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Therapeutic Potential and Pharmacological Applications of Costus pictus D. Don in Cancer: Integrating Traditional Medicine with Contemporary Science

Pawar Sagar Namdeo[1], Ashwini[1], Y. R. Karthik[2], Padmalatha. S. Rai[3*] and Y.L. Ramachandra[1]
1Department of Biotechnology and Bioinformatics, Kuvempu University, JnanaSahyadri, Shankaraghatta, Shivamogga -577 451, Karnataka, India.
2Department of Paediatrics, Shridevi Institute of Medical Sciences and Research Centre, Sira Road, Tumakuru-572106, Karnataka, India.
3*Department of Biotechnology, Manipal School of Life Sciences, Manipal Academy of Higher Education,Manipal-576 104, Karnataka. India

Abstract

Medicinal plants have played an important part in medicinal care throughout history, including modern times. Costus pictus, also referred to as the "insulin plant," has a wide range of noteworthy bioactivities, including hepato protective, antioxidant, anti-cancer, anti-inflammatory, and anti-diabetic properties. Due to its abundance of phytochemicals, particularly flavonoids and phenolic compounds, it possesses diverse qualities. As a result, the focus of this review is on exploring C. pictus therapeutic potential as well as the mechanism of action underlying these encouraging results. A rich profile of bioactive substances, including as glycosides, phenolic acids, steroids, flavonoids, and terpenoids, is shown by phytochemical investigations and supports the plant's wide range of pharmacological effects. C.pictus has long been known to have anti-cancer and anti-diabetic effects. Research has shown that it can improve glycemic control by increasing muscle cell absorption of glucose and stimulating pancreatic beta cell release of insulin. The plant also demonstrates strong antioxidant and anti-inflammatory properties, scavenging free radicals to shield cells from oxidative stress and lowering levels of pro-inflammatory cytokines including TNF-α and IL-6. When relevant, the review provides discrete relevance to the in vivo findings by addressing the phytochemicals that correspond to these effects, leading to a mechanistic explanation from Ayurvedic to modern techniques. Over time, there has been increased interest in the design of functional foods that include medicinal plant supplements. Further research is required to confirm the effects of C. pictus incorporation on foods and to conceptualise dietary intake for the prevention of various illnesses.

Keywords: Traditional medicine, Costus pictus, Pharmacological activity, Bioactive compounds, anti-cancer

Introduction

Since medicinal plants have been used to treat illnesses since prehistoric times, the term "medicinal plants" has been used extensively. The ancient Rig Veda has the earliest descriptions of therapeutic herbs. Due to their pharmacological potency, these plants have remained a global source of medications and natural products. Owing to the growing demands of the worldwide market and the strong interest in ethnopharmacy, natural medicines derived from these therapeutic plants are currently being investigated. Plants created unique natural substances called phytochemicals that gave them evolutionary advantages including enhancing defence mechanisms for the plant. These undergo secondary metabolization. Since their roles in plant metabolism, phytochemicals are divided into primary and secondary components. Common carbohydrates, proteins, and chlorophyll are classified as primary components, while phenolics, alkaloids, and terpenoids are considered secondary components. This increased interest in coordinating plant phytochemicals to their medicinal value. Disease prevention was greatly aided by the consumption of these plants.

Medicinal plants are used as an herbal cure in both developed and developing nations to manage health care; worldwide, 80% of the population relies on traditional medicine, which includes homoeopathy, naturopathy, Ayurveda, and Unani, which have been key sources of medicine since ancient times to treat various disorders. Large-scale natural products made from plants that have drawn the attention of several researchers because they have little or no negative consequences.

C. pictus, also referred to as "Fiery Costus," "Step Ladder," "Spiral Flag," or "Insulin Plant," is a native of South and Central America. It was recently introduced to India due to its valuable medicinal properties, including the ability to cure diabetes by consuming leaves orally every day. The plant is most widely used in Kerala for both decorative and everyday culinary purposes [1]. There is a wide distribution of *Costus* species across the world's tropical regions. It has been observed in India in the Western Ghats, in parts of central India, and in the sub-Himalayan range. *C. pictus*was first employed in traditional medicine due to its antibacterial, diuretic, and carminative qualities. The leaves were a useful tool in the management of diabetes. Rhizomes were utilised to

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treat a variety of illnesses. While the Japanese used it to treat syphilis, people in Southeast Asia used it to treat vomiting, headaches, and diarrhoea. It was used to treat rheumatism and pneumonia in India [2].

History of *C.pictus*

Taxonomy

Kingdom	: Plantae
Phylum	: Tracheophyta
Class	: Liliopsida
Order	: Zingiberales
Family	: Costaceae
Genus	: *Costus*
Species	: *C. pictus*

Earlier, all *Costus* plants were classified under Zingiberaceae. Later, after numerous more floras were added, Costaceae were divided into a subfamily within Zingiberaceae called Costoideae. A new family of Costaceae was formed from the Zingiberaceae family, which explained the rationale behind classifying Costaceae as a distinct family. This was followed by the addition of genera such as Dimerocostus, Monocostus, and Tapeinochilus to the genus *Costus*. The *Costus* species' transition from a genus to a family was made possible by the peculiarity of its leaf and root architecture. Because of its unique monistichous spiral phyllotaxy, the Costaceae family of Zingiberales could be easily identified from the other families.The four genera that comprised the earlier Costaceae were *Costus*, *Monocostus*, *Dimerocostus*, and *Tapeinochilos*. According to recent phylogenetic analyses of the Costaceae, Tapeinochilos, Monocostus, and Dimerocostus all maintained monophyletic lineages, whilst *Costus* was found to be polyphyletic. The taxonomic categorization was revised because of this. To balance the taxonomy within the phylogeny, three new genera-Paracostus, Cheilocostus, and Chamaecostus-were separated from *Costus.*

C. pictus is a perennial herb with rhizomatous roots. This is grown, ideally in the shade, on rich, moist soils. It grows best in a tropical area with high humidity and temperatures of about 13°C. The leaves are oblong-lanceolate in shape and have a straightforward spiral arrangement. A leaf's typical length is between 10 and 25 cm, while its typical breadth is between 2.5 and 6 cm. A leaf's midrib was visible when it was cut transversely. It is made up of thick epidermal cells on the abaxial side and a thin layer of epidermal cells on the adaxial side. Small, square-shaped cells make up the thin layer, while cylindrical epidermal cells were visible in the thick layer. The vascular system in the midrib is composed of one median bundle on the adaxial side and three abaxial vascular bundles. On the other hand, the lamina showed that the adaxial side of the epidermis has a dense, cylindrical layer of epidermal cells, whereas the abaxial side of the epidermis has thin, tubular cells. While the abaxial side of the epidermis is stomatiferous, the adaxial side is apostomatic. In *C. pictus*, hexacytic stomata are observed. The cortical bundle is made up of tiny phloem clusters scattered across the upper edge of the leaf and thin-walled xylem vessels [3]. The internode measured 2.5–5 cm in length. The sections from which new branches emerge are called rhizomes. Rhizomes are thick, horizontal subterranean sections that, in the right growth conditions, can spread up to three feet in width in just two years. Rhizomes were the primary vegetative means of reproduction for *C. pictus*, while stem cuttings may also be useful. Given the poor germination rate of the seed, germination had little effect [4]. Bracts of green colour surround yellow blooms with red stripes. Only in the late summer did flowers appear. Typically, flowering started in July and lasted until September. Cone-shaped bracts took centre stage later, as the blooms faded. Fruits stayed unnoticeable. The tiny, black seeds have a white, fleshy aril.

Among its many medicinal qualities, *C. pictus* primarily has anti-diabetic qualities. Other qualities include anti-bacterial, anticancerous, diuretic, anti-helminthic, antioxidant, anti-fertility, and anti-glycation effects [5]. In addition to this, *C. pictus* leaves' methanol and ethanolic extract is known to have a strong enzymatic effect on pepsin, α amylase, mitochondrial enzymes, and enzymes that hydrolyze carbohydrates, as well as to stimulate the generation of insulin. The primary bioactive component of leaves, methyl tetracosonoate, is revealed by phytochemical analysis to function as a precursor for the synthesis of bixin and as an antidiabetic agent. Along with trace elements, the rhizome, stem, and flowers are rich in primary and secondary metabolites, including alkaloids, flavonoids, phenolics, saponins, terpenoids, tannins, and steroids. According to pharmacoepidemiologic surveys and clinical trials on animal cells line *in-vitro* and *in-vivo* research, *C. pictus* is now well recognised as an anti-diabetic plant. Eating one leaf per day is reported to lower blood glucose levels (Biospectrum 2013). Because of the increasing daily utilisation of this plant, mass production and in-vitro propagation have been conducted.

Health promoting effects of *Costus pictus:*

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There is a wealth of evidence to support the role that diet plays in managing disease. There have been reports that some diets can help avoid certain ailments. Drinking green tea helped to slow down the ageing process and prevented Alzheimer's. In a similar vein, eating a Mediterranean diet reduced the risk of heart disease and cancer. These impacts on intake are largely, or at least partially, attributed to the phytochemicals. The insulin plant has been the focus of numerous studies aiming at examining its potential to promote health because it possesses a wide variety of phytochemicals. Due to the presence of main and minor phytochemical constituents as primary and secondary metabolites, *C. Pictus* utilised a folk medicine to cure a variety of chronic ailments. Numerous researchers identify and characterise the chemical and bioactive components in the *C. Pictus* for the treatment of major diseases which shows biological activity.

Sl No	Compounds	Properties	References
1	Quercetin	Anti-diabetic effects	[6]
		Antioxidant property	[7]
		Anti-cancer property	[8]
		Anti-inflammatory effects	[9]
		Hepatoprotective property	[10]
2	Astragalin	Antioxidant property	[11]
		Anti-inflammatory effects	[12]
3	Kaempferol	Anti-cancer property	[13]
		Anti-inflammatory effects	[14]
4	**Licochalcone *A***	Anti-cancer property	[15]
	Gentisic acid	Antioxidant property	[7]
		Anti-cancer property	[15]
		Anti-inflammatory effects	[16]

Anti-cancer activity:

One of the most common diseases affecting people nowadays is cancer, and finding novel anticancer drugs is of great scientific interest. Many naturally occurring anticancer drugs were found when the anticancer potential of natural sources was identified in the 1950s. To effectively treat tumours, a few plant-based chemotherapeutic medications, including vinblastine, taxol, camptothecin, and podophyllotoxin, have been created. The fibrosarcoma HT-1080 cell line was subjected to anticancer activities by the leaves of *C. pictus*. While normal lymphocytes showed no cytotoxic effects, fibrosarcoma cells were found to be susceptible to the anti-proliferative and cytotoxic actions of the ethanolic extract, even at lower concentrations. The *C. pictus* leaves' anticancer properties were also assessed using MCF-7 breast cancer cell lines. Leaf extracts from petroleum ether, ethanol, and water all slowed the growth rate, which in turn decreased the MCF-7 cells' ability to survive [17]. Hep G2 liver hepatocellular cancer cells were cytotoxically affected by the methanolic leaf extracts of *C. pictus*. The direct ionic contact between the active plant components and the zinc-dependent active site of the histone deacetylase (HDAC) enzyme was the cause of the inhibitory impact. The active region of this enzyme features a zinc domain that is highly conserved. The epigenetic regulation of gene expression approach, which has recently been identified as a cutting-edge cancer treatment strategy, depends heavily on HDAC. According to [18], HDAC inhibitors are acknowledged as possible anticancer medicines because tumour cells exhibit elevated levels of this enzyme.

Anti-diabetic effect

Chronic hyperglycemia affects how people generally metabolise fat, protein, and carbohydrates. It results in the development of "*Diabetesmellitus*." Insulin malfunction, aberrant insulin production, or both may be the cause of hyperglycemia. Because there are no functioning beta cells in the body, type I diabetes is entirely insulin-dependent and is characterised by insulin insufficiency. Type 2 diabetes is described as a condition of insulin resistance. Type 2 diabetes is more prevalent in humans. With increasing incidence, diabetes had become the major concern in the field of medicine. In spite of many glucose lowering drugs, the prolonged usage and side effects pose a great threat to mankind. These resulted in the inclination towards herbal medicine.

Human blood glucose levels were shown to decrease when *C. pictus* leaves were given at dosages of 500 to 2000 mg daily. On rats given diabetes, the methanolic leaf extracts of *C. pictus* also showed anti-diabetic properties. These extracts increased insulin secretion, which amplified its effects. An increase in the amount of insulin in the bloodstream has an antihyperglycemic effect. Furthermore, the liver's ability to use glucose is restricted in diabetes conditions, which lowers the amount of glycogen stored in the liver.

According to some of the scientists [19], the extracts from *C. pictus* enhanced the influx of calcium ions (Ca2+) into the β-cells of pancreatic islets by means of voltage-gated calcium channels. Patients with diabetes experienced an increase in insulin release from their glucose-unresponsive β-cells as a result. Additionally, they investigated the molecular mechanism behind the *C. pictus* extracts' induction of insulin sensitivity. The phosphorylation of protein kinase C (PKC) θ and extracellular signal-regulated kinase (ERK) was decreased by these extracts, leading to an increase in insulin sensitivity and a downregulation of inflammatory cytokines. These demonstrated that, in contrast to manufactured medications, it might be a useful herbal cure. The extracts were also shown to be non-toxic. Because of the anti-diabetic properties of the methanolic extract of *C. pictus* leaves and their ability to prevent damage to muscle tissues brought on by a hyperglycaemic state, *C. pictus* extracts also improved body weight. They discovered an active substance called methyl tetracosanoate, which inhibited the PTP1B enzyme and increased the expression of GLUT4 mRNA. These led to an upregulation of PI3K and IRβ protein expression, which in turn affected insulin sensitivity. High quantities of flavonoids, including isoquercetin, astragalin, kaempferol, and quercetin, were found in the leaves of *C. pictus*. Fig. 1 shows the mechanism to produce flavonoids, kaempferol, and quercetin.

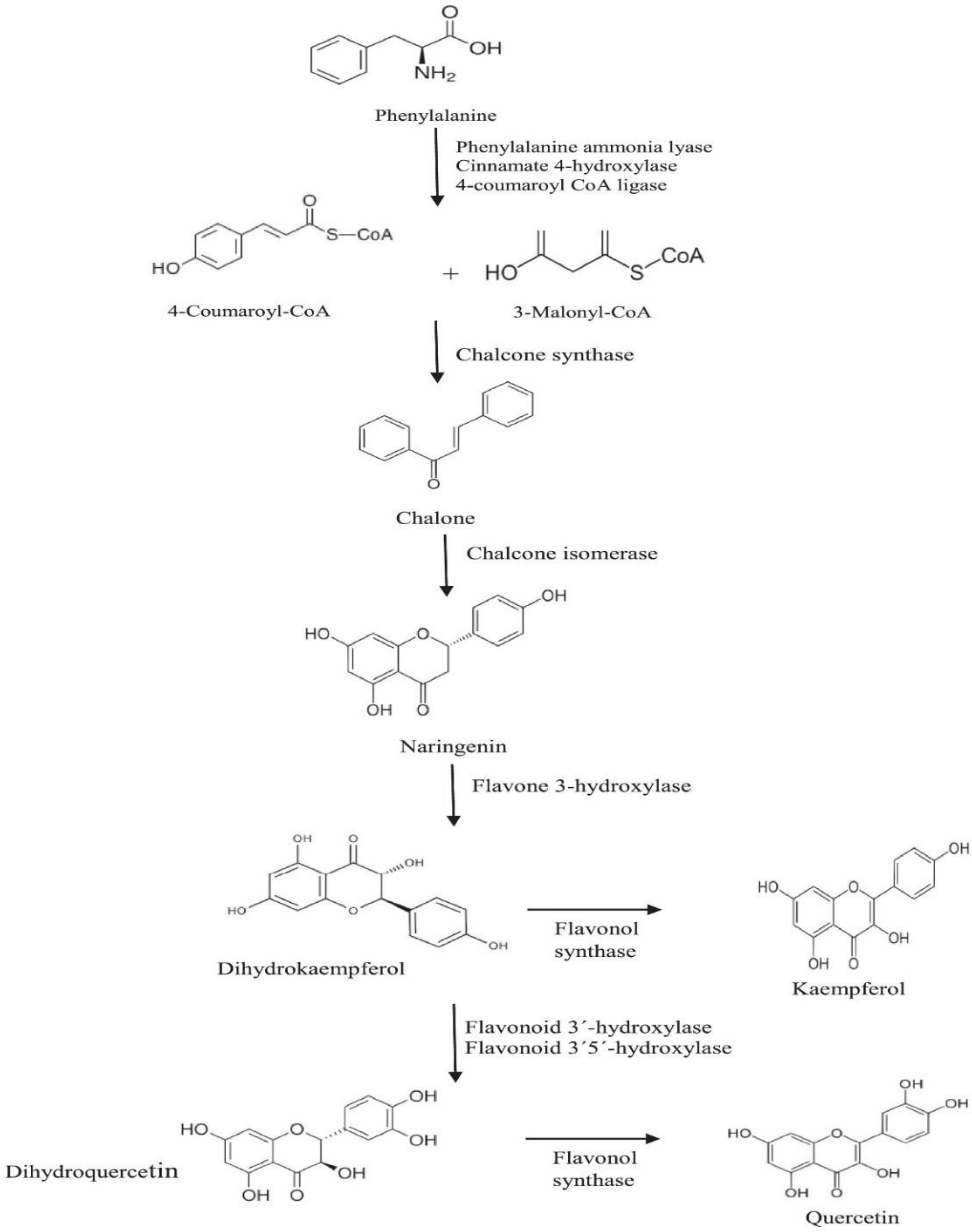

Fig. 1. Pathway for the formation of quercetin and kaempferol.

Quercetin generally promoted the anti-diabetic effects by stimulating the release of insulin and regenerating the pancreatic β-cells. Scientist [20] reported that daucosterol (β-sitosterol-3-O-β-D-glucoside), which was extracted

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from *C. pictus* leaves, exhibited anti-hyperglycemic properties. One steroidal sapogenin that is abundant in the rhizomes of *C. pictus* is called diosgenin. Anti-diabetic properties were demonstrated by diosgenin [21]. The terpenoids and glycosides found in *C. pictus* leaves are listed in Table 2.

Table 2. Summary of the major bioactive properties of glycosides and terpenoids associated with *C. pictus* leaves.

Sl No	**Compounds**	Properties	Refs.
	GLYCOSIDES		
	Daucosterol (β-sitosterol-3-*O*-β-D-glucoside)	Anti-diabetic effects	[20]
		Neuroprotective effects	[22]
	TRITERPENOIDS		
	α-amyrin	Antioxidant property	[23]
		Anti-inflammatory effects	[24]
	β-amyrin	Antioxidant property	[23]
	Empty Cell	Anti-inflammatory effects	[24]

Antioxidant activity

Reactive oxygen species (ROS), also known as free radicals, are produced as byproducts of cellular respiration. Examples of ROS include nitric oxide, super oxide, peroxyl radicals, and hydroxyl radicals. Oxidative stress can result from the oxidation of proteins, lipids, and nucleic acids. Numerous diseases, including cancer, neurological disorders, cardiovascular diseases, alcohol-induced liver disease, Alzheimer's disease, atherosclerosis, and ageing, are caused by free radicals. Under normal circumstances, antioxidant enzymes including glutathione peroxidase, catalase, and superoxide dismutase help the human body naturally remove reactive oxygen species (ROS). Certain non-enzymatic substances, including as selenium, α-tocopherol, and vitamin C, also support defence against ROS. Because of their extensive range of phytochemicals, plant-based dietary antioxidants thus emerged as the new area of focus.

C. pictus leaves were found to have antioxidant activity [25]. The strongest antioxidant activity was seen in methanolic extracts. He also mentioned the presence of antioxidants in flowers and stems. The liver's levels of aspartate amino transferase, alanine amino transferase, and alkaline phosphatase increased whereas the key antioxidant enzymes, such as glutathione S-transferase, glutathione peroxidase, superoxide dismutase, and catalase, decreased because of external stimulation. When the leaf extracts were given, all those marker enzyme levels returned, demonstrating their potential to reduce hyperglycaemic oxidative damage. The rhizomes of *C. pictus* were also observed to have antioxidant action.

Numerous phytochemical substances, including alkaloids, glycosides, tannins, phenols, steroids, terpenoids, and flavonoids, were identified in *C. pictus*. Table 3 lists the biological characteristics of the flavonoids and phenolics found in *C. pictus* rhizomes. Diosgenin from rhizomes disrupted the order of lipid peroxidation in cell membranes, shielding them from the oxidative stress caused by polyunsaturated fatty acids [26]. Quercetin, a flavonoid found in *C. pictus* leaves, shown a strong antioxidant potential. Its ability to scavenge superoxide radicals and inhibit xanthine oxidase was the cause of this. The structural chemistry of polyphenols is perfect for their ability to scavenge radicals. Because of its propensity for metal chelation, particularly with iron and copper, it prevented the production of free radicals that were catalysed by metals [7].

Table 3. Summary of the major bioactive properties of the compounds associated with *C. pictus rhizomes.*

Sl No	**Compounds**	**Properties**	**Refs.**
	FLAVONOIDS		
	Quercetin	Anti-diabetic effects	[27]
		Antioxidant property	[7]
		Anti-cancer property	[8]
		Anti-inflammatory effects	[28]
		Hepatoprotective property	[29]
	Diosgenin	Anti-diabetic effects	[21]

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		Antioxidant property	[26]

Anti-inflammatory activity
Despite its significance for the immune response, the inflammatory process is the root cause of many chronic illnesses, including diabetes, arthritis, cardiovascular disease, and other inflammatory diseases. To treat inflammatory illnesses, herbal remedies have become increasingly important as synthetic pharmaceuticals have various harmful side effects. There has been evidence of anti-inflammatory properties in *C. pictus* leaves. These extracts reduced the levels of pro-inflammatory cytokines, including tumour necrosis factor-α and C-reactive protein, by inhibiting the components linked to the stress-sensitive signalling cascade. Additionally, it suppressed the expression of monocyte chemotactic protein and interleukin 6 (IL-6). The elevated insulin resistance caused by inflammatory cytokines can result in several problems, including obesity, diabetes, and metabolic syndrome [19]. One possible explanation for the anti-inflammatory effect could be the abundance of phenolic chemicals found in *C pictus* leaves. It has been shown that flavonoids, and quercetin in particular, can lower low-grade inflammation. Quercetin inhibits the NF-κB and ERK cascades, which lowers the gene expression of TNF-α in blood mononuclear cells. Researchers found that quercetin also inhibits lipoxygenase and cyclooxygenase, two enzymes that cause inflammation [30].

Antimicrobial potential
The investigation of therapeutic plants has been expedited by the emergence of new illnesses and the developme nt of antibiotic resistance brought about by bacteria. The leaf, stem, root and flower extracts of *C. pictus* were tested against *Escherichia coli, Klebsiella pneumoniae, Shigella flexnerii, and Bacillus subtilis*[25].According to their findings, the methanolic extracts exhibited a superior zone of inhibit ion in comparison to the aqueous extracts. Furthermore, methanolic root extract showed a superior zone of inhibition for *Shigella flexnerii*, whereas methanolic leaf extracts had the highest inhibition against *Escherichia coli, Klebsiella pneumoniae, and Bacillus subtilis*.

The antimicrobial activity of *C. pictus* aqueous leaf extracts were reported [31] against the following pathogens: methicillin-resistant *Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis*, Multidrug resistant (MDR) *P. aeruginosa,* MDR K. pneumoniae, E. coli producing extended spectrum beta-lactamases (ESBL). In comparison to the non-resistant strains, these resistant strains had noteworthy outcomes at higher doses. It was also examined how effective the essential oils from *C. pictus* leaves were against bacteria. Significant zone of inhibition was demonstrated by them against *Salmonella paratyphi, Bacillus cereus, Enterobacter faecalis, Pseudomonas aeruginosa, Proteus vulgaris, Staphylococcus aureus, and Streptococcus faecalis*. The findings suggested that these essential oils could be used in medication formulations as strong antiseptics. Antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, and Bacillus subtilis* was demonstrated by the rhizome preparations of *C. pictus*. *Bacillussubtilis* was barely affected by rhizome extracts, while *S. aureus* was effectively inhibited [32].

Anti adipogenic activity
The process by which new fat cells arise from their adipocyte precursor fat cells is known as adipogenesis. For the duration of the organism's life, this process is ongoing. But because fat cells are bigger in obese people, the consequences of these things are amplified. Increased levels of markers, such as PPARγ, CCAAT/enhancer binding protein (C/EBP) alpha (C/EBPα), and sterol regulatory element-binding protein 1c (SREBP 1c), were often observed during the development of adipocytes. There was anti-adipogenic action in the methanolic extract of *C. pictus* leaves [33]. Adipogenic markers such PPARγ, C/EBPα, and SREBP 1c showed decreased intensity after being exposed to C. pictus extracts. Additionally, it increased the levels of adiponectin expression. Under normal circumstances, adiponectin levels are higher, but in obese people, the concentration is lower. These demonstrated that *Costuspictus* may be a viable treatment for diabetes brought on by obesity.

Nanoparticles
Because of its unique qualities-such as size, selectivity, and biocompatibility-
nanotechnology has become a spectacular discipline with a wide range of applications.
The use of hazardous chemicals and high expense of chemical synthesis methods led to their demise.Using biolo gical organisms—plants, bacteria, plant biomass, or enzymes—
to synthesise nanoparticles has resulted in a new, economical, and environmentally beneficial method. [34] assessed the anti-diabetic properties of *C pictus* leaf methanolic extract and its silver nanoparticle. When compared to their extracts, the nanoparticles demonstrated superior anti-diabetic benefits. The authors evaluated the effects of their nanoparticles and the methanolic extract of C. pictus leaves. At a given dosage, the nanoparticles showed greater activity than the plant extracts, despite the fact that both the methanolic extracts and their nanoparticles

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displayed antioxidant qualities in a dose-related way. Additionally, the methanolic extracts' silver nanoparticles showed a rise in the flavonoid and phenolic contents, which supported the increase in antioxidant activity.The silver and gold nanoparticles from the *C. pictus* leaf aqueous extract were examined by [35]. Antioxidant qualities were demonstrated by both nanoparticles. Additionally, they reported on the degradation of methylene blue dye, in which aqueous leaf extracts and silver nanoparticles had the highest decrease, followed by gold nanoparticles. These focused on the potential applications of nanoparticles for treating wastewater and purifying water.

The green manufacture of magnesium oxide nanoparticles from *C. pictus* aqueous leaf extract was reported [36]. Hexagonal-shaped nanoparticle production was shown by SEM investigations. These nanoparticles demonstrated notable antifungal activity against *Aspergillus niger* and potent antibacterial activity against *Bacillus subtilis and Salmonella paratyphi.* The nanoparticles demonstrated anticancer properties as well.

Conclusion

The extensive background represents the plant *C. pictus* numerous effects. This plant, though frequently recognized for its hypoglycemic properties, exhibits a complex nature because of its vast array of valuable phytochemicals. The therapeutic herbs that were formerly part of ancient customs are now part of today's future. In the modern day, the transition from nutraceuticals to functional foods is becoming increasingly significant. But the most crucial thing is to comprehend the intrinsic elements that go into human digestion. Considering the intriguing potential of *C. pictus* and its ingredients, more research is required to have a deeper comprehension of their effects on human health. With knowledge of the underlying processes and interrelationships of the components, a suitable phytochemical dosage might be created.

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