption of the fruits and leaves of *C. indica* in diet lowered fasting blood glucose levels, lowered urine glucose, albumin excretion, and also improved kidney functions like glomerular filtration rate thus indicating that the ingestion of *C. indica* is useful in controlling secondary complications of diabetes.

Attanayake, *etal*(2013)evaluated the potency of leaf water extract of *Coccinia grandis(* CLE*t)*in reducing higher levels of blood glucose and toxicological considerations in AIDRs and healthy Wistar rats. Graded single dose of the leaf extract of C. *grandis* (0.25-2.00 g/kg) was orally given. Dosage of 0.75 g/kg of Clet lowered glucose levels and no toxicity was observed up to 2.00 g/kg. Researchers concluded that a dose of 0.75 g/kg was safe for use as antihyperglycemic agent.In addition, percentage decrease in glycosylated hemoglobin with concomitant increase in level of serum insulin and C-peptide when rats were treated with plant extracts and glibenclamide ($p<0.05$). In addition, administration of leaf extract of *C. grandis*, also caused β-cell rejuvenation in treated diabetic rats as the concentration of insulin secreting β-cells increased with enhancement of islet profile diameter ($p<0.05$).

Ghosh, *et al.* (2013) carried out studies on normal hyperglycemic rats using methanolic extracts of *Coccinia indica* leaves at conc. of 150 and 300 mg/kg. 10 days of treatment, with methanolic extracts of *C. indica*, led to decrease in the level of blood glucose by 36.10% and 41.87% in the two groups of rats. The activity was similar to glibenclamide (standard drug) which showed a decrease of 43.50%.

Kohli et al 2014 investigated the combined effect of *Coccinia indica* and acrabose at low conc. on diabetic neuropathic pain on diabetic rats. The rats were treated for period of seven weeks with acrabose, quercetin, ethanolic extract of *Coccinia indica* separately and in combination with acrabose. After 7 weeks of treatment, the diabetic rats which were given dose of *C. indica* alone and low dose of acrabose displayed decline in the level of blood glucose. There was no damage to Sciatic nerve of the groups administered with ethanolic extract of *Coccinia indica*. The *Coccinia indica* in combination with low dose of acrabose also showed no damage to Sciatic nerve thereby, proving useful effect of the plant extract on pain.

Sharma *et al.*(2016)studied the hypoglycemic effect of the methanolic extract of leaf and fruit of *Coccinia grandis* in AIDRs using Glibenclamide (5 mg/kg, p.o) as reference drug. There was substantial hypoglycemic activity ($P < 0.01$ and $P < 0.001$). when, methanolic extract at a dosage of 400 mg/kg of b.w.was administered. The activity of methanolic extract was due to presence of bioactive molecules like alkaloids, saponins, steroids and flavinoids.

Meenatchi,*et al*(2016)studied the fruits *Coccinia indica* for their antioxidant, antiglycation potential and insulinotropic properties in RINm5F cells. The study performed by researchers revealed that the *C. grandis* extract possesses radical scavenging activity in concentration dependent manner and considerable antiglycation ability. The *C. grandis* extract also displayed insulinotropic activity with 1.28 and 1.71- fold increase in release of insulin as compared to control at 0.25 and 0.50 mg/mL, respectively. Hence, *C. grandis* fruit extract was thus reported to exhibit antioxidant, antiglycation and insulin secretary effects and hence, can be used for advancement of natural anti-glycating agents and for promoting insulin secretion.

Mohammed, *et al.* (2016) evaluated ethanolic extract of *Coccinia grandis* leaves for their antihyperglycemic and antioxidative potential in STZ induced albino Wistar diabetic rats.The administration of leaf extract (500 mg/kg orally to STZ diabetic rats for 21 days, depressed blood glucose level (312–169 mg/100 mL) significantly ($P < 0.001$) and at the same time increased body weight (181–210 g) and insulin in the serum (1.28–3.10 IU/dL) in experimental animals. Lipid profile, liver functions and kidney functions also restored to normal. The activity was comparable with standard drug metformin. Histopathology of pancreas revealed repair in islet of Langerhans.

Kaushik, *et al* (2017) performed study to examine the effect of extracts of *Momordica balsamina* and *Coccinia indica* fruits. Fruits of both the plant were first extracted

with chloroform followed by their further fractionation with n-hexane in order to obtain polar compounds predominantly. Chloroform extract of fruits of both plants at conc. of 250 mg/kg of body weight were given orally to STZ nicotinamide-induced diabetic animals for 07 days separately, revealed that the extracts are effective in lowering FBG levels to considerable extent ($P < 0.05$ versus diabetic control).Extracts of *C.indica* and *M. balsamina* yielded six cucurbitane-type triterpenoids. The isolation of six cucurbitacins from bioactive extracts of *C. indica* (Coccinioside A, B, and C) and *M. balsamina* (cucurbit-5, 7-dien-3ß-ol, cucurbita-5-en-3ß-ol-3-*O*-ß-d-glucopyranoside and cucurbit-5-en-3ß-ol-3-O-ß-d-glucopyranosyl-(4'→1")-*O*-ß-d-glucopyranoside)andtheir characterization was reported for first time by the researchers.

Packirisamy *et al* (2018) studied the hypoglycemic potential of the unripe fruits of Coccinia grandis in STZ-induced diabetic rats. The ethanolic *Coccinia grandis* extract (CGE) was administered to four groups of diabetic rats for 30 daysat graded concentration of 125, 250,500 and 750 mg/kg of body weight. The results were evaluated as compared to glibenclamide. *Coccinia grandis* extract at concentration of 250 mg/kg body caused remarkable lowering in the level of BG and glycosylated hemoglobin coupled with considerable rise in the levels of carbohydrate metabolizing enzymes. The activity of gluconeogenic enzymes secreted by liver of diabetic treated rats also showed decrease. The anti-hyperglycemic efficacy was almost equivalent to standard drug glibenclamide. Phytochemical examination showed good presence of phenols, saponins and dietary fibersin fruits of *C. grandis* and hence showing their importance as functional food for diabetes.

Jamwal *et al. (2019)* screened the various compounds isolated from ethyl acetate fraction of methanolic extract of *C. indica* for antidiabetic potential in STZ-nicotinamide induced diabetic rats. Researchers isolated a bioflavonoid quercetin from C. *indica* aerial parts for the first time. At a conc. of 5 mg/kg, p.o, lowered the sugar levels in type-2 diabetic rats besides increase in insulin levels and serum HDL-cholesterol levels. The studies were conducted using Metformin as the reference drug. The researchers also observed alteration in liver marker enzymes as well as kidney functions markers in diabetic rats inferring that antidiabetic potential of the aerial parts of *C. indica* is because of Quercetin.

Islam, *et al.*(2019)studied the hypoglycemic potential of ethanolic extract of *Coccinia grandis* leaves and its safety profile. The ethanolic extract of leaves to the diabetic rats at a dose of 750 mg/kg was administered. Theliver enzymeslike SGOT, SGPT and creatinine level in diabetic and non-diabetic rats was measured before and after administration of the dose of ethanolic extract. Researchers observed same level of the hypoglycemic potential of C.*grandis* leaves extract asthat of metformin ($p > 0.05$) given at a dose of 500 mg/kg. Hence, leaf extract of Coccinia grandis like metformin ameliorated the clinicaldisordercaused by diabetes. Both metformin and *C. grandis*leaf extract did not cause change in any of the physiological parameters in case of healthy individual rats, thus ensuing its safe consumption.

Pochhi(2019) administered aqueous leaf extracts of *C. indica* (200 mg/kg to diabetic rats (alloxan induced)for 14 days. The aqueous extract of *C. indica leaves* improved the blood glucose level besides metabolizing enzyme activity of serum Lipids, lipoproteins and lipids (HMG CoA reductase, LCAT).

In-vitro Enzyme Assay

Jaiboon *et al* 2011 investigated the inhibition of alpha amylase by using chili paste prepared from vegetables like *Coccinia grandis, Piper retrofractum, Gynura divaricata, Thunbergia laurifolia* and *Cyperus rotundus.* The Alpha amylase inhibition of the products was assessed after 10-15 minutes of roasting. The studies conducted demonstrated that all the studied vegetables and herbs exhibited more than 80% alpha amylase inhibition, which can be regarded as a high level of inhibition. The chili paste comprising of *Gynura divaricata, Piper retrofractum* and *Cyperus rotundus* showed decreased alpha amylase inhibition. However, there was contradictory result when the *C.grandis* added paste was administered. *C. grandis* added paste increased the enzyme inhibition quite significantly. In case of fresh material, increase was 23%, whereas in case of 10 min roasted sample, an increase in enzyme inhibition activity was 45%. However, there was insignificant change in the enzyme inhibition at15minute roasting.

Alagar *et al*(2014) estimated *in vitro* alpha glucosidase antihyperglycaemic activity of water maceration, Decoction (water), ethanolic and methanolic extracts of fruits of *Coccinia indica*. The process initiated by addition of 1 ml of alpha-glucosidase enzyme (1U/ml) to the said extracts followed by incubation for 40 min at 35°C. Percentage inhibition at 540nm was maximum for ethanol extract 68.35%.

Table 3: Clinical Trials

Design	Sample	Intervention	Control	Outcome	Reference
Double-blind; 2-parallelgroups	32-type-2 (Diabetic patients); uncontrolled	1800mg/d(freeze-dried powder from fresh leaves in tablets); for 6weeks	Placebo tablet	Decrease Fasting blood glucose, Post prandial glucose	(Khan,1979)
Non-randomized;open-label	60(both types of diabetes);untreated	50 mg/kg (dried pellets from fresh leaves);for 6weeks	No treatment	Decrease Fasting blood glucose, Post prandial glucose and enzymes levels	(Kamble, 1998)
Three-armcontrolledgroups	70-type-2(Diabeticpatients) uncontrolled	6g/d(dried pellets from fresh leaves);for 12weeks	No treatment and Chloproamide	Change was similar to that of conventional drug	(Kamble, 1996)
Non-randomized;open-	70-type-	6g/d(dried pellets from	No treatment	---------	(Kuppurajan,

label prospective	2(Diabeticpatients)uncontrolled	freshleaves);for 6weeks			1986)
Double-blindphaseIrandomized	122 healthy Volunteers controlled	20g (with meal)	Erythrina indica 20g	Decrease Postprandial Glucose and Improved glucose tolerance	(Munasinghe, 2011)
Random Double-blind	16-type-2(Diabetic patients) uncontrolled	Homogenized and freeze-dried powder from fresh leaves in tablets; for 6weeks	Placebo tablet	Improved glucose tolerant	(Khan,1980)
Double blind; Randomized	60-type-2(Diabetic patients); controlled	1g of aqueous alcoholic extract(Freeze-dried powder from fresh leaves and fruits in tablets); for90 days	Maltodextin capsule(500mg)	Decrease Fasting blood glucose, Postprandial glucose and action independent of energy/food intake or weight loss	(KurpadandRaj,2008)
Double blind; randomized	60-type-2(Diabetic patients); controlled	Two500mg capsule daily;for90 days	Maltodextrin capsule(500mg)	Decrease Fasting blood glucose, Postprandial glucose	(Kuriyan, 2008)

Kurpad *et al* (2008) carried out a double-blind, placebo-controlled, randomized clinical trial on 60 subjects having type 2 diabetes (35–60 years of age) from St. Johns Medical College Hospital, Bangalore, India. The diabetic subjects were administered with 1 g alcoholic extract of aerial parts of *Coccinia grandis* for 03 months. There was marked reduction inlevel of blood glucose at fasting, postprandial and A1C of the subjects of investigational group as compared with that of the subjects of placebo group. A decrease of 16% and 18% was reported in fasting and postprandial sugar level of the subjects at 90thday of administration. However, serum lipid levels showed no significant changes implying that extract of aerial parts of *C. cordifolia* do possess hypoglycemic action in patients with prediabetes or mild diabetes.

Munasinghe,(2011) carried out a double-blind phase I clinical trial on 61 volunteers in two groups at the general hospital and a private hospital in Matara in August, 2009. Each of the subject was given diet containing 20g of *Coccinia grandis* leaves and a 10-hour fasting period was maintained. The experimental subjects showed lowering of level of blood sugar than the subjects of control group {F(1,117) 5.56, P<0.05}. There was a significant mean difference of the postprandial blood sugar levels (mg/dL) after one hour (20.2, 95% confidence interval, 4.81 to 35.5) and two hours (11.46, 95% confidence interval; 1.03 to 21.9) between the experimental and control group subjects. So, the study clearly demonstrated that *Coccinia grandis* exerted a blood sugar lowering effect.

Conclusion

From the above discussion, it is clear that *Coccinia grandis* do exhibit strong hypoglycemic effect because of presence of flavinoids like quercetin, saponins and phenols. These molecules have been reported to restore beta cell function and enhancement in insulin secretion. Moreover, as the studies revealed that *in vivo*, the aqueous extract of leaves of *C. grandis* exerts anti-hyperglycemic, antihyperlipidemic, antioxidant activities, it can safely be employed for developing potential neutraceuticals against diabetes mellitus. However, more structured randomized well controlled clinical trials need to be conducted before its recommendation as an effective dietary supplement for patients with diabetes mellitus.

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None

Conflict of Interest (if no conflict of interest among authors)
The authors declare that there is no conflict of interest.

Authors' Contributions
Madhvi Parasher (Parasher, M) drafted the manuscript, compiled information from the literature, and designed the figures and tables. Devendra Pandey (Pandey, D) drafted the manuscript and gathered information from the literature.

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All datasets generated or analyzed during this study are included in the manuscript.

Ethics Statement
Not applicable

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