A review on Insulin plant (*Costus igneus* Nak)

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ABSTRACT

Costus igneus Nak and *Costus pictus* D. Don, commonly known as Spiral flag, is a member of Costaceae and a newly introduced plant in India from South and Central America. It is a perennial, upright, spreading plant reaching about two feet tall, with spirally arranged leaves and attractive flowers. In southern India, it usually grows as an ornamental plant and its leaves are used as a dietary supplement in the treatment of diabetes mellitus. Recently, a number of researches have been carried out to evaluate the anti-diabetic potential of this plant. Besides, it has been proven to possess various pharmacological activities like hypolipidemic, diuretic, antioxidant, anti-microbial, anti-cancerous. Further, various phytochemical investigations reveal the presence of carbohydrates, triterpenoids, proteins, alkaloids, tannins, saponins, flavonoids, steroid, and appreciable amounts of trace elements. This work is an attempt to compile and explore the different pharmacological and phytochemical studies reported till date.

Key words: Anti-diabetic activity, *Costus igneus* Nak, *Costus pictus* D. Don, diabetes mellitus, insulin plant

INTRODUCTION

Costus igneus Nak (syn. *Costus pictus* D. Don, *Costus mexicanus* Liebm ex Petersen or *Costus congenitus* Rowle), commonly known as fiery costus, Step ladder or Spiral flag or Insulin plant, is native to South and Central America. This is a recent introduction to India from America as an herbal cure for diabetes and hence commonly called as 'insulin plant.'[1] It is widely grown in gardens as ornamental plant in South India and also run wild in many places.[2] It is used in India to control diabetes, and it is known that diabetic people eat one leaf daily to keep their blood glucose low.[3] Leaves of *C. igneus* were one among the plants known to be effectively used for treating diabetes by the tribal people of Kolli hills of Namakkal district, Tamilnadu.[4] In Mexican folk medicine, the aerial part of *C. pictus* D. Don is used as an infusion in the treatment of renal disorders.[5]

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The plant belongs to the family Costaceae. The Costaceae was first raised to the rank of family by Nakai on the basis of spirally arranged leaves and rhizomes being free from aromatic essential oils. Before the elevation to family status, Engler and Prantl recognized Costoideal as a subfamily under Zingiberaceae. Several anatomical and morphological features support this isolated position including well developed aerial shoot with distinct, rigid, and commonly branched stems. The leaves are inserted in a low spiral with divergences. The family Costaceae consists of four genera and approximately 200 species. The genus Costus is the largest in the family with about 150 species that are mainly tropical in distribution.[2,6] The present review deals with the recent research carried out in the area of phytochemistry, pharmacological, biological activities, and safety of *Costus igneus* Nak.

Taxonomy

Botanical name:[7]	*Costus igneus* N.E.Br
Domain:	Eukaryota
Kingdom:	Plantae
Subkingdom:	Viridaeplantae
Phylum:	Tracheophyta
Subphylum:	Euphyllophytina
Infraphylum:	Radiatopses
Class:	Liliopsida
Subclass:	Commelinidae
Superorder:	Zingiberanae
Order:	Zingiberales
Family:	Costaceae
Subfamily:	Asteroideae
Tribe:	Coreopsideae
Genus:	Costus
Specific epithet:	Igneus

Morphology

It is a perennial, upright, spreading plant reaching about two feet tall, with the tallest stems falling over and lying on the ground. Leaves are simple, alternate, entire, oblong, evergreen, 4-8 inches in length with parallel venation. The large, smooth, dark green leaves of this tropical evergreen have light purple undersides and are spirally arranged around stems, forming attractive, arching clumps arising from underground rootstocks. Beautiful, 1.5-inch diameter, orange flowers are produced in the warm months, appearing on cone-like heads at the tips of branches.[8] Fruits are inconspicuous, not showy, less than 0.5 inch, and green-colored [Figure 1].

Growth and propagation

Spiral flag grows in either full sun or partial shade. It needs fertile soil and ample moisture, and is often planted near water. Propagation is by division of the clumps, cuttings, or by separating the offsets or plantlets that form below the flower heads. Mites and nematodes can be a problem, especially on light, sandy soil. The plant has no diseases are of major concern.[8]

Phytochemical study

Sequential screening for phytochemicals of *C. igneus* leaves revealed that it is rich in protein, iron, and antioxidant components such as ascorbic acid, α-tocopherol, β-carotene, terpinoids, steroids, and flavonoids.[9,10] It was revealed in another study that methanolic extract was found to contain the highest number of phytochemicals such as carbohydrates, triterpenoids, proteins, alkaloids, tannins, saponins, and flavonoids.[11] Preliminary phytochemical evaluation of Insulin plant (*C. pictus*) revealed that the leaves contain 21.2% fibers. Successive extracts gave 5.2% extractives in petroleum ether, 1.06% in cyclohexane, 1.33% in acetone, and 2.95% in ethanol. Analysis of successive extracts showed presence of steroids in all extracts. The ethanol extract contained alkaloid also. The major component of the ether fraction was bis (2'-ethylhexyl)-1,2-benzenedicarboxylate (59.04%) apart from α-tocopherol and a steroid, ergastanol.[12] Stem showed the presence of a terpenoid compound lupeol and a steroid compound stigmasterol.[13] Bioactive compounds quercetin and diosgenin, a steroidal sapogenin, were isolated from *C. igneus* rhizome.[14] Trace elemental analysis showed that the leaves and rhizomes of *C. pictus* contains appreciable amounts of the elements K, Ca, Cr, Mn, Cu, and Zn.[15] Steam distillation of stems, leaves, and rhizomes of *C. pictus* D. Don yielded clear and yellowish essential oils. The major constituents identified[1] in the essential oil are enlisted in Table 1.

Major pharmacological activities

Anti-diabetic activity

Of late, a lot of research work has been conducted to evaluate the anti-diabetic effect of insulin plant.[3,11,14-30] The summary of the animal experimentations done are tabulated [Table 2]. In a cross- sectional clinical study, patients consuming either one fresh leaf or 1 teaspoon of shade-dried powder/day of *C. igneus* in conjunction with other modalities of treatment had effectively produced glycemic control in diabetics.[31]

However, an *in vitro* study of ethanolic extract of *C. pictus* leaf was analyzed to study GLUT4 translocation and glucose uptake activity, which showed no direct peripheral action at 300 μg/ml dose comparable with insulin and metformin.[32] A study evaluated the ability of a tea made from the leaves of *C. spicatus* to alter glucose homeostasis in C57BLKS/J (KS) *db/db* mice, a model of obesity-induced hyperglycemia, with progressive beta-cell depletion. Intraperitoneal (IP) insulin tolerance testing after the 10-week study period showed that *C. spicatus* tea consumption did not alter insulin sensitivity, which suggested that at the dose given, tea made from *C. spicatus* leaves had no efficacy in the treatment of obesity-induced hyperglycemia.[33]

Toxicity study

Acute toxicity studies were studied with different doses of aqueous extract of *C. pictus* from 5, 10, 20, and 40 g/kg body weight. None of the doses of this extract produced mortality or any behavioral disorders.[5] Acute toxicity studies revealed that the administration of aqueous extract 1 g/kg b.w/day for 30 days produced no effect on the general behavior and all the animals survived the test period.[30] Administration of ethanolic

Figure 1: Insulin plant

Table 1: Major constituents of essential oil

Stem oil (%)	Leaf oil (%)	Rhizome oil (%)
Hexadecanoic acid (28.3)	Hexadecanoic acid (24.51)	Hexadecanoic acid (25.26)
9,12-octadecadienoic acid (18.33)	2-pentanol (22.48)	9,12-octadecadienoic acid (7.74)
Dodecanoic acid (5.62)	Dodecanoic acid (3.96)	Dodecanoic acid (16.56)
Linalyl propanoate (6.03)	ß-ionone (8.69)	Tetradecanoic acid (10.20)
Tetradecanoic acid (4.82)	Farnesyl acetone (7.04)	Linalool (8.48)
A-eudesmol (3.55)	A- ionone (8.01)	α-terpineol (4.44)
γ-eudesmol (3.21)		
4-ethoxy phenol (3.06)		

Table 2: Studies carried out to evaluate anti-diabetic effect

Author, year	Model	Part/extract used	Results
S P Dhanabal, 2007	Normoglycemic rats and Hyperglycemic rats	200, 400 mg/kg b.w of ethanolic leaf extract	Both the doses did not significantly reduce the blood glucose levels in Normoglycemic rats. 400 mg/kg b.w of extract led to significant blood glucose-lowering effect in hyperglycemia rats
Nandhakumar Jothivel, 2007	Alloxan induced in Male Wistar Albino rats	120 mg/kg b.w of methanolic leaf extract, p.o, single dose/day for 21 days	The methanolic extract significantly decreased serum glucose level and increase in liver glycogen, which shows its anti-diabetic effect. It also showed increase in plasma insulin level and improvement in lipid profile (cholesterol, triglyceride, HDL, LDL, VLDL, and phosopholipids), which indicates it is useful in hyperlipidemia consequent upon diabetes mellitus
Gireesh 2007	STZ induced in Male Albino Wistar rats	250 mg/kg b.w of crude aqueous extract, orally for 14 days	*C. pictus* leaf extract significantly reduced the blood glucose to near the control in diabetic rats. *In vitro* studies showed *C. pictus* leaf extract induced glucose-stimulated insulin secretion in pancreatic islets. *C. pictus* extracts have a regulatory role in the secretion and glucose homeostasis through muscarinic receptors.
M A Jayasri, S Gunasekaran, 2008	STZ induced in Albino Wistar rats	2 gm/kg b.w of aqueous solution, orally for 28 days	It was evident that the aqueous solution of *C. pictus* leaves was effective in maintaining the blood glucose levels in normal and STZ-induced diabetic rats. Morphometric analysis of *C. pictus*-treated rat pancreatic islets showed a significant increase in the number and area of islets.
V Devi, Asna Urooj, 2008	STZ induced in Male Albino Wistar rats	500 mg/kg b.w of crude leaf powder, orally for 15 days	Preliminary data of this study indicates that leaf powder is effective in lowering blood glucose
Gireesh G, Santhosh K, 2009	STZ induced in Male Albino Wistar rats	250 mg/kg b.w of crude aqueous extract, orally for 14 days	It significantly increased the plasma insulin level to near control in diabetic rats. *In vitro* insulin secretion study using rat islet culture revealed that aqueous extract of *C. pictus* enhanced insulin secretion.
P P Sethumathui, J Nandakumar, 2009	Alloxan induced in Male albino Wistar rats	120 mg/kg and 180 mg/kg b.w of methanolic leaf extract, p.o, single dose/ day for 21 days	Extract at both doses produced significant reduction in blood glucose and lipid peroxidation (LPO)
Bhat Vishnu, Asuti Naveen, 2010	Alloxan induced in Male albino Wistar rats	500 mg ethanolic leaf extract, orally for 7 days	The extract significantly decreased glucose level in diabetic rats
Pangal Mani, 2010	Alloxan induced in Male Albino Wistar rats	50, 100, 200 mg/kg b.w of methanolic and aqueous leaf extract, intra peritoneally for 30 days	Among these extracts, methanolic extract at 200 mg/kg b.w was found to be almost significant as the standard drug (Glibenclamide-0.5 mg/kg) in lowering blood glucose level when compared to aqueous extracts
Altaf Al- Romaiyan, 2010	*In vitro* study in Mouse and Human Islets of Langerhans	Methanolic leaf extract	*In vitro* observations suggest that one mode of action of *C. pictus* is through stimulating insulin secretion, which may be mediated, in part, by the ability of the plant extract to increase [Ca^{2+}] levels through voltage-gated Ca^{2+}channel (VGCC)
Akhila J Shetty, 2010	Dexamethasone in Male Albino Wistar rats	100, 250, 500 mg/kg b.w leaf powder, orally for 7 days	250, 500 mg/kg leaf powder reduced the fasting and post-prandial blood sugar levels, bringing them to normal.
V Devi, Asna Urooj, 2011	STZ induced in Male Albino Wistar rats	500 mg/kg b.w of leaf powder for 45 days	Supplementation of *C. pictus* powder resulted in a consistent and gradual decrease in blood glucose levels
Kripa Krishnan, 2011	STZ induced in Male Albino Sprague- Dawley	100 mg/kg b.w of aqueous, methanolic, and ethanolic leaf extract, orally for 30 days	Of the three extracts, methanolic extract at 100 mg/kg b.w showed optimum benefits by eliciting pronounced hypoglycemia and antioxidant activities
Pazhanichamy Kalailingam, 2011	STZ induced in Albino Wistar rats	100, 200 mg/kg b.w of ethanol rhizome extract, orally for 30 days	Study showed that the extracts significantly reduced blood glucose levels in diabetic rats and also reversed levels of carbohydrate metabolic, hepatoproductive, and antioxidant enzymes
Stabitha T Issac, 2011	STZ induced in Male albino rats	500 mg/kg b.w of aqueous leaf extract of *C. pictus* and *C. pictus*, orally for 15 days	Both are highly effective in lowering the blood glucose levels; however, hypoglycemic activity of *C. pictus* was found to be higher than *C. pictus*
Pazhanichamy Kalailingam,	STZ induced in Albino Wistar	100, 200 mg/kg b.w of methanolic rhizome	Results showed that fasting blood glucose, lipid profile levels were significantly decreased, and hence *C. igneus*

Contd..

Table 2: contd...

Author, year	Model	Part/extract used	Results
2011	rats	extract, orally for 30 days	rhizome showed potent anti-diabetic and hypolipidemic effect
S Suganya, 2012	Alloxan induced in Female Albino Wistar rats	200 mg/kg b.w of aqueous extract, orally for 30 days	Significantly reduced the levels of blood glucose, lipid profile, lipid peroxidation, liver marker enzymes, liver marker enzymes, urea, creatinine and increased the antioxidant enzymes
M V Kumudhavalli, 2012	STZ induced in Male Albino Wistar rats	250, 500 mg/kg b.w each of aqueous and ethanolic leaf extract, orally for 15 days	500 mg/kg b.w of both aqueous and ethanolic extracts showed significant reduction in blood glucose level and lipid profile. However, anti-diabetic activity of 500 mg/kg b.w of ethanolic extract was more significant than the aqueous extract
R Remya, M Daniel, 2012	Alloxan induced in Male Sprague Dawley rats	200, 400 mg/kg b.w of fresh leaf extract, orally for 60 days	Results show significant decrease in blood glucose level and lipid profiles

extract of *C. igneus* leaves from 50 mg/kg b.w up to the dose of 5000 mg/kg b.w did not show significant toxicity signs during the first four hours and followed by daily observations for 14 days, and no mortality was also observed; the drug was found to be safe at the tested dose level of 5000 mg/kg b.wt.[20] However, in a study carried out on the methanolic extract of *C. igneus*, findings indicated toxicity at 250 mg/kg body weight.[25] Further, in another investigation, palmitic acid was found to be the major component in the stem, leaf, and rhizome oils of *C. pictus*. Palmitic acid is found to induce degeneration of myofibrils in healthy adult rat cardiomyocytes, enhance LDL to HDL cholesterol ratio, and it was found to be the important precursor for the development of coronary heart diseases. So, the constant use of *C. pictus* leaves for diabetic treatment may cause serious cardiac diseases, and it is not recommended for the treatment.[1]

Hypolipidemic activity

A study was carried out to comparatively evaluate the methanolic and aqueous extracts of *C. igneus* in diabetes-induced hyperlipidemia in rats. The study revealed that methanolic and aqueous extracts at a dose of 200 mg/kg body weight reversed the diabetes-induced hyperlipidemia.[21] Alcoholic extract of *C. igneus* at the dose of 400 mg/kg (p.o) had significantly decreased the levels of serum cholesterol, triglycerides, LDL in Triton-induced hyperlipidemic rats.[34]

Diuretic effect

A study was carried out to measure the diuretic effect of an aqueous extract of *C. pictus* D. Don at doses of 100 and 200 mg/kg body weight and to compare it with the one induced by furosemide at 4 mg/kg. The results revealed that *C. pictus* induced a natriuretic effect similar to furosemide. The aqueous extract induced an increment in sodium and potassium clearance similar to the one obtained with furosemide, suggesting that it represents significant diuresis.[5]

Antioxidant activity

An *in vitro* study of alcoholic extract of leaves of *C. mexicanus* showed moderate antioxidant activity.[16] The antioxidant activities of leaves and rhizomes in methanol, aqueous, ethanol, and ethyl acetate extracts were assessed using different models like DPPH, β-carotene, Deoxyribose, superoxide anion, reducing power, and metal chelating assay at different concentrations. Leaves and rhizomes of *C. pictus* showed good antioxidant activity of about 89.5% and 90.0% when compared with standard BHT (Butylated Hydroxy Toulene) (85%) at a concentration of 400 μg/ml. Results obtained revealed that methanolic extracts of both leaves and rhizomes of *C. pictus* possess higher antioxidant activity when compared with other extracts.[35] In another study, methanolic leaf extract of *C. pictus* D. Don caused significant increase in superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, vitamin A, vitamin C, vitamin E and reduced glutathione, and thus, could be effective in reducing oxidative stress and free radical-mediated diseases. The antioxidant property of this plant may be due to the presence of phenolic substances.[19] Methanolic extracts of flower and stem of *C. pictus* possess *in vitro* antioxidant activity against oxidative protein damage.[36] Among the extracts tested for, chloroform extract of *C. pictus* D. Don bark possessed high antioxidant activity.[37] Oral administration of ethanolic extract of *C. igneus* rhizome at 200 mg/kg body weight to diabetic rats for 30 days induced a significant antioxidant effect. The bioactive compound quercetin and diosgenin present in the plant exhibited antioxidant activity, which was sufficient to reverse oxidative stress in liver, pancreas, and kidney of diabetic rats as well as to stimulate glycolytic enzymes and control gluconeogenesis in diabetic animals.[14]

Ameliorative effect

A study was conducted to evaluate the ameliorative effect of ethanolic extract (50 mg/kg b.wt, orally) of rhizome on mitochondrial enzymes in alcohol-induced free radical toxicity in male albino rats. After 21 days of treatment, mitochondrial enzymes were restored to normal levels, which showed that *C. pictus* improved mitochondrial activities during alcohol-induced free radical stress.[38]

Anti-microbial activity

Methanolic extract of *C. igneus* showed maximum anti-bacterial activity against g*ram-positive Bacillus cerus, Bacillus megaterium, Micrococcus leuteus, Staphylococcusn aureus, Streptococcus lactis*, and

gram-negative strains *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter aerogenes, Klebsiella pneumoniae,* and *Salmonella typhimurium*.[39] The isolated compound from the ethanolic extract of *Costus igneus* showed moderate anti-bacterial and anti-fungal activity against *Staphylococcus aureus, Eschericia coli, and Candida albicans*.[40] Among the extracts of various parts of *C. pictus*, methanolic extracts of stem and flower exhibited maximum inhibitory activity on the growth of tested microbes, *viz*., *Shigella flexneri, Klebsiella pneumonia*, *Bacillus subtilis*, *Escherichia coli* at the concentration of 150 μg/ml.[36]

Anti-cancer effect

The ethanolic extract of leaves of *C. pictus* was found to have anti-proliferative and anti-cancer potential in *in-vitro* mammalian fibrosarcoma (HT-1080) cells.[41] All the extracts of bark had potent anti-cancer properties against HT 29 and A549 cells.[37]

Putative activity

Aqueous extract of *Costus* stem and isolated compounds lupeol, and stigmasterol had an inhibitory effect on calcium oxalate urolithiasis, and its putative activity was confirmed by the promotion of formation of calcium oxalate dehydrate (COD) crystals and may possibly treat urinary stones by inhibiting the formation of calcium oxalate monohydrate (COM) crystals.[13]

CONCLUSION

This review supports the therapeutic potential of the leaves in diabetes. However, these results have to be further evaluated and revalidated by clinical trials. The anti-diabetic effect of its leaves is currently been tested in diabetic patients. Studies reveal its role in various diseases, which opens up new clinical research areas. Furthermore, it paves new avenues to explore the compounds responsible for these therapeutic effects, and study the mechanism of its action.

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