THERAPEUTIC EXPLORATION OF INSULIN PLANT

Abstract

The family *Costaceae* consists of *Costus igneus* Nak (also known as *Costus pictus* D. Don, *Costus mexicanus* Liebm ex Petersen, and *Costus congenitus* Rowle). This family contains four genera with approximately 200 species, the largest of which is *Costus*, which represents nearly 150 species. *Costus igneus* is native to Southeast Asia. It is used as an ornamental plant in India to enhance the value of the landscape. In India, people call it as the "insulin plant" because of its ability to raise insulin levels in the body, acting as an anti-diabetic agent. Insulin plant leaves were phytochemically screened and found to be high in protein, iron, and antioxidant components such as ascorbic acid, α-tocopherol, β-carotene, terpenoids, steroids, and flavonoids. Historically it was used to extend life span, reduce skin-related diseases like rash, relieve symptoms of fever, treat asthma and bronchitis and obliterate intestinal worms. Besides, it has diverse uses, including anti-diabetic activity, antiproliferative activity, anti-microbial activity, anti-urolithiatic activity, effects on learning and memory, anti-oxidant activity, hepatoprotective activity, and so on. The objective of this section is to carry out a pharmacognostic study on the healing properties of a promising insulin plant and to explore its therapeutic potential.

Keywords: Insulin plant, anti-diabetic activity, hypolipidemic, antioxidant, antiurolithiatic.

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I. INTRODUCTION

Medicinal herbs have been used since the Vedic times. The Rigveda (4500-1600 B.C.) contains numerous shlokas and hymns written in appreciation of plants and it contains the earliest reference to the use of herbal remedies in India. They were being used to reduce the risk of developing a variety of illnesses, including epidemics, for thousands of years. A few plants are also used as delectable sauces, food preservatives, dyes, and flavours (Bamola *et al*., 2018).

The therapeutic benefits of the plant are almost universal. The medications are either made from the entire plant or from various plant components like leaves, stems, bark, roots, flowers, and seeds, among others. Some are even made from excretory plant materials such as gums, resins, and latex. A significant portion of the modern medical system now offers a variety of plant-derived medications. Plants are also a source of certain significant chemical intermediates used in the production of contemporary medications, such as diosgenin, solasodine, and -ionone. In addition to providing a steady and expanding market on a global scale, plants remain a significant source of novel pharmaceuticals and nutraceuticals (Santosh, 2015).

Phytochemicals are bioactive chemical compounds produced in fruits, vegetables, grains and other plant foods through primary and secondary metabolism and are called as primary and secondary metabolites. Although these secondary metabolites are, in theory, not necessary for existence, they unquestionably help ensure the fitness and survival of the species as a whole. In order to utilise them now and in the future, plants make secondary metabolites and store them in a variety of organs, including leaves, roots, stems, bark, flowers, and fruits. Based on their chemical makeup, these secondary metabolites are categorised as steroids, terpenoids, flavonoids, glycosides, alkaloids, etc. These different naturally occurring substances found in plants have a significant therapeutic efficacy and can affect nearly all bodily systems (Santosh, 2015). These phytochemicals offer notable medicinal properties that include antidiabetic, anti-oxidative, anti-allergic, antibiotic and anti-carcinogenic properties.

Costus igneus Nak, also known as the blazing *Costus*, Step ladder, Spiral flag or Insulin plant, is a native of South and Central America. Its synonyms are *Costus pictus* D. Don, *Costus mexicanus* Liebm ex Petersen, or *Costus congenitus* Rowle. This is a new American import to India as a natural treatment for diabetes, hence the widespread name "insulin plant" (Jose and Reddy, 2012). In South India, it is a common ornamental plant grown in gardens, but also naturally grows in various locations (Benny, 2004). In India, it is employed to treat diabetes, and it is widely accepted that diabetics should consume at least one leaf every day to keep normal blood sugar levels. (Devi and Urooj, 2008).

The "insulin plant," or *Costus pictus*, has a huge spectrum of significant bioactive components, including hepatoprotective, antioxidant, anti-cancer, anti-inflammatory and anti-diabetic properties. The presence of numerous phytochemicals, especially flavonoids and phenolic substances, contributes to its distinctive properties (Selvakumarasamy *et al*., 2021). As a result, the focus of the current research is on discussing the medicinal benefits of *C. pictus* and the mechanisms underlying these encouraging outcomes.

II. MORPHOLOGY OF INSULIN PLANT

Tropical, upright, perennial plant belonging to the *Costaceae* family is called *Costus igneus*. It has simple, alternating, whole, oblong, evergreen leaves that range in length from 4 to 8 inches and have a parallel venation system. The tree's enormous, velvety, dark-green leaves are spirally coiled around the stems in elegant, arching bunches that emerge from underground rootstocks. The leaves have light purple undersides. The tallest stems can reach a elevation of 60 cm before bending over and lying dead. On cone-like crowns at the ends of branches, stunning orange blooms with a 2.5–12.5 cm diameter are produced on hot days. Stem cutting is used in the multiplication of insulin plants. Common names include the Insulin plant, Stepladder, Fiery Costus, Spiral Flag, and Spiral Ginger (Harini *et al*., 2016). 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.

III. MEDICINAL PROPERTIES OF INSULIN PLANT

Costus pictus has been used as a medicinal herb for centuries, primarily for its tonic, stimulant, carminative, diuretic, digestive and antiseptic properties (Sivarajan and Balachandran, 1994). Various parts of the medicinal plant *Costus* species are used to treat a variety of diseases.

The leaves of the insulin plan have a high hypoglycemic potential. The stem has been shown to have significant antiurolithiatic activity. Besides, significant antioxidant activity has been demonstrated in both the stem and the root (Meti, 2018). The rhizome of the insulin plant has a variety of medicinal properties, including bitterness, astringency, cooling, stimulant, laxative, antiparasitic, detoxifying, and cough suppressant. It can also be used to treat wounds, bowel problems, Hansen's disease, intestinal parasites, skin lesions, pyrexia, breathing problems, bronchitis, inflammations, and anaemia. (Urooj and Devi, 2010).

Table 1: Major Components 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)		

Internally, the rhizome is used to treat abdominal discomfort, heart palpitations, liver problems, jaundice, gall bladder pain and other ailments (Sivarajan and Balachandran, 1994). *Costus pictus* rhizomes are used to treat colds, pneumonia, and rheumatism in India. It is used in Southeast Asia to cure diarrhoea and vomiting, lightheadedness, headache, and ear, eye and nose pain. The rhizome extract was used by the Japanese to treat syphilis (Khare, 2007).

Costus pictus leaves and rhizomes are said to contain a steroid called diosgenin, which is anti-diabetic and used to treat type 2 diabetes. In glucose-fed mice, a methanolic extract of insulin plant leaf (200mg/kg, 500mg/kg b.w.) demonstrated significant hypoglycemic activity (Shiny *et al*., 2013). In addition to lowering blood glucose, the medicinal preparation has insulin-potentiating properties. Table 1 outlines the major components recognised in essential oil.

IV. ANTIDIABETIC ACTIVITY

The insulin plant is a medicinal plant that is also a common ornamental plant in the gardens of south India. One of the crucial plant parts is the leaves, generating high anti-diabetic activity. It lowers both fasting as well as post-meal blood sugar levels. The anti-diabetic property's exact mode of action, however, remains unknown. Along with the hypoglycemic effect, insulin plant lowers the likelihood of type 1 & 2 diabetic complications, stabilises kidney and liver functions, lowers HbA1c levels, maintains a balanced lipid metabolism, raises insulin levels, and significantly improves histopathological inspection. (Mathew and Varghese, 2019).

Chowdary *et al*. (2020) formulated a nutritionally rich cookie with *Costus igneus* leaf extract and determined the effect of cookie consumption on decreasing blood glucose levels in type 2 diabetic patients. A sample of 30 patients suffering from type 2 diabetes was chosen whose blood glucose levels were tested on the 1st, 15th day and 30th day of cookie consumption. The developed cookies were analysed for proximate and physicochemical properties and revealed that it contained high amounts of secondary metabolites, including antioxidant compounds. The average level of FBS and PBS in all four groups declined substantially from day 0 to day 30, implying that *C.igneus* cookies consumption had a good effect on controlling blood sugar levels. Moreover, in all four study groups, HbA1C was reduced by one unit.

Shetty *et al*. (2010) analyzed glycaemic control in diabetic patients who had been consuming insulin plant leaves and tried to determine the adverse effects/benefits of its intake. All thirty patients either took one fresh leaf or one tea-spoon full of shade dried insulin plant leaf powder on an empty stomach in the early hours without discontinuing their previous diabetes treatments. The results showed that the fasting blood sugar levels were lowered in all thirty patients. The insulin leaf therapy was found to be beneficial as early as day fifteen. Intake of the leaves for a longer period of time continued to improve glycaemic control. The glycaemic control on the 60th day was better than on the 15th and 30th days. Moreover, the problem of non-healing ulcers and recurrent urinary tract was resolved in patients between 15 to 60 days of leaf consumption. Besides, cataract surgery could be performed successfully after fifteen days of treatment with insulin plant leaves. In all 12 insulin-treated patients, the dose of insulin could be cut in half while the glucose levels are better controlled in patients who were on oral hypoglycaemic drugs. As a result, the patients continued to consume the leaves as it was beneficial for glycaemic control as well as protecting them from the development of diabetic comorbidities like neuropathy, retinopathy, nephropathy etc.

Al-Romaiyan *et al*. (2010) estimated the impact of aqueous *C.pictus* extract on insulin release *in vitro* from the MIN6 β-cell line and secluded mouse and human islets. The findings suggest that C. Pictus increases -cell intracellular Ca2+ levels, which has a significant triggering effect on insulin production. This effect is entirely reversed by eliminating extracellular Ca2+ or inhibiting voltage-gated Ca2+ channels (VGCC). These in vitro data indicated that one of CP's actions is to increase insulin production, which may be usually affected by *C. pictus's* capacity to raise (Ca2+) levels through voltage-gated channels. C. pictus extracts may be a feasible and inexpensive solution as a therapy for type 2 diabetes. Shiny *et al*. (2013) evaluated the presence of phytochemical components and anti-diabetic potential of *C.pictus* plants from Kerala and Tamilnadu. A total of 24 extracts were made from three plant materials like rhizome, stem and leaf from both regions employing various solvents like hexane, ethyl acetate, methanol and water. The preliminary phytochemical screening revealed a high degree of resemblance in the presence or absence of chemical constituents in all 24 extracts of selected three samples from both regions. However, the methanol extract at the rate of 200mg/kg and 500mg/kg body weight of the plant leaf demonstrated significant glucose-lowering activity in mice fed with glucose. The research shows that C. pictus can be grown on a large scale in a variety of locational contexts since the phytochemical profile is almost steady with exogenous conditions.

Mechanism of action: Chronic hyperglycemia affects how people generally metabolise carbohydrates, proteins, and fats. It causes the ailment known as "Diabetes mellitus." Hyperglycemia may result from dysfunctional insulin, aberrant insulin production, or both. Type 1 diabetes is also called insulin-dependent diabetes as such patients lack beta cells and are insulin insufficient and thus completely rely on exogenous insulin. Insulin resistance is a term used to describe the condition of type 2 diabetes. Diabetes had elevated to the top medical issue due to its rising prevalence. Despite the availability of numerous medications to lower blood sugar, the long-term use and negative effects pose a serious hazard to humankind. The tendency toward herbal medicine was a result of these. Numerous local plants have been claimed to be successful in managing diabetes (Selvakumaraswamy *et al*., 2021).

Diabetes inhibits the liver's ability to use glucose, which lowers the amount of hepatic glycogen. Extracts of *C. pictus* facilitated the entry of calcium ions into the beta cells of the pancreas with the help of voltage-gated calcium channels. As a result, the amount of insulin secreted by the glucose-insensitive -cells in diabetes patients increased. These extracts reduced the phosphorylation of the proteins protein kinase C (PKC) and extracellular signal-regulated kinase (ERK), decreasing inflammatory cytokines and improving insulin resistance. Hence, *C.pictus* can act as a non-toxic & viable plant-based substitute for synthetic medications. The methanolic extract of *C. pictus* leaves prevented hyperglycemia-induced muscular tissue damage and increased body weight. Methyl tetracosanoate raised the expression of GLUT4 mRNA and inhibited the PTP1B enzyme which subsequently impacted insulin sensitivity. (Ashwini *et al*., 2015).

Significant amounts of bioactive compounds were found in insulin plant leaves. Tri-terpenoids primarily work by obstructing alpha-glucosidase and alpha-amylase activity, which slows down the absorption of carbs in the intestine and lowers postprandial insulin levels 40. It results in the correction of plasma glucose, insulin levels, glucose metabolism, and insulin resistance. Corosolic acid aids in the absorption of glucose. Diosgenin which is a steroid present in insulin plants reduces the efficiency of diabetes-related enzymes like ATP-citrate lyase, pyruvate kinase, and glucose -6-phosphate dehydrogenase in the liver of diabetic rats. It increases pancreatic insulin secretion, which in turn causes plasma insulin levels to rise and blood glucose levels to be managed. It also aids in the repair of partially destroyed beta-cells. In addition, stigmasterol prevents beta-cell dysfunction brought on by glucolipotoxicity by reducing LDL-induced pro-inflammatory cytokine release and increasing cholesterol efflux. Because too much cholesterol may contribute to beta cell failure, glucolipotoxicity decreases insulin production by causing it to accumulate (Laha and Paul, 2019). By decreasing the buildup of free cholesterol and reactive oxygen species (ROS), enhancing insulin production, and raising insulin context, stigmasterol shields pancreatic beta cells from the harmful effects of glucolipids (Manjula *et al*., 2013).

The insulin plant provides beta-sitosterol, another anti-diabetic component. Fasting plasma insulin levels rise as a result. A rise in the glucose-triggered release of insulin enhances the oral glucose tolerance test. Additionally, it induces adipogenesis in differentiating preadipocytes and boosts glucose absorption in adipocytes. It inhibits GLUT4 similarly to insulin, albeit no clinical studies have been done so far. (Behera *et al*., 2017).

Table 2: Major Compounds Isolated from Costus Igneus Showing Anti-Diabetic Activity

Name of the Compounds	Activities
Triterpenoid (Corosolic acid)	Increases glucose entry into the cell
Steroid (Diosgenin)	Antidiabetic activity
Steroid (β- sitosterol)	Raises the amount of plasma insulin and the amount of glucose that enters the cell.
Flavonoid (Quercetin)	Increases the amount of glucose taken up by the cell, insulin and the activity of antioxidant enzymes
Phenol (catechin)	α- glucosidase and antioxidant activity inhibition
Insulin like protein	Antidiabetic activity
Fatty acid (Oleic acid)	Antidiabetic activity

Source: Laha and Paul, 2019

V. HYPOLIPIDEMIC ACTIVITY

Kanivalan *et al*. (2014) explored the hypoglycemic and hypolipidemic activity of *Costus igneus* leaf extract on Streptozotocin (STZ) induced diabetic albino rats. The treatment led to a significant increase in blood glucose levels as well as modifications in lipid profile, haemoglobin and insulin levels. This could be due to the excess of hepatic glycogenolysis and gluconeogenesis and decreased glucose uptake by tissues. The administration of ethanolic extract of the leaf to rats for twenty-eight days at the rate of 200 and 300mg/kg body weight caused a significant reduction in glucose levels, recovered haemoglobin, lipid profile and insulin.

Chacko *et al*. (2012) looked into the antihyperlipidemic activity of *Costus igneus* in Triton X-100-induced hyperlipidemic rats. Hyperlipidemic rats were given *Costus igneus* extract at different doses of 100mg/kg, 200mg/kg, and 400mg/kg daily for 1 week. The reference standard used was atorvastatin. At a dose of 400mg/kg (p.o), *Costus igneus* significantly reduced serum cholesterol, triglycerides, LDL, VLDL, and significantly increased serum HDL levels in Triton-induced hyperlipidemic rats. In 400mg/kg extract treated animals, there is also a substantial improvement in atherogenic index. As a result, it effectively suppressed Triton-induced hyperlipidemia in rats, implying a possible defensive function in Coronary heart disease.

1. **Mechanism of action:** Hyperlipidemia emerges as a result of abnormal glucose, fat, and protein metabolism in diabetes. A biochemical situation that is highly desired for the prevention of atherosclerosis and ischemia circumstances is a significant reduction in total cholesterol. Reduced cholesterogenesis and fatty acid production may be the origin of the hypolipidemic impact of insulin plant. A highly ideal biochemical situation for preventing atherosclerosis and is chaemia is a considerable reduction in total cholesterol and an increase in HDL cholesterol (Luc and Fruchart, 1991).

2. **Antioxidant activity:** Shivaprakash *et al*. (2014) assessed the antioxidant potential of *C.igneus* leaves in albino rats subjected to ethanol-induced peroxidative damage. Four groups of Wistar albino rats of either sex was formed. Group I was the control group and received normal saline, Group II ethanol, Group III test drug CI at 300 mg/kg, and Group IV CI at 600 mg/kg for 30 days. The results after antioxidants estimation revealed that in the ethanol-treated group, levels of reduced glutathione, superoxide dismutase, catalase and malondialdehyde were significantly lower than in the control group. Reduced glutathione, SOD and catalase enzyme levels recovered completely in a dose-dependent manner. As a result, *Costus igneus* has the potential to boost antioxidant defence and thus prevent oxidative stress injury.

   The current study was carried out by Kripa *et al*. (2014) employing an *in vitro* model of lipopolysaccharide-persuaded human peripheral blood mononuclear cells and a carrageenan-induced rat model, researchers examined the mechanism of pro-inflammatory action of β-amyrin extracted from *C. igneus* leaves. At a dosage of 100 mg/kg body weight in methanolic extract, the differential fractionation of *C. igneus* leaves showed the best percentage suppression of paw edema (MEC). When compared to the carrageenan control, MEC inhibited cyclooxygenase (COX), lipoxygenase (LOX), myeloperoxidase (MPO) and nitric oxide synthase (NOS) activities in monocytes. MEC had an intense effect than the standard drug Diclofenac (20 mg/kg body weight).

3. **Mechanism of action:** Free radicals, also known as reactive oxygen species (ROS), are byproducts of cellular respiration and include substances like nitric oxide, super oxide, peroxyl radicals, and hydroxyl radicals. Many diseases, including cancer, neurological disorders, cardiovascular diseases, alcohol-induced liver disease, Alzheimer's disease, atherosclerosis, and ageing, are caused by free radicals. Under typical circumstances, antioxidant enzymes including glutathione peroxidase, superoxide dismutase, and catalase work to naturally remove ROS from the human body. Some non-enzymatic substances, such as ascorbic acid, vitamin E, beta-carotene and selenium, also help mitigate ROS’s effects. Due to the broad variety of phytochemicals found in plants, dietary antioxidants derived from plants became the newest area of research (Selvakumaraswamy *et al*., 2021).

   The leaf extracts' ability to prevent hyperglycemic oxidative damage was demonstrated by the fact that when provided, they restored the levels of glutathione S-transferase, glutathione peroxidase, superoxide dismutase and catalase enzymes. *C. pictus* rhizomes also demonstrated antioxidant action (Majumdar and Parihar, 2012). Diosgenin in rhizomes was responsible for the protection of cell membranes from peroxidation of polyunsaturated fatty acids. *C.pictus* leaves contain flavonoids like quercetin (also found in onions) that had a strong antioxidant effect (Son *et al*., 2007). This was caused by its ability to scavenge superoxide radicals and inhibit xanthine oxidase. The structural chemistry of polyphenols is optimal for their capacity to scavenge free radicals. It prevents the formation of metal-catalyzed free radicals by exhibiting chelation properties predominantly for iron and copper. (Rice-Evans *et al*., 1996).

VI. ANTIUROLITHIATIC ACTIVITY

Yuvarani *et al*. (2017) probed the inhibitory action of *C.igneus* aqueous extract on the development of calcium hydrogen phosphate dihydrate (CHPD) crystals. CHPD crystals were grown using the single diffusion gel growth method. The results of the investigation demonstrate that the weight of the CHPD crystals fell from 2.03 g to 0.06 g in leaves, 0.05 g in the rhizome and 0.03 g in the stem when the quantity of aqueous leaf extract of *C.igneus* rose. Fourier Transform Infrared Spectroscopy (FTIR) was used to confirm the functional groups, and Powder X-Ray Diffraction Technique (XRD) was used to confirm the crystalline phases of the CHPD and hydroxyapatite (HAP) crystals. All three sections of *C.igneus* namely leaves, stems and rhizome were found to have the potential to block the formation of calcium hydrogen phosphate dihydrate crystals. This research proves that an aqueous extract of *C.igneus* stem and rhizome can facilitate the growth of hydroxyapatite (HAP) crystals while decreasing the nucleation rate of CHPD crystals, a crucial constituent of calcium urinary stones.

Kushagra *et al*. (2020) examined the *in-vitro* anti-urolithic efficacy of a methanolic extract of *Costus igneus* leaves. The amount of calcium oxalate that dissolved in semipermeable egg membrane in the presence of extract was investigated and contrasted with that of the reference medication cystone. The percentages of methanolic extract and the common medication cystone that dissolved were discovered to be 86.12 and 80.34 percent, respectively. According to the findings, the plant can be used to make polyherbal formulations and treat urolithiasis in an efficient manner.

Mechanism of action: The hydroxyapatite (HAP) crystals were ready to develop when the insulin plant extract was added, and it also slows the formation of CHPD crystals, a substantial part of urinary calcium stones (Yuvarani *et al*., 2017).

VII. CONCLUSION

The thorough background illustrates the insulin plant's numerous effects. This plant exhibits a complex identity despite frequently being praised for its antidiabetic activity because of the large variety of potent phytochemicals it contains. The potential of tomorrow is the therapeutic herbs, which were once the customs of antiquity. Today, the transition from nutraceuticals to functional foods is becoming more significant. However, it is crucial to comprehend the internal elements that affect human digestion. Considering the alluring potential of insulin plants and their components, more research is required to fully comprehend their effects on human health. To provide the distinctiveness of functional foods, proper knowledge of the mechanisms and interactions between the ingredients is crucial.

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