

Costus speciosus: Traditional Uses, Phytochemistry, and Therapeutic Potentials

Ali Hafez El-Far, Hazem M. Shaheen¹, Abdel Wahab Alsenosy, Yasser S. El-Sayed², Soad K. Al Jaouni^{3,4}, Shaker A. Mousa⁵

Departments of Biochemistry, ¹Pharmacology and ²Veterinary Forensic Medicine and Toxicology, Faculty of Veterinary Medicine, Damanhour University, Damanhour 22511, Egypt, ³Department of Hematology/ Pediatric Oncology, Faculty of Medicine, King Abdulaziz University, ⁴Yousef Abdulatif Jameel scientific chair of Prophetic Medicine Application, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, ⁵Department of Drug Discovery and Drug Development, Pharmaceutical Research Institute, Albany College of Pharmacy and Health Sciences, Albany, New York, USA

ABSTRACT

Medicinal plants are sources of novel drug discovery targets. *Costus speciosus* is an important medicinal plant widely used for the treatment of various ailments. The plant has multiple active ingredients and has been found to possess many pharmacological activities such as antioxidant, anticancer, anti-inflammatory, antidiabetic, hypolipidemic, hepatoprotective, steroidogenic, adaptogenic, and antimicrobial effects. This review gives an account of unique studies on *C. speciosus* phytochemical, toxicological, and pharmacological studies and traditional uses of *C. speciosus* based on searching the databases of Google Scholar, PubMed, Science Direct, and Springer Link. The previous studies stated the pharmacological potentials of *C. speciosus*, but it is still needed for more research efforts concerning molecular basis of its biological activities, especially *in vivo* models and safety assessment of its different extracts.

Key words: *Costus speciosus*, Islamic traditional medicine, therapeutic potentials

COSTUS SPECIOSUS TRADITIONAL USES AND TAXONOMY

Plant active principles are a source of bioactive molecules that have the potential for being incorporated into novel drugs.^[1] The herbal products somewhat safe in contrast to the synthetics.^[2] A medicinal plant family named *Zingiberaceae* comprises about 52 genera and more than 1300 species distributed throughout tropical Africa, Asia, and Americas. It includes shell gingers (*Alpinia*), summer tulip (*Curcuma alismatifolia*), ginger lily (*Hedychium*), torch ginger (*Etlingera elatior*), ginger (*Zingiber officinale*), turmeric (*Curcuma longa*), and cardamom (*Amomum elevaria*).^[3] *Costus speciosus*, the member of *Zingiberaceae*, is an erect plant of about 2.7 m in height and is root-stock tuberous and stem subwoody.^[4] Taxonomic classification and vernacular names of *C. speciosus* are specified in Table 1.

C. speciosus is among the most effective Islamic traditional medicinal plants.^[5] It has been proven in the authentic Hadith present in Sunan Abi Dawud, the Book of Medicine (Kitab Al-Tibb) in which Umm Qasis, the daughter of Mihsan said: I brought my son to the Messenger of Allah while I had compressed his uvula for its swelling. He said: Why do you afflict your children by squeezing for a swelling in the uvula? Apply this Indian aloeswood (costus), for it contains seven types of remedies,

among them being a treatment for pleurisy. In prophetic medicine, the use of *C. speciosus* was specifically recommended as a remedy for pharyngitis and tonsillitis in children, pleurisy, and as a snake venom antidote.^[6]

In Indian traditional medicine, the *C. speciosus* rhizomes and roots are ascribed to have anthelmintic, anti-inflammatory, antidiabetic, hepatoprotective, antihyperlipidemic, antispasmodic, and antimicrobial activities.^[7,8] Moreover, *C. speciosus* leaf is used as a bath for patients with high fever. Rhizome juice is given traditionally with sugar to treat leprosy and for headache relief.^[9,10] Furthermore, its alkaloid extract is used as a muscle relaxant with an antispasmodic effect.^[11] *C. speciosus* is also used as a plant food in Southeast Asia.^[12]

PHYTOCHEMISTRY OF COSTUS SPECIOSUS

C. speciosus is commonly called "Crepe ginger." Its rhizomes are bitter, astringent, anthelmintic, expectorant, tonic, and aphrodisiac (Warrier *et al.* 1995). Phytochemical screening of *C. speciosus* detected the presence of alkaloids, glycosides, steroids, phenolic,^[1,14] flavonoids, polyphenols, tannins, and β -carotene.^[15] Diosgenin, β -sitosterol, furostanol saponins-costusosides, β -D-glucoside, prosapogenins, dioscin, gracillin, dihydrophytylplastoquinone, and α -tocopherolquinone were isolated from *C. speciosus* and have a wide variety of biological activities,^[16,17] which will be discussed below. Moreover, β -amyrin, camphene, costunolide, diosgenin, α -Humulene, lupeol, and zerumbone for anticancer activity were recognized.^[18-22] The chemical structures of some active principals isolated from different parts of *C. speciosus* are presented in Figure 1.

Correspondence:

Dr. Ali Hafez El-Far,
Department of Biochemistry, Faculty of Veterinary Medicine, Damanhour University, Damanhour 22511, Egypt.
E-mail: ali.elfar@damanhour.edu.eg

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BIOLOGICAL ACTIVITY OF *COSTUS SPECIOSUS*

Different extracts of *C. speciosus* have numerous biological and pharmacological potentials, as evidenced by the traditional practices of *C. speciosus* in various complaints as discussed below and summarized in Figures 2 and 3.

Antioxidant activity

Antioxidants are a group of substances that marked defeat the oxidation processes through scavenging of free radicals and induction of cellular antioxidant enzymes.^[23] Oxygen prefers to accept its electrons one at a time, leading to the generation of reactive oxygen species (ROS).^[24] ROS molecules play an important role in oxidative stress involved in atherosclerosis, cancer, cirrhosis, and diabetes.^[25,26] Oxidative stress is

counteracted by enzymatic antioxidant systems that include a variety of enzymatic scavengers, such as superoxide dismutase (SOD, EC 1.15.1.1), glutathione peroxidase (GPx, EC 1.11.1.9), catalase (CAT, EC 1.11.1.6), and glutathione S-transferases (EC 2.5.1.18) in addition to the nonenzymatic molecules that include ascorbic acid (Vitamin C), α -tocopherol (Vitamin E), glutathione (GSH), and β -carotene.^[27,28]

Phenolics and flavonoids, present in medicinal plants, could provide protection for living organisms against ROS hazards due to their redox properties including free-radical scavenging and strong metal ions chelation.^[29] *In vitro* trials have stated the antioxidant activity of *C. speciosus* methanolic, ethanolic, and chloroform extracts of leaves, stem peel, peeled stem, and roots. The antioxidant activity was assessed with 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid, and thiobarbituric acid (TBA) methods. The methanolic extracts showed more hydroxyl radical scavenging activity and free-radical quenching ability.^[30] This study confirmed the traditional uses of the root and peel of the stem of *C. speciosus* for different diseases and complaints. Further study studies using different solvents such as n-hexane, petroleum ether, and water should be considered. In another *in vitro* study, it was found that *C. speciosus* rhizome methanolic extract had powerful free radical and nitric oxide (NO) scavenging activities in comparison with ascorbic acid and quercetin standards assayed with DPPH and NO scavenging methods.^[31] The authors suggested that the antioxidant effect of the methanolic extract might be owing to the presence of glycosides, flavonoids, triterpenoids, tannins, and steroids. In the same context, *in vitro* evaluation of the antioxidant potential of *C. speciosus* rhizomes was done with different extracts of petroleum ether, cyclohexane, benzene, ethyl acetate, chloroform, acetone, methanol, and water. Some extracts exhibited potent DPPH radical scavenging, total antioxidant capacity (TAC), NO scavenging, ion chelation, and hydroxyl radical scavenging activities that return to the phenolic contents of *C. speciosus*. Among all extracts, a significant phenolic content and antioxidant activity were found for benzene extract because it contains a maximum phenolic content of 4.38%.^[26] Moreover, the antioxidant effect of *C. speciosus* is due to the antioxidants molecules present in it such as ascorbic acid, β -carotene, α -tocopherol, glutathione, phenolic, and flavonoids.^[32]

An *in vivo* rat experiment was done with the administration of either costunolide (20 mg/kg/day) or eremanthin (20 mg/kg/day), the components of *C. speciosus*, for 2 months orally using an intragastric

Table 1: Taxonomic classification and vernacular names of *Costus speciosus*

Item	Name
Taxonomic classification	
Kingdom	Plantae
Subkingdom	Tracheobionta
Super division	Spermatophyta
Division	Magnoliophyta
Class	Liliopsida
Sub class	Zingiberidae
Order	Zingiberales
Family	Costaceae
Genus	<i>Costus</i>
Species	<i>Speciosus</i>
Vernacular names	
Assam	Tara
Bengali	Keu, Keumut
Kannada	Changalvakostu, Chikke
Malayalam	Channakoova
Marathi	Penva, Pinnha, Kobee, Peva
Tamil	Kostam
Sanskrit	Kembuka, Kebuka, Kembu
Telegu	Kashmeeramu, Cengalvakostu
Classical name	Kebuka
English	Crepe ginger
Guajarati	Paskarmula, Valakdi
Hindi	Keu, Keukand, Kemuka, Kemua
Latin name	<i>Costus speciosus</i>

Source: Swati and Agarwal^[12], Srivastava *et al.*^[13]

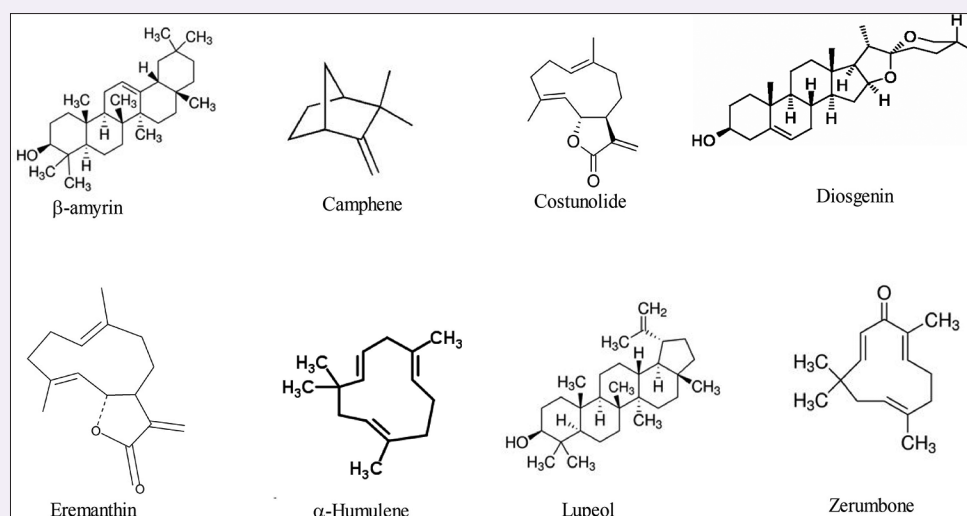


Figure 1: Chemical structures of some *Costus speciosus* active ingredients

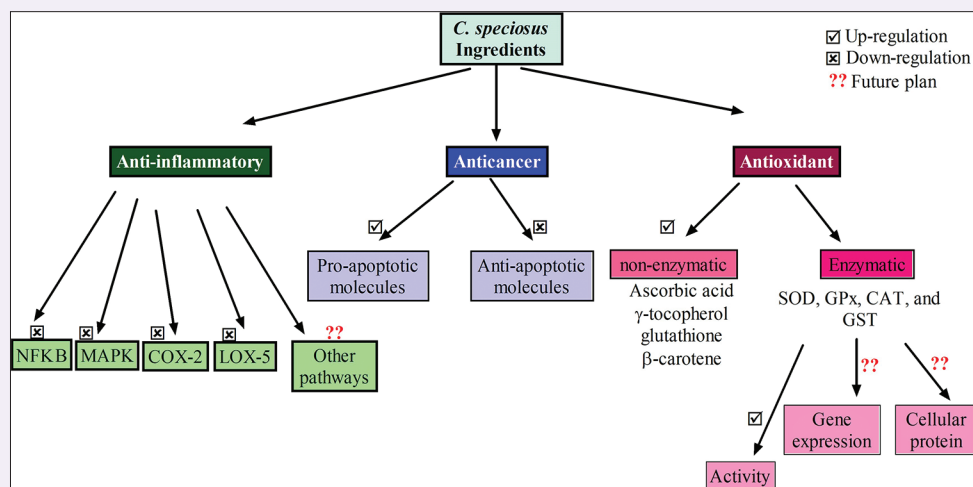


Figure 2: Summary of the antioxidant, anticancer, and anti-inflammatory of *Costus speciosus*

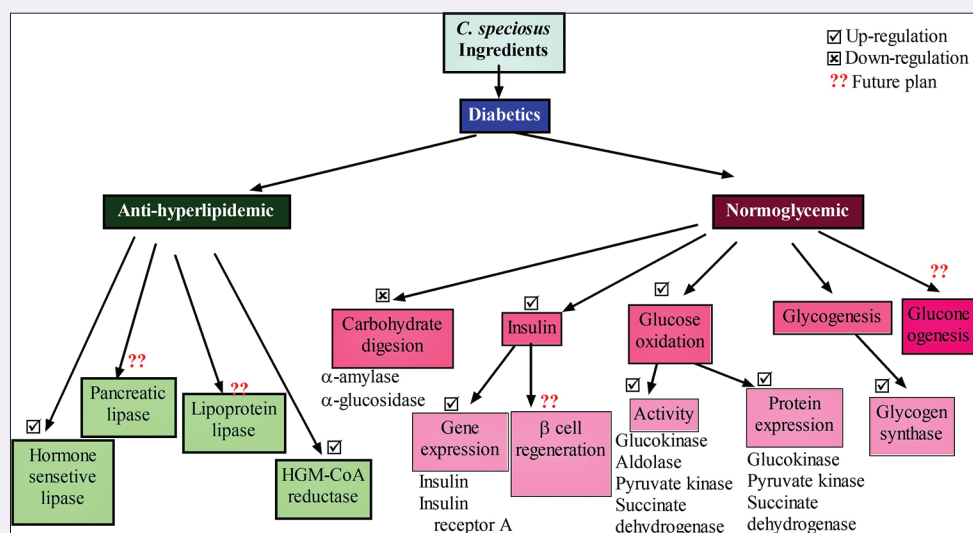


Figure 3: Summary of the normoglycemic and antihyperlipidemic potentials of *Costus speciosus*

tube. Results revealed a significant reduction in elevated TBA reactive substances in streptozotocin (STZ)-diabetic rats and an increment in GSH content and the activities of SOD, CAT, and GPx in brain, liver, heart, kidney, and pancreas.^[33] What is still needed is to investigate the effect of *C. speciosus* and its active constituents on the cellular antioxidant enzymes genes and protein expression. In 2013, the antioxidant potential of *C. speciosus* ground rhizomes was evaluated by its supplementation in the diet of Egyptian buffalo heifers with concentrations of 2.5 and 5 kg/ton ration for 1 month. In comparison to the control group that received the basal diet with no treatments, *C. speciosus*-supplemented animals possessed a higher erythrocytes' antioxidant potential as indicated by the marked decline in malondialdehyde (MDA) and the improvement of TAC.^[34] A future framework of studies is indicated to investigate the potential antioxidant properties of *C. speciosus* based on the molecular and proteomic aids in *in vivo* models [Figure 2].

Anticancer activity

Many of the current chemotherapeutic agents that have cytotoxic potency *in vitro* or *in vivo* inhibit specific molecular targets essential

for tumor growth.^[35] Anticancer potentials of *C. speciosus* rhizome extracted with hexane, ethyl acetate, and methanol were evaluated against human colon adenocarcinoma cell lines (COLO 320 DM). the authors stated that all tested extracts of *C. speciosus* rhizome showed significant antioxidant and antiproliferative activities in a dose- and time-dependent manners.^[36] This study evidenced the tied relationship between the antioxidant contents of *C. speciosus* and its anticancer effect. A study on the *C. speciosus* leaf methanolic extract was done in doses of 1, 10, 50, 100, and 200 µg/ml of Eagle's modified minimum essential medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin. HepG2 cells treated with 100 µg/ml for 24 h displayed a significant reduction in cell viability.^[37] The methanolic extract perturbed cell cycle progression that was monitored by increased caspase-3 activities in treated cells. Still needed is an investigation on the effect of this extract on cellular antiapoptotic and pro-apoptotic molecules by molecular approaches.

In the previous studies, the authors investigated the cytotoxicity of *C. speciosus* extracts regardless of its mechanism of anticancer action. Costunolide has mediated the cancer cell cycle arrest at the G2/M

phase of human breast adenocarcinoma (MDA-MB-231) as determined by flow cytometry and induced cell viability inhibition assayed with (3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide). Moreover, costunolide downregulated the overexpression of NF- κ B subunits – p65, 52, and 100 present in MDA-MB-231 doses of 20 and 40 μ M of costunolide.^[38] Moreover, costunolide-mediated anticancer activities were related to the induction of apoptosis in MCF-7 with an half maximal inhibitory concentration (IC₅₀) value of 40 μ M. Costunolide-treated MCF-7 cells showed overexpression of cyclin D1, D3, CDK-4, CDK-6, p18 INK4c, p21 CIP1/Waf-1, p27 KIP1, caspase-3, and caspase-9 in comparison with their expressions in normal breast cell line (MCF-10A).^[35]

Another active constituent, diosgenin, isolated from *C. speciosus*, has an apoptotic effect on cancer cell proliferation. The treatment of hepatocellular carcinoma HepG2 cells with diosgenin resulted in a cytotoxic effect with the IC₅₀ value of 32.62 μ g/ml, as compared with paclitaxel-treated HepG2 cells with an IC₅₀ value of 0.48 μ g/ml. The study was extended to determine the IC₅₀ value of diosgenin against breast adenocarcinoma MCF-7 cells and resulted in an IC₅₀ value of 11.03 μ g/ml. Diosgenin has increased the levels of death receptor-4 and caspase-3 that induce apoptosis in MCF-7 cells.^[39]

The possible mechanisms of anticancer potentials of *C. speciosus*' active constituents might be mediated through upregulation of pro-apoptotic and downregulation of antiapoptotic molecules that concomitantly diminish cancer cell proliferation and progression.^[40] A summary of the antioxidant mechanisms of *C. speciosus* is presented in Figure 2.

Anti-inflammatory activity

Inflammation is a pathophysiological response of tissues injuries that is closely associated with the pathogenesis of various inflammatory diseases.^[41] Regarding the adverse side effects of synthetic and chemical drugs, several medicinal plants were used as an alternative source with little side effects. *Z. officinale*, *C. longa*, and *C. speciosus* have been shown to exhibit potent anti-inflammatory effects.^[42,43] Numerous studies have been done to investigate the traditional uses of *C. speciosus* for the treatment of inflammation, rheumatism, bronchitis, fever, and headache. An *in vitro* study targeted the effect of costunolide on the production of pro-inflammatory mediators and mechanisms stimulated with lipopolysaccharides (LPS) in a murine BV-2 cell culture. Costunolide attenuated the expression of tumor necrosis factor alpha (TNF- α), interleukin (IL), IL-6, inducible NO synthase (NOS), and cyclooxygenase (COX-2) in activated microglia through inhibition of NF- κ B and mitogen-activated protein kinase pathways.^[44] In the same manner, the n-hexane-chloroform soluble fraction of methanolic *C. speciosus* rhizomes extract contained 22, 23-dihydrospirosterone, dehydrodihydrocostus lactone, dehydrocostus lactone, stigmasterol, arbusculin A, santamarine, and reynosin which induced prominent decrease in the levels of IL-1 β , IL-6, TNF- α , prostaglandin E2, lipoxgenase-5, and COX-2 in isolated peripheral blood mononuclear cells.^[45] The above-mentioned anti-inflammatory activities revealed by *C. speciosus* prove the usefulness of *C. speciosus* application against inflammatory diseases. Similarly, diosgenin isolated from *C. speciosus* with high-performance thin-layer chromatography possessed a highly significant inhibitory effect on LPS-stimulated TNF- α in the macrophage (RAW 264.7) culture supernatant in a dose of 50 μ g/ml of medium in a similar manner to methotrexate inhibitory effect on RAW 264.7 cells.^[46]

In 2013, an *in vivo* study was done the methanolic extracts of *C. speciosus* aerial parts (400 and 800 mg/kg, orally). The anti-inflammatory effect of the extract was assessed using carrageenan-induced paw edema test by injection of 0.1 ml of 1% carrageenan in 0.9% saline into subplantar

region of the left hind paw. Furthermore, acetic acid-induced writhing and Eddy's hot plate models were used to determine the analgesic effect. In addition, the antipyretic activity was evaluated by the Brewer's yeast-induced pyrexia in rats. The methanol extract doses of 400 and 800 mg/kg had significant anti-inflammatory activity at 5-h postmedication by inhibition percentages of 19.36 and 40.05%, respectively. Furthermore, writhings caused by acetic acid were reduced by 14.24 and 31.90%, respectively, and it also increased the latency period at both high and low doses that exhibited the mean reaction time at 16.60 ± 0.355 s and 14.12 ± 0.355 s, respectively, when compared with control in hot-plate test. Regarding the Brewer's yeast-induced pyrexia, 400 and 800 mg/kg doses significantly reduced the rectal temperature of the animals ($37.03^\circ\text{C} \pm 0.108^\circ\text{C}$ and $36.63^\circ\text{C} \pm 0.098^\circ\text{C}$, respectively).^[43] This finding was in accordance with the traditional uses of *C. speciosus* in the treatment of fever. Thus, the anti-inflammatory activities exhibited by the isolated compounds from *C. speciosus* serve as a promising and expanding strategy for treatment of various inflammatory disorders and related symptoms. The anti-inflammatory effects of *C. speciosus* are summarized in Figure 2. Further, we recommend investigating the effect of *C. speciosus* on other inflammatory pathways such as the toll-like receptor, B-cell receptor, T-cell receptor, and receptor for advanced glycation end products (RAGE) signaling.

A pilot cohort trial was done at King Abdulaziz University in Saudi Arabia between May and December 2014, among 15 patients with acute pharyngitis and tonsillitis. The aqueous solution of *C. speciosus* was administered as nasal drops at a dose of 0.75 ml (15 drops containing 210 mg extract) for patients aged 2–6 years, and 1.5 ml (30 drops containing 420 mg of the extract) for patients older than 6 years, every 8 h for 3 days. The treatment of patients with *C. speciosus* induced an improvement in acute symptoms in 60% of the patients treated within the first 24 h and remission rate of 93% by the day 5.^[47]

Antidiabetic activity

Diabetes mellitus is a metabolic disease with about 4% incidence all over the world.^[48] Besides drugs commonly used for the treatment of diabetes such as insulin, sulfonylureas, biguanides, or thiazolidinediones, several species of medicinal plants have been described as normoglycemic agents of higher effectiveness, minimal side effects, and relatively small costs.^[49-51] The normoglycemic effect of *C. speciosus* is discussed below and is presented in Figure 3.

Mosihuzzaman *et al.*^[52] studied the effect of juice prepared from *C. speciosus* rhizome on serum glucose levels in noninsulin-dependent diabetic rat model. Results showed that in nondiabetic rats, *C. speciosus* had no significant effect on the fasting or postprandial state when fed along with glucose. However, when fed 30 min before the glucose administration, *C. speciosus* resulted in a hypoglycemic effect. To understand this finding, we need to investigate the effect of *C. speciosus* on intestinal absorption of glucose through determination of the glucose transporter gene expression. Furthermore, knowledge of the serum levels of insulin and glucagon are of vital importance to understand the effect of *C. speciosus* on glucose levels in fasting and feed states.

Another study investigated the protective effects of *C. speciosus* rhizome different extracts on hyperglycemia in STZ-induced male diabetic Wistar rats (50 mg/kg, intraperitoneal [i.p.]), and glibenclamide (0.6 mg/kg BW, orally) was used as a reference hypoglycemic drug. Hexane, ethyl acetate, and methanol crude extracts were administered to diabetic and nondiabetic rats orally at doses of 250, 400, and 400 mg/kg, respectively, for 60 days. The plasma glucose concentration was significantly decreased by all three extracts in comparison with control. Moreover, hexane extract significantly decreased the glycosylated hemoglobin, total cholesterol, and triacylglycerol (TAG).^[23] The authors attributed

this effect to the elevated serum insulin level associated with *C. speciosus* administration.

In 2008, the antihyperglycemic, antihyperlipidemic, and antioxidant potentials of an ethanol extract of *C. speciosus* root were studied on alloxan-induced diabetes in male rats by a single i.p. injection of alloxan monohydrate (120 mg/kg BW) dissolved in normal saline. Four groups of six alloxan-diabetic rats were administered orally with *C. speciosus* ethanolic extract at doses of 150, 300, and 450 mg/kg BW and a standard drug, glibenclamide (0.6 mg/kg BW) orally for 4 weeks. Administration of 300 and 450 mg/kg doses of *C. speciosus* ethanolic extract resulted in a significantly lowered blood glucose concentration (26.76% and 34.68%, respectively), increased glycogenesis, and decreased gluconeogenesis, bringing the glucose to its normal levels. Moreover, these doses also significantly reduced the total plasma lipids (12.87% and 178.24%, respectively), cholesterol (21.92% and 30.77%, respectively) and TAG (25.32% and 33.99%, respectively) levels, and improved hepatic antioxidant enzymes' activities.^[53] The antidiabetic effects of *C. speciosus* may be related to its content of costunolide that stimulating the β cells to secrete insulin by inhibition of the NOS expression and leading to the regeneration of β cells.^[54] The same authors prepared hexane, ethyl acetate, methanol, and aqueous crude extracts of *C. speciosus*, and administered them separately through oral intubation to STZ-induced diabetic rats at doses of 250, 400, 400, and 600 mg/kg BW, respectively, for 2 months. They found a significant decrease in the elevated plasma glucose in diabetic rats treated with those extracts when compared with control. In addition, hexane crude extract restored the altered tissue protein and pancreatic DNA and normalized both plasma insulin and C-peptide levels.^[55] Furthermore, the expression levels of insulin, insulin receptor A, glucokinase (GK), pyruvate kinase (PK), succinate dehydrogenase (SDH), and glucose transporting protein were elevated on oral administration of 400 and 600 mg *C. speciosus*/kg BW to STZ-diabetic rats for 4 weeks when compared to glibenclamide-treated group.^[56] *C. speciosus* could be increased the serum insulin level along with significant increases in the hepatic GK (EC 2.7.1.2), aldolase (EC 4.1.2.13), PK (EC 2.7.1.40), SDH (EC 1.3.5.1), and glycogen synthase (EC 2.4.1.11) activities.

Another recent study was conducted to investigate protection for diabetes patient from the complications of glycation. Methanolic extract of *C. speciosus* leaves from Moratuwa, Sri Lanka, was used to investigating its inhibitory effect on porcine pancreatic α -amylase and α -glucosidase purified from *Saccharomyces cerevisiae*. The authors verified the *in vitro* inhibitory effect of *C. speciosus* extract on α -amylase (EC 3.2.1.1) and α -glucosidase (EC 3.2.1.20) activities. Inhibition of α -amylase and α -glucosidase delayed the carbohydrate digestion and decreased glucose absorption, lowering the postprandial elevation of blood glucose, and decreasing glycation plasma protein.^[57] Further investigations about the effect of *C. speciosus* and its active ingredients on the expressions of intestinal monosaccharide transporter genes, and the gluconeogenic enzymes, and their ability to regenerate β cells are needed to complete our view of the normoglycemic effect of *C. speciosus*.

Hypolipidemic activity

The abnormally high concentrations of serum lipids in diabetes patients as insulin inhibit hormone-sensitive lipase (EC 3.1.1.79). Therefore, in insulin deficiency, fatty acids are liberated from adipose tissue that concomitantly leads to hyperlipidemia.^[58] Further, insulin has an inhibitory action on 3-hydroxy-methylglutaryl coenzyme A reductase (EC 1.1.1.88), a key rate-limiting enzyme in charge of the metabolism of cholesterol-rich low-density lipoprotein (LDL) particles. This results in increasing the production of cholesterol-rich LDL particles^[59] as shown in Figure 3.

The possible normoglycemic and hypolipidemic effects of costunolide in STZ-diabetic male Wistar rats were evaluated after administration of doses of 5, 10, and 20 mg costunolide/kg BW orally for 30 days. It was found that 20 mg costunolide/kg BW significantly decreased the total serum cholesterol, TAG, and LDL-cholesterol. At the same time, plasma insulin, glycogen (liver and muscles), and high-density lipoprotein (HDL)-cholesterol levels were significantly increased. The authors hypothesized that costunolide might stimulate the β cells to secrete insulin by inhibiting the expression of NOS.^[54] Similarly, a research study was done to evaluate the hypolipidemic effect of eremanthin at the same doses in STZ-diabetic rats for 60 days. They found that oral administration of 20 mg eremanthin/kg BW significantly decreased the total serum cholesterol, TAG, and LDL-cholesterol along with the significant increment of plasma insulin, tissue glycogen, and HDL-cholesterol.^[60] For future research, we suggest investigating the effect of *C. speciosus* on lipid digestion and absorption regarding the gene expression of intestinal fatty acid transporters in addition to the effects of *C. speciosus* on pancreatic lipases and adipose tissue hormone-sensitive lipase.

Hepatoprotective activity

The serum enzymes, including aspartate aminotransferase (AST, EC 2.6.1.1), alanine aminotransferase (ALT, EC 2.6.1.2), lactate dehydrogenase (LDH, EC 1.1.1.27), alkaline phosphatase (ALP, EC 3.1.3.1), and acid phosphatase (ACP, EC 3.1.3.2), are used as hepatic biomarkers. An increase in the activities of AST, ALT, LDH, ALP, and ACP in plasma/serum might be due to their leakage from the liver cells into the bloodstream.^[61] In a hepatotoxicity study, carbon tetrachloride (CCl₄)-induced alterations in liver function profiles of Swiss albino mice due to CCl₄ intoxication (at a dose of 0.1 ml/100 g BW, twice a week, i.p.), which was ameliorated by the methanolic extract of *C. speciosus* rhizomes (100 mg/kg body BW for 14 consecutive days). The extract brings the serum levels of AST, ALT, ALP, bilirubin, and total protein to their normal levels in comparison with silymarin-treated animals, as a reference hepatoprotective drug.^[62] The same observations were recorded following oral administration of *C. speciosus* ethanolic extract at a dose of 500 mg/kg BW in Wistar albino rats when also compared with silymarin, a standard drug of a hepatoprotective power.^[63] This part needs further studies about the hepatoprotective effect of *C. speciosus* against drugs and chemicals that induce liver injuries, that is, paracetamol, nonsteroidal anti-inflammatory, glucocorticoids, isoniazid, aflatoxins, arsenic, vinyl chloride, and other ingredients.

Adaptogenic activity

A variety of stresses produces a significant alteration in various neurotransmitters in the central nervous system (CNS) as well as peripheral nervous system, which causes depletion of norepinephrine and dopamine levels in the brain.^[64] It appears that norepinephrine is utilized in response to stress, which leads to increase in dopamine concentrations.^[65] Monoamine oxidase (MAO, EC 1.4.3.4) is mostly involved with the upkeep of the normal levels of biogenic amines in the brain. It is postulated that the executive function of MAO is to prevent the release of 5-hydroxytryptamine (5-HT).^[64] *C. speciosus* extracts significantly reduced the stress-induced rise of 5-HT and 5-HIAA levels in brain tissues by preventing the alarm reaction, which elicits a significant increase in 5-HT and 5-HIAA levels.^[66] The authors studied the *C. speciosus* on MAO but some consideration must be given to catechol-O-methyltransferase (EC 2.1.1.6), the enzyme that acts along with MAO in catecholamine catabolism. This study stated the antidepressant effect of *C. speciosus* that may be used in the new drug formulation against CNS disorders. As a recommendation for

future research, the effect of *C. speciosus* against a headache needs an investigation to study the traditional medication of *C. speciosus* against a headache.

Antimicrobial activity

Undesirable side reactions may occur with oral administration of antibiotic substances; thus, oral administration of penicillin may cause heartburn, nausea, vomiting, and diarrhea. Therefore, numerous trials were conducted on herbs and spices as antibiotic replacements.^[67] Hexane and methanol extracts of *C. speciosus* leaf and rhizomes exhibited a lysis zone against *Shigella* spp., *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas* spp., *Bacillus subtilis*, and *Salmonella* spp. in comparison to silver sulfadiazine cream.^[68] The antifungal effect of costunolide showed significant minimal inhibitory concentration values of 62.5 µg/ml against *Trichophyton mentagrophytes*, 62.0 µg/ml against *Trichophyton simii*, 125 µg/ml against *Epidermophyton floccosum*, 31.25 µg/ml against *Trichophyton rubrum*, 125 µg/ml against *Curvularia lunata*, 62.5 µg/ml against *T. rubrum*, 250 µg/ml against *Scopulariopsis* sp, 250 µg/ml against *Aspergillus niger*, and 250 µg/ml against *Magnaporthe grisea*.^[17] There is a necessity to investigate the antiviral potential of *C. speciosus*, in particular against the more common diseases such as avian influenza disease, infectious viral hepatitis, and human immunodeficiency viruses.

TOXICOLOGICAL STUDIES

The collected stem, leaves, and flower were shade-dried and powdered in a grinder to get a coarse powder. The powdered plant material (5000 g) was extracted with 50% ethanol by using maceration apparatus. The aqueous extract was evaporated to obtain a viscous dark green extract. The ethanolic extract was analyzed as a standardized extract following Indonesian herbal pharmacope. There were no contaminants of arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb) and no bacterial and fungus contaminants (*E. coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *S. aureus*, and *Candida albicans*). There is only one research trial that has been done to evaluate the subacute toxicity test of *C. speciosus*. *C. speciosus* at 275–1100 mg/kg/day was administered to male mice for 90 days. Food and drink intakes were measured every day, and toxic symptoms were observed every day. The animals were sacrificed at the end of the study and the weights of vital organs were examined and subjected to histological examination. The results showed that the administration of *C. speciosus* ethanolic extract at 275–1100 mg/kg/day for 90 days did not show any significant disturbance in all parameters, except for reductions of cholesterol and blood glucose levels of test animals.^[69] Finally, to determine the safety of *C. speciosus*, different extracts of all plant parts were examined separately to determine the LD₅₀ of *C. speciosus* extracts and their safety limits.

RECOMMENDATIONS

This review supports the various therapeutic potentials of *C. speciosus* and its role in different diseases, which opens new clinical research areas. Furthermore, it covers new ways to explore the compounds responsible for these therapeutic effects and to study the mechanism of its action. However, these data must be further studied on the molecular basis. Therefore, we recommend the following research studies:

- *C. speciosus* safety assessments of different extracts of various plant parts
- Therapeutic possibilities of different solvents of *C. speciosus* extract such as methanol, ethanol, hexane, and chloroform, and its active constituents either alone or in combination with drugs
- Mechanism of action of *C. speciosus* and its active components through various cellular signaling pathways

- Therapeutic effect of *C. speciosus* against pleurisy and respiratory diseases, especially following intranasal administration
- Effect of *C. speciosus* and its active ingredients on the monosaccharides, fatty, and amino acid's intestinal transporter genes
- *In vivo* effect of *C. speciosus* on the antioxidant molecules using molecular biology techniques
- Effect of *C. speciosus* on the toll-like receptor, B-cell receptor, T-cell receptor, and RAGE signaling pathways
- Mechanisms, by which *C. speciosus* induce normalization of plasma insulin and C-peptide levels. Furthermore, does *C. speciosus* regenerate β cells or not?
- Effect of *C. speciosus* on gluconeogenesis
- Effect of the protective possibility of *C. speciosus* against neurotoxins and aging-related diseases
- Effect of *C. speciosus* on viral diseases.

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