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Review Article

Exploring the anticancer potential of *Costus speciosus*: a comprehensive review

Explorando o potencial anticancerígeno de *Costus speciosus*: uma revisão abrangente

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Abstract

Costus speciosus is a medicinal plant with a long history in Indian Ayurvedic medicine, recognized for its diverse bioactive properties, including antibacterial, anticancer, anti-inflammatory, and antidiabetic effects. This review highlights its therapeutic potential, particularly in cancer treatment, where its bioactive compounds exhibit cytotoxic effects against breast, ovarian, and uterine cancers. These compounds have shown the ability to induce apoptosis, regulate the cell cycle, and inhibit cancer progression, offering a promising alternative to conventional chemotherapy with potentially fewer side effects. Additionally, *C. speciosus* demonstrates antioxidant, antimicrobial, and antidiabetic properties, expanding its clinical applications. Despite its promising pharmacological profile, further research is required to understand the molecular mechanisms underlying its therapeutic effects and ensure the safety and efficacy of its various extracts for therapeutic use.

Keywords: *Costus specious*, anticancer, antioxidant, antimicrobial, antidiabetic, anti-inflammatory, therapeutic medications.

Resumo

Costus speciosus é uma planta medicinal com uma longa história na medicina ayurvédica indiana, reconhecida por suas diversas propriedades bioativas, incluindo efeitos antibacterianos, anticâncer, anti-inflamatórios e antidiabéticos. Esta revisão destaca seu potencial terapêutico, particularmente no tratamento do câncer, onde seus compostos bioativos exibem efeitos citotóxicos contra cânceres de mama, ovário e útero. Esses compostos demonstraram a capacidade de induzir apoptose, regular o ciclo celular e inibir a progressão do câncer, oferecendo uma alternativa promissora à quimioterapia convencional com potencialmente menos efeitos colaterais. Além disso, C. speciosus demonstra propriedades antioxidantes, antimicrobianas e antidiabéticas, expandindo suas aplicações clínicas. Apesar de seu perfil farmacológico promissor, mais pesquisas são necessárias para entender os mecanismos moleculares subjacentes aos seus efeitos terapêuticos e garantir a segurança e eficácia de seus vários extratos para uso terapêutico.

Palavras-chave: *Costus speciosus*, anticâncer, antioxidante, antimicrobiano, antidiabético, anti-inflamatório, medicamentos terapêuticos.

1. Introduction

Uncontrolled, aberrant cells are a hallmark of cancer, a group of malignant disorders (Gurunanselage Don and Yap, 2019). Despite improvements in diagnosis, treatment, and preventative tools, cancer has a relatively high fatality rate in humans (Mohd-Salleh et al., 2020). Even with new chemotherapeutic techniques and other therapies, the incidence of cancer continues to rise and it remains a major global public health concern (Mahmod et al., 2020). According to global cancer estimates, 1 in 5 men and 1 in 6 women are likely to develop cancer, and 1 in 8 men and 1 in 10 women will die from the disease (Ali et al., 2021). At present, cancer represents the main cause of death for humans and animals throughout the world.

Cancer is characterised by uncontrolled cell cycle progression, apoptosis suppression, and increased angiogenic potential as well as proliferation, invasion, and metastatic capacities. Genetic instability and changes inside cells and tissues lead to the unchecked proliferation of normal cells, turning them into cancerous cells (Stadlbauer et al., 2019). The multi-step process of carcinogenesis is initiated by alterations in the expression of oncogenes and transcriptional factors involved in

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cell proliferation, cell cycle regulation, cell apoptosis, differentiation, angiogenesis, invasion, and metastasis (Ramasamy and Agarwal, 2008). Indeed, a myriad of genes can be involved in cancer, including oncogenes, tumour suppressor genes, DNA repair genes, and genes involved in cell growth metabolism (Mota et al., 2020; Negrao et al., 2021). This genetic instability is caused by both external and internal factors (Abdullahi et al., 2019). Therefore, the best cancer chemopreventive medicines should be those that target one or more of these mechanisms (Liu et al., 2014). According to Geiger et al. (2020), malignancies such as breast cancer, ovarian, colorectal, bladder, kidney cancer, and other tumour diseases.

Although great advancements have allowed clinicians to treat cancer more effectively, several adverse effects are associated with modern chemotherapy. Natural remedies, such as the use of medicinal plant or their products, to treat cancer may decrease these side effects. Recently, innovative screening practices utilising herbs or plants have enabled the discovery of phytochemicals with anticancer properties (Abd El-Hack et al., 2023). Because of their unmatched chemical variety, natural medicines derived from medicinal plants as opposed to pure chemicals or crude extracts offer endless sources of novel pharmaceuticals (Mat Jusoh et al., 2023).

Herbal medicine is the study of employing medicinal herbs that exert pharmacologic effects (Sharma et al., 2020). There has been great research interest on medicinal plants (Darkhor et al., 2018). According to Larki et al. (2020), a medicinal plant is any plant that contains compounds in one or more of its organs that can be utilised therapeutically. The utilisation of medicinal plants is not a recent phenomenon. For millennia, they have been used to treat and prevent illnesses. Various chemical families of natural phytochemicals, acting as natural antioxidants, and other substances are responsible for the efficacy of these therapeutic medications made from natural products (Larki et al., 2020). According to World Health Organization (WHO), the illnesses of an estimated 1.5 billion people are treated with medicinal, primarily herbal, plants (Dutta et al., 2020). More specifically, approximately 80% of people in developing nations use traditional plant-based therapies, and roughly 25% of the medications provided today are derived from medicinal plants (Dutta et al., 2020).

In addition to being safer than manufactured medications, medicinal plants contain a variety of bioactive compounds that can be utilised to prevent and treat a number of illnesses (Rajashree et al., 2012). Herbal medicine aims to enhance human well-being and to delay the course of diseases. Examples of medicinal plants that have been used as herbal treatments include ginseng, ginger, and creep ginger (*C. speciosus*). They contain metabolites that can contribute to halt the progression of many diseases (Oladeji et al., 2020; Maji et al., 2020). There are two types of metabolites in medicinal plants: primary and secondary (Dhaniaputri et al., 2022). While secondary metabolites are byproducts of a plant's metabolism rather than a contributor to its growth, primary metabolites contribute directly to the development of a plant (Saltveit, 2017). Primary metabolites include hormones and carbohydrates, whereas secondary metabolites include polyphenols, flavonoids, steroids, alkaloids, terpenoids, and tannins (Aristina et al., 2019).

A common medicinal herb used to treat and prevent a variety of ailments is *C. speciosus* (Ahmad et al., 2018), a perennial rhizomatous herb that is also known as spiral ginger, crepe ginger, or the insulin plant. It contains a variety of important bioactive phytochemicals that have antimicrobial, insecticidal, antioxidant, anticancer, and antidiabetic qualities. This plant has many ethnobotanical uses and is extensively dispersed throughout India (Bahshwan and Aljehany, 2020).

2. Phytochemicals Found in *Costus speciosus*

C. speciosus is employed in the production of several medications as well as the synthesis of oral contraceptives, sex hormones, and cortisone. About 3.4% of *C. speciosus* rhizomes are composed of diosgenin, an asteroidal sapogenin (Singh et al., 2017). *C. speciosus* has a variety of medicinal advantages (Table 1). While its leaves are utilized to treat fever, its rhizome juice is employed to relieve headaches (Srivastava et al., 2011). According to Bavarva and Narasimhacharya (2008), the rhizomes of *C. speciosus* have tonic, expectorant, astringent, bitter, and digestion-improving properties. Additionally, the rhizomes have anabolic and antifertility effects (Bhattacharya and Nagaich, 2010). According to Lijuan et al. (2011), the rhizome extract also promotes uterine contraction. The rhizomes have also demonstrated depressive effects on the central nervous system (CNS) and heart. Fever and dysentery are treated with a decoction of the stems (Pawar and Pawar, 2014). According to Ariharan et al. (2012), young stems are used to treat intestinal worms, bronchitis, asthma, anaemia, and antiemetic medications.

Based on phytochemical screening, alkaloids, glycosides, steroids, natural antioxidants, tannins, and vitamin B have been found in *C. speciosus* (Singh et al., 2014). Figure 1 displays the chemical structures of a few active principles that have been identified in various *C. speciosus* components (Duraipandiyan et al., 2012; Rasul et al., 2013).

3. The Activity of *Costus speciosus*

3.1. Antioxidant activity

Antioxidants are a class of chemicals that significantly inhibit oxidation processes by scavenging free radicals and inducing cellular antioxidant enzymes (Daisy et al., 2008). Reactive oxygen species (ROS) are produced as byproducts of cellular metabolism and enzymatic reactions, and they can also be induced by a wide range of chemicals (Navrot et al., 2007). According to Nehete et al. (2010), ROS are crucial in the oxidative stress linked to diabetes, cirrhosis, cancer, and atherosclerosis. Antioxidant systems—which include nonenzymatic molecules such as ascorbic acid, α-tocopherol, glutathione, and β-carotene, as well as a range of enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase, and glutathione S-transferases—combat oxidative stress (Gottfredsen et al.,

Table 1. Active compounds found in *C. speciosus*.

Active compound	Cell line	References
Diosgenin	Human osteosarcoma (1547)	Corbiere et al. (2004)
	Cervix carcinoma (HEp-2)	
	Human melanoma (M4Beu)	Corbiere et al. (2003)
	Human osteosarcoma (1547)	Moalic et al. (2001)
	Human hepatocellular carcinoma (HepG2)	Li et al. (2015)
	Human hepatoma cells (SMMC-7721)	
	Human osteosarcoma (1547)	Moalic et al. (2001)
	Human erythromyeloblastoid leukemia (K562)	Liu et al. (2005)
	Human colon carcinoma (HCT-116)	Raju and Bird (2007)
Zerumbone	Human lung cancer (NSCLC)	Hu et al. (2014)
	Human pancreatic carcinoma (PANC-1)	Zhang et al. (2012)
Costunolide	Human prostate cancer (PC-3)	Hsu et al. (2011)
	Breast cancer (MDA-MB-231)	Choi et al. (2012)
Lupeol	Human osteosarcoma cells (MNNG/HOS)	Liu et al. (2015a)
	Human osteosarcoma cells (MG-63)	
	Human pancreatic cancer (PCNA-1)	Liu et al. (2015b)
	Melanoma (451Lu)	Saleem et al. (2008)
Camphene	Murine melanoma cell (B16F10-Nex2)	Girola et al. (2015)
	Human pancreatic carcinoma (MIA PaCa-2)	Mulyaningsih et al. (2010)
	Human hepatocellular carcinoma (HepG2)	
	Human colon adenocarcinoma (SW-480)	
α-Humulene	Human colon carcinoma (CaCo-2)	Ambrož et al. (2015)
β-Amyrin	Human bladder carcinoma (NTUB1)	Lin et al. (2011)

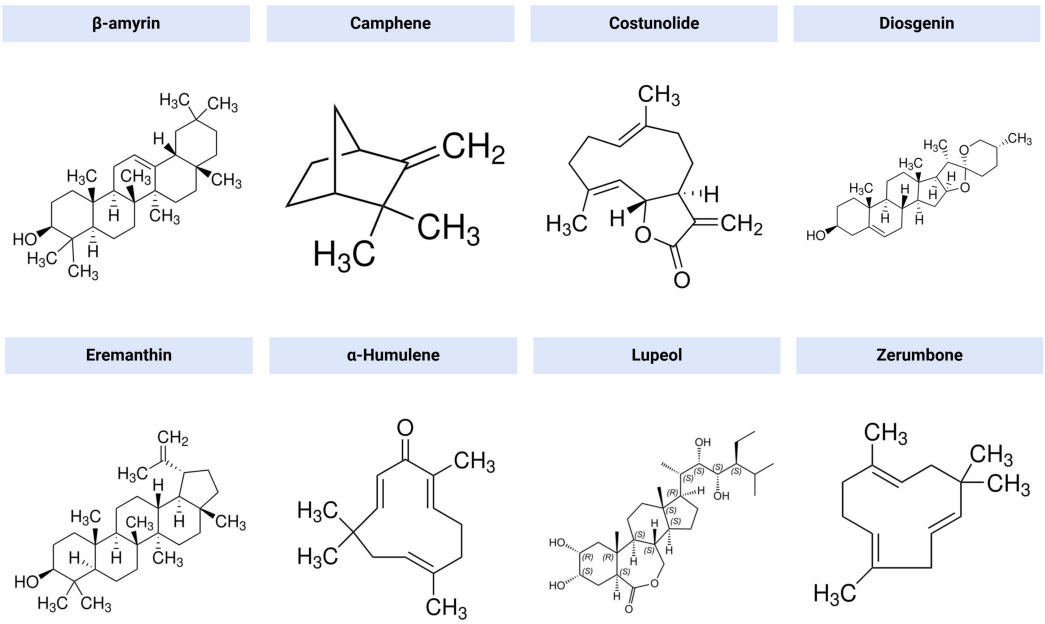

Figure 1. Examples of active compounds found in *Costus speciosus*.
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2013). Phenols and flavonoids, which are found in medicinal plants, may offer living organisms a defence against ROS risks due to their redox characteristics, including strong metal ion chelation and free radical scavenging (Govindarajan et al., 2005).

Researchers have extracted the compounds present in *C. speciosus* leaf, stem peel, peeled stem, and roots in different solvents, and have demonstrated their antioxidant activity *in vitro* by using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging and thiobarbituric acid (TBA) techniques (Vijayalakshmi and Sarada, 2008). The traditional use of *C. speciosus* root and stem peel for a variety of illnesses and ailments has been validated. Jha et al. (2010) found that *C. speciosus* rhizomes exhibited a stronger ability to scavenge nitric oxide (NO) compared with vitamin C and quercetin, which are typically used as standards in procedures such as the DPPH radical scavenging assays. The authors proposed that the presence of glycosides, flavonoids, triterpenoids, tannins, and steroids in the methanolic extract of *C. speciosus* may be responsible for the antioxidant action. In the same setting, several solvents have been used to produce *C. speciosus* rhizome extracts and assessed *in vitro* for their antioxidant capacity. The benzene extract presented the highest levels of phenolics (4.38%), flavonoids, and some vitamins (Devi and Urooj, 2010), and thus better antioxidant activity (Nehete et al., 2010).

In an *in vivo* study, researchers administered a component of *C. speciosus*, costunolide, orally via an intragastric tube to rats (20 mg/kg/day) for 2 months (Eliza et al., 2010). The rats had been treated with streptozotocin to induce diabetes. The authors noted a significant decrease in TBA reactive substances and an increase in enzyme activities in the brain, liver, heart, kidney, and pancreas. In another study, buffalo calves were fed ground *C. speciosus* rhizomes. Compared with the control group, which was fed the basal diet, there was a significant drop in malondialdehyde (MDA), a product of lipid peroxidation, and an increase in the total antioxidant capacity (TAC) of erythrocytes of the *C. speciosus*–supplemented animals (El-Far and Abou-Ghanema, 2013) (Figure 2).

3.2. Anti-inflammatory effects

According to Vazquez et al. (2011), inflammation is a pathophysiological reaction to tissue damage and is intimately linked to the aetiology of a number of inflammatory disorders. A number of medicinal plants have shown anti-inflammatory properties, including *Zinger officinale*, *Curcuma longa*, and *C. speciosus* (Singh et al., 2013). Traditional folk forages have utilised *C. speciosus* to cure conditions such as headaches, rheumatism, fever, and bronchitis. The bioactive components of *C. speciosus*, including diosgenin and costunolide, have been used to treat a number of inflammatory diseases. They can inhibit

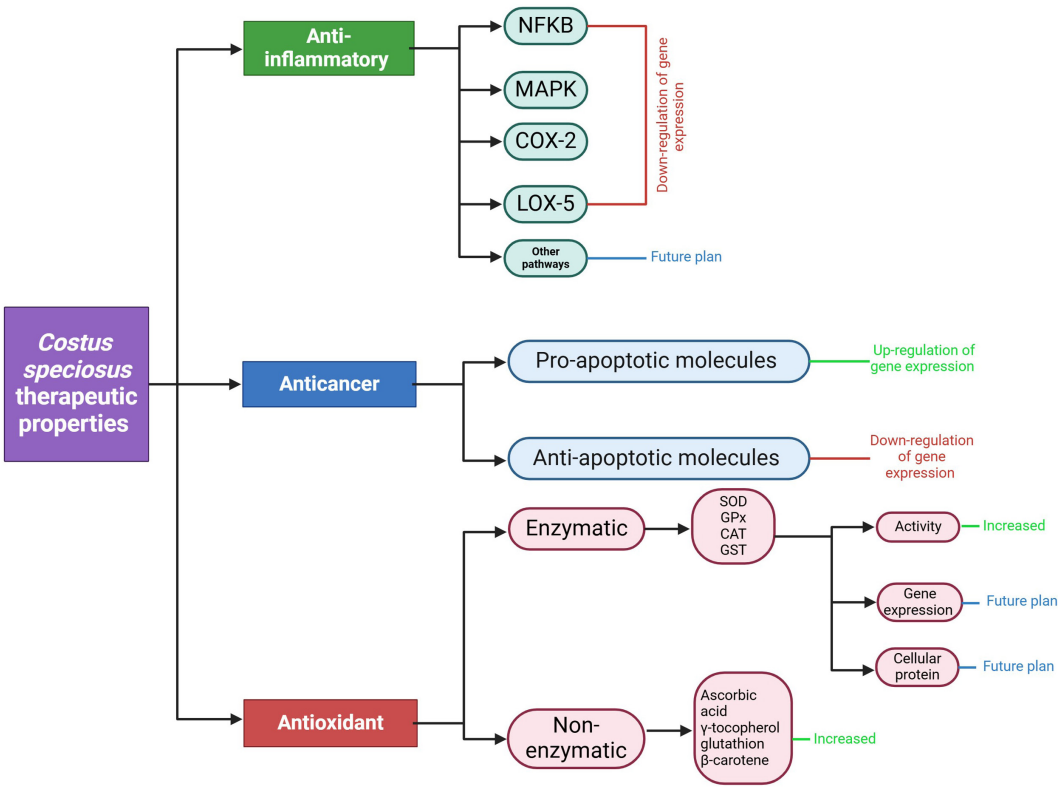

Figure 2. An overview of the anti-inflammatory, anticancer, and antioxidant properties of *Costus speciosus.*
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the activity of tumour necrosis factor alpha (TNF-α), a cytokine that is released in response to infections and amplifies inflammation. In RAW 264.7 cells, a mouse macrophage cell line, diosgenin showed activity similar to the popular immune system suppressor methotrexate. It had an inhibitory or suppressive impact on the virus (Selim and Al Jaouni, 2016). Costunolide inhibits TNF-α, as well as cyclooxygenase (COX) and interleukins (e.g., interleukin 6 [IL-6] and IL-1), by blocking nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in mitogen-driven protein kinase pathways and activated microglia (Rayan et al., 2011; Al Attas et al., 2015). A number of other bioactive compounds, including dehydrodihydrocostus lactone, reynosin, arbusculin A, santamarine, and stigmasterol, were separated from the chloroform extract of *C. speciosus* and showed anti-inflammatory activity on isolated blood mononuclear cells (Al-Attas et al., 2015).

Singh et al. (2013) reported the *in vivo* anti-inflammatory qualities of a methanolic *C. speciosus* extract. There was notable anti-inflammatory effects 5 hours after administering 400 or 800 mg/kg of the methanolic extract. In a pilot study conducted at King Abdulaziz University in Saudi Arabia, 15 patients who had acute tonsillitis and pharyngitis were treated with an aqueous *C. speciosus* extract as nasal drops (0.75 mL every 8 hours for patients aged 2–6 years, and 1.5 mL every 8 hours for patients aged >6 years). Sixty percent of patients treated with the extract presented an improvement within in first 24 hours, and 93% showed remission by day 5 (Bakhsh et al., 2015). Figure 2 summarises the anti-inflammatory properties of *C. speciosus*.

3.3. Antidiabetic activity

Diabetes mellitus is a metabolic disorder in which a relative or absolute lack of insulin raises blood glucose levels. The global prevalence of this condition is approximately 4% (Rani et al., 2012; Sulakshana and Rani, 2015). In addition to medications such as insulin, sulfonylureas, biguanides, and thiazolidinediones that are frequently used to treat diabetes, a number of medicinal plant species have been identified as normoglycemic agents; they are more efficacious, have fewer adverse effects, and are comparatively less expensive (Medagama and Bandara, 2014). One of these therapeutic plants is *C. speciosus*, which is known as the insulin plant because it contains the crucial antidiabetic compound diosgenin (Rani et al., 2012; Sulakshana and Rani, 2015). Figure 3 illustrates the normoglycemic impact of *C. speciosus* .

Daisy et al. (2008) examined the antidiabetic potential of *C. speciosus* in diabetic rats. Administering the methyl acetate, hexane, or methanolic extracts reduced the blood glucose levels in these rats. The hexane extract had the strongest hypoglycaemic action and antidiabetic potential of these three extracts. Furthermore, there was a reduction in the glycosylated haemoglobin and cholesterol levels. Mosihuzzaman et al. (1994) examined the antihyperlipidemic, antidiabetic, and antioxidant qualities of an ethanolic *C. speciosus* extract. It significantly reduced glucose levels, perhaps due to elevated glycogenesis and reduced gluconeogenesis. Furthermore, it decreased cholesterol, plasma lipids, and triacylglycerol, and improved the activity of liver enzymes. In another study, a methanolic leaf extract inhibited α-glucosidase and α-amylase, which ultimately lowered protein glycation (Perera et al., 2016). Moreover, costunolide stimulates beta cells, which results in the release of insulin (Eliza et al., 2009). Figure 4 displays the antidiabetic effects of active ingredients of *C. speciosus*, such as costunolide and eremanthin.

3.4. Antimicrobial activity

When antibiotics are administered orally, undesirable side effects can occur. For example, taking penicillin orally can result in heartburn, nausea, vomiting, and diarrhoea.

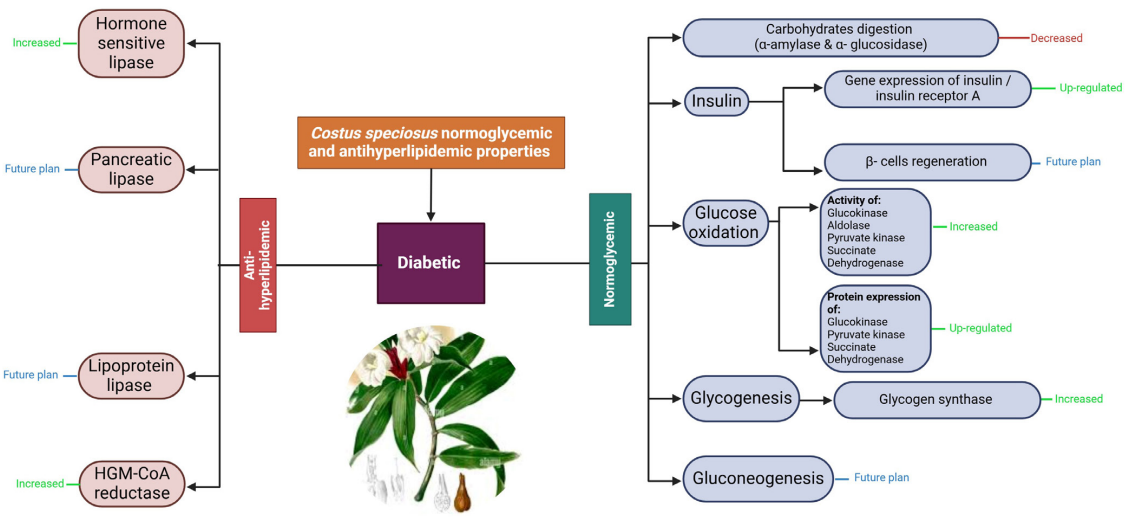

Figure 3. An overview of the normoglycemic and antihyperlipidemic properties of *Costus speciosus*.
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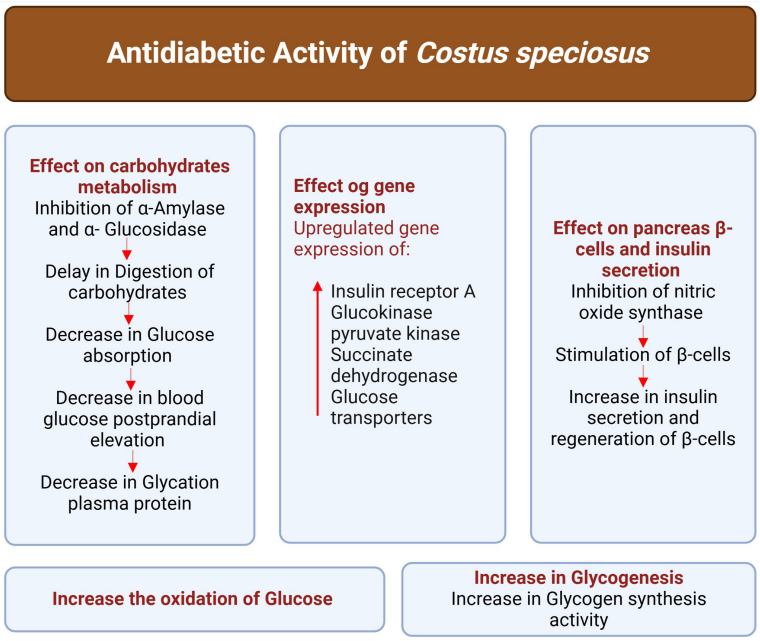

Figure 4. *Costus speciosus* exhibits antidiabetic properties.
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As a result, researchers have evaluated the use of spices and herbs as replacements for antibiotics (Lai and Roy, 2004). The hexane and methanolic extracts of *C. speciosus* leaves and rhizomes could inhibit *Salmonella* spp., *Pseudomonas* spp., *Salmonella* spp., *Escherichia coli*, *Shigella* spp., *Staphylococcus aureus*, and *Klebsiella pneumoniae* (Malabadi, 2005; Ariharan et al., 2012). A hexane extract demonstrated notable antifungal effects, with a minimal inhibitory concentration of 31.25–250 µg/mL against *Trichophyton mentagrophytes*, *Trichophyton simii*, *Epidermophyton floccosum*, *Trichophyton rubrum*, *Curvularia lunata*, *Scopulariopsis* sp., *Aspergillus niger*, and *Magnaporthe grisea* (Duraipandiyan et al., 2012). The authors also separated eremanthin and costunolide from the rhizome extract and found that at extremely low concentrations, they inhibited the growth of numerous fungi. According to Al-Ameri and Falah (2014), a methanolic rhizome extract inhibited *Aspergillus* spp. that can cause lung infections. Additionally, *Aspergillus fumigatus* was well suppressed in experimental mice by the ethanolic rhizome extract (Al-Ameri and Azaaz, 2013). Finally, Salim et al. (2019) examined the antibacterial and antifungal properties of *C. speciosus* ethanolic and aqueous extracts. The aqueous extract exerted an antibacterial effect, whereas the ethanolic extract possessed strong antifungal and antibacterial properties.

4. Anticancer Effects of *Costus speciosus*

It is believed that the secondary metabolites of medicinal plants are the source of their numerous biological activities. There have been reports of anticancer properties in plants that contain bioactive chemicals with heterocyclic structures (Ramazani et al., 2014). Flavonoids and terpenoids are present in the nonpolar and semipolar fractions of methanolic extracts of *C. speciosus*, whereas the water-soluble fractions contain saponins (Gheraibia et al., 2020). Triterpenes have been extracted from the roots of *C. speciosus*. Flavonoids have also been extracted from *C. speciosus* (Silva et al., 2000). Other polyphenolic compounds and beneficial compounds have been found in a number of *C. speciosus* tissues (Binny et al., 2010).

Interestingly, a large number of cancer cells have been demonstrated to be susceptible to the cytotoxic effects of *C. speciosus*. Methanolic extracts have been shown to inhibit the growth of triple-negative breast cancer (TNBC), human colon adenocarcinoma cells (Baskar et al., 2012), metastatic breast cancer cells (Gheraibia et al., 2020), and hepatoblastoma (Bawakid et al., 2021). The nonpolar components of these extracts include compounds that inhibit the cell cycle, downregulate mutant p53, and induce apoptosis (Gheraibia et al., 2020). Furthermore, crude ethanolic *Costus cuspidatus* extracts demonstrated cytotoxic effects on human T cells and human leukemia (Siqueira et al., 2016). Although these compounds have relevant biological activity, the mechanisms of action remain poorly understood. Only a few molecular docking simulations of bioactive chemicals from *C. speciosus* have been published, including caspases (Pawar and Pawar, 2014) and COXs (Naznin et al., 2022).

When tested against human colon cancer cell lines, a number of *C. speciosus* rhizome extracts showed dose-dependent antioxidant and antiproliferative effects (Baskar et al., 2012). Moreover, 100 µg/mL of a methanolic *C. speciosus* leaf extract dramatically reduced the viability of hepatocellular carcinoma cells (Nair et al., 2014). In another study, diosgenin demonstrated strong cytotoxic effect on hepatocellular carcinoma and breast cancer cells.

Furthermore, diosgenin exerted cytotoxic effects that were similar to those of paclitaxel. It upregulated the expression of death receptor 4 and caspase-3 to induced apoptosis of MCF-7 cells, a human breast cancer cell line (Selim and Al Jaouni, 2015). The effects of *C. speciosus* rhizome extracts were evaluated using human colon adenocarcinoma cell lines. They exerted notable antiproliferative and antioxidant effects in a dose- and time-dependent manner (Baskar et al., 2012). Nair et al. (2014) found that treatment with 100 µg/mL of a methanolic *C. speciosus* extract for 24 h significantly reduced the viability of breast cancer cells. Figure 5 summarises the anti-cancer properties of *C. speciosus*.

4.1. Mechanisms that underlie the anticancer activity of Costus speciosus

Natural, plant-derived molecules have structurally favourable molecular properties compared with synthetic molecules and represent a prominent source of anticancer drugs (Pan et al., 2010). The main plant-derived molecules that are currently utilised in medicine as single entities are alkaloids, lignans, and alkaloid derivatives. Researchers have reported several mechanisms by which the components of *C. speciosus* exert anticancer effects. Figure 6 summarises the anti-inflammatory, anticancer, and antioxidant properties of *C. speciosus*.

Elkady (2019) evaluated the anticancer effectiveness *C. speciosus* extracts against the cell cycle distribution of human prostate cancer cells. The findings demonstrated that by inducing apoptosis, *C. speciosus* extracts prevented PC-3 cell clonal development, invasion, proliferation, and migration

A methanolic *C. speciosus* extract disrupted progression of the cell cycle, as evidenced by elevated casapase-3 activity in the treated cells. Research on how this extract affects cellular pro-apoptotic and anti-apoptotic molecules using molecular methods is still required.

The tumour suppressor p53 is a transcription factor that reacts to various forms of cellular stress. It is acknowledged as the genome protector (Lyle et al., 2014). The expression of growth arrest genes such as p21 is promoted by p53. According to Masgras et al. (2012), p21 is a tumour suppressor that can stop the growth of cancer cells. PUMA, Noxa, BAX, and p53AIP1 are examples of pro-apoptotic genes that localise to the mitochondria and encourage cytochrome *c* release and reduce mitochondrial membrane

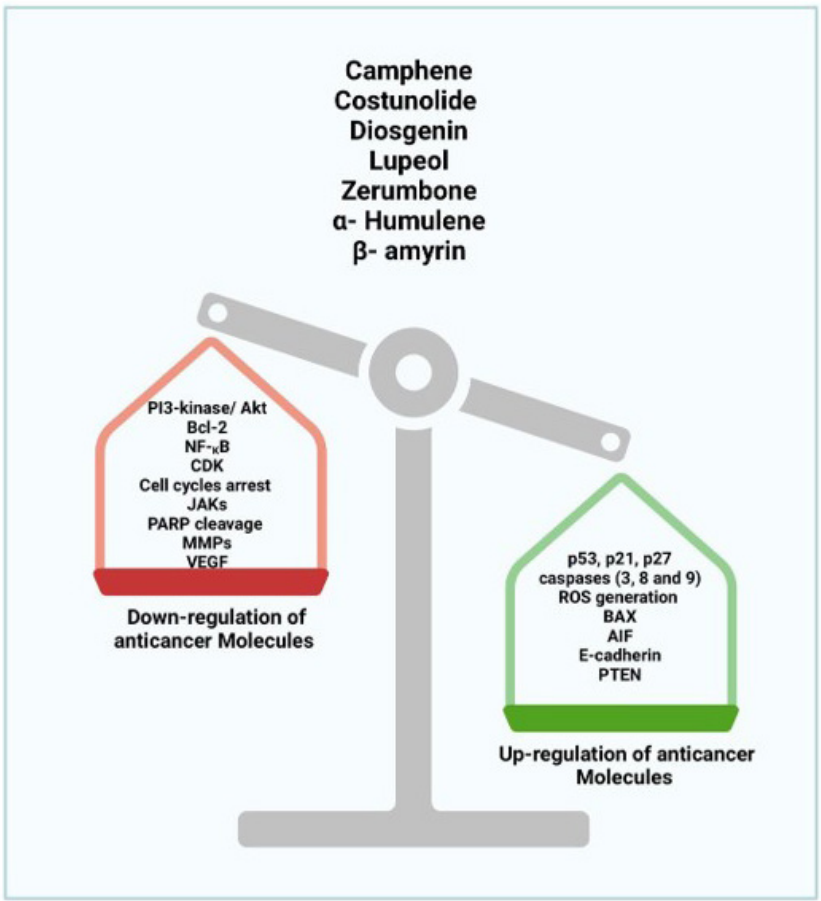

Figure 5. A summary of the anticancer properties of the active components in *Costus speciosus*.
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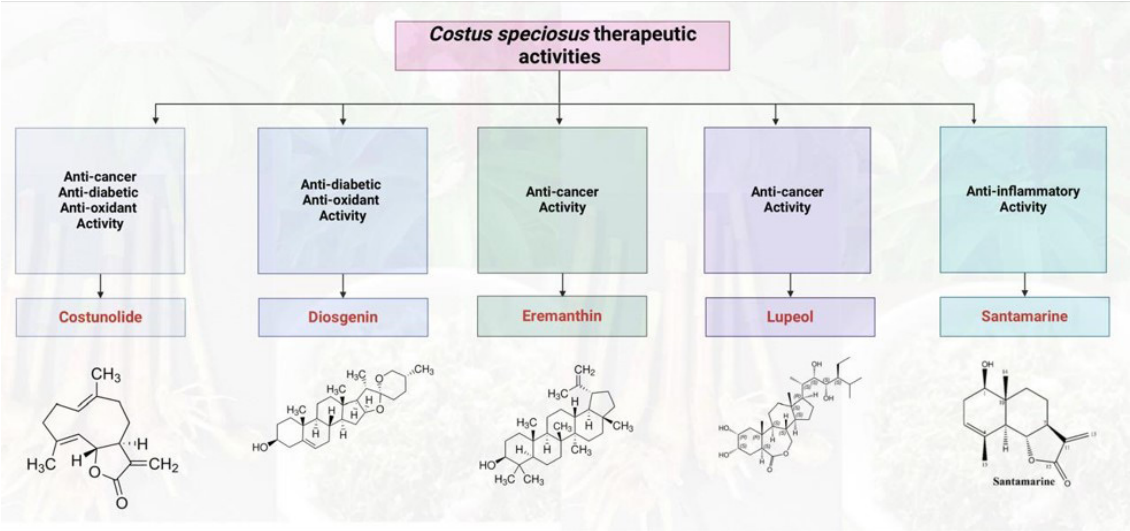

Figure 6. An overview of the anti-inflammatory, anticancer, and antioxidant properties of *Costus speciosus*.
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potential. Furthermore, p53 controls elements that are involved in the extrinsic apoptotic pathway, such as Fas or DR5/KILLER. Lastly, p53 induces the generation of ROS, which harm the mitochondria and trigger apoptosis (Polyak et al., 1997).

Pitchai et al. (2014) examined the cytotoxicity of costunolide to human breast adenocarcinoma cells (MDA-MB-231, a TNBC cell line). It led to cell cycle arrest, as determined by flow cytometry. Additionally, at 20 and 40 µM, costunolide inhibited the overexpression of NF-κB subunits. Roy and Manikkam (2015) reported a half-maximal inhibitory concentration (IC_{50}) of 40 µM for costunolide to induce apoptosis of MCF-7 cells. Moreover, there was upregulated expression of cyclin, caspase-3, and caspase-9 in costunolide-treated MCF-7 cells compared with normal breast cells (MCF-10A).

Cyclin-dependent kinase inhibitor 1B (p27Kip1) is an enzyme inhibitor that binds to and stops the activity of the cyclin E–CDK2 and cyclin D–CDK4 complexes. According to Møller (2000), this causes G1-phase arrest, which may stop or slow the growth of cancer cells.

Caspases are endoproteases that hydrolyse peptide bonds in cell proteins to carry out their functions. There are two groups of apoptotic caspases: executioners and initiators (McIlwain et al., 2013). They are triggered in the two primary apoptotic pathways—intrinsic, in which mitochondria are essential, and extrinsic, which is regulated by death receptors. Together with cytochrome *c*, apoptotic protease activating factor 1 (Apaf-1), and deoxyadenosine triphosphate (dATP), caspase-9 is activated by the mitochondrial route and forms an apoptosome in the cytosol. Caspase-3 is activated by the apoptosome (Zou et al., 1997). On the other hand, Fas ligand interaction with Fas complexes triggers caspase-3 and apoptosis, activating the extrinsic pathway (Wajant, 2002).

Changes in cytosolic calcium (Ca^{2+}) levels support a variety of cellular processes, including myofibril contraction, hormone production, and metabolic control (Berridge et al., 2003). Too much Ca^{2+} in the cell can lead to cytotoxicity and apoptosis (Mattson and Chan, 2003).

A Ca^{2+}-dependent cytosolic enzyme called nitric oxide synthase converts l-arginine to NO, which then combines with the free superoxide radical to generate the hazardous free peroxynitrite radical. These free radicals increase the risk of harming intracellular proteins, enzymes, DNA, and cellular membranes. When arachidonic acid is converted to prostaglandin G2, COX2-dependent processes produce ROS, which cause direct oxidative damage to DNA and promote apoptosis (Nikolic and van Breemen, 2001).

A mitochondrial intermembrane flavoprotein known as apoptosis-inducing factor (AIF) causes DNA breakage and chromatin condensation. Through mitochondrial membrane permeabilisation, AIF can also play a role in controlling apoptosis (Candé et al., 2002).

Cell–cell adhesion is influenced by E-cadherin. Downregulation of E-cadherin reduces cell–cell adhesion and promotes metastasis; it enhances invasiveness and favours circulation access, dispersion to distant anatomic sites, extravasation, and colonisation. E-cadherin expression can be increased by combining diosgenin with RNAs that silence hypoxia-inducible factor 1-alpha (HIF-1α) (Berx et al., 1995). By blocking phosphorylated protein kinase B (p-Akt) and mouse double minute 2 homolog, phosphatase and tensin homolog (PTEN) increases p53 levels, which causes G1-phase arrest and apoptosis. According to Haas-Kogan et al. (1998), PTEN works by dephosphorylating phosphatidyl inositol 3-phosphate (PIP3) and inhibiting survival signalling that is mediated by Akt.

According to Youle and Strasser (2008), the B cell lymphoma-2 (BCL2) protein family includes important regulators of apoptosis. It can be divided into three subgroups: pro-apoptotic (BAX, BAK, and BOK), anti-apoptotic (BCL2, BCL-xL, and BCL2L10), and BH3-only

pro-apoptotic members. BAX is a tumour suppressor gene, while BCL2 is an oncogene. BCL2 overexpression enhances cell survival both *in vivo* and *in vitro*. BAX overexpression accelerates cell death; indeed, cell survival or death is determined by the BCL2/BAX ratio (Chao and Korsmeyer, 1998). Additionally, NF-κB p65–p52 signalling mediated the effects of glial cell line–derived neurotrophic factor on BCL2 and BCL2-w expression (Cao et al., 2013).

NF-κB activates groups of pro-apoptotic and anti-apoptotic genes in addition to its own inhibitor, IκB (Perkins, 2007). NF-κB inhibits the action of the caspase cascade and stimulates the transcription of the inhibitor of apoptosis protein (IAP) gene. IκB is broken down once the cell is stimulated by different substances, which enables NF-κB to move to the nucleus and attach to the promoter regions of its numerous target genes to support cell survival (Park and Hong, 2016).

Diosgenin inhibits the growth of cancer cells by inducing apoptosis. Diosgenin presented an IC_{50} of 32.62 µg/mL for HepG2 cells (a hepatocellular carcinoma cell line), more efficacious than paclitaxel, and 11.03 µg/mL for MCF-7 cells. Selim and Al Jaouni (2015) claimed that diosgenin increases the levels of caspase-3 and death receptor 4, which trigger apoptosis in MCF-7 cells. The active components of C. speciosus may have anticancer properties through upregulating pro-apoptotic and downregulating antiapoptotic molecules, which simultaneously reduce the growth and spread of cancer cells (El-Far et al., 2016).

Dehydrocostus lactone and other sesquiterpene lactones that are found in *C. speciosus* also have notable anticancer effects (DeVita et al., 2008; Kumar et al., 2024). According to Hua et al. (2016), in human lung squamous carcinoma cells, dehydrocostus lactone triggered mitochondria-mediated apoptosis and induced G1/S-phase arrest. Dehydrocostus lactone may be useful in the treatment of cancer because it reduces osteoclastogenesis and osteoclast-induced bone loss (Hu et al., 2019), perhaps by altering the NF-κB pathway (Lu et al., 2023). Hoesel and Schmid (2013) reported that dehydrocostus lactone targets the phosphoinositide 3-kinase (PI3K)/Akt signalling pathway to suppress cell growth and to encourage apoptosis in a variety of cancer cells.

Another substance found in *C. speciosus*, cyanaropicrin, has also demonstrated encouraging anticancer activity. Cynaropicrin efficiently suppresses leukocyte cancer cell proliferation and induces apoptosis and cell cycle arrest (Lau et al., 2008). Zimmermann et al. (2012) stated that cynaropicrin may be a cytotoxic substance because it demonstrated cytotoxicity against a variety of cell types. De Cicco et al. (2021) investigated how cynaropicrin inhibited the growth of human melanoma and emphasised its potential lethal effects. Pulito et al. (2015) validated the cytotoxic actions of cynaropicrin by showing that it promotes apoptosis.

Diosgenin has the ability to inhibit proliferation by producing abundant ROS. This oxidative stress causes HepG2 cells to undergo apoptosis by activating the c-Jun N-terminal kinase (JNK/p38) MAPK pathway (Kim et al., 2012).

Numerous medicinal plants, including *Laurus nobilis*, *Saussurea lappa*, and *C. speciosus*, contain costunolide (El-Far et al., 2018). Costunolide prevents the growth, invasion, metastasis, and angiogenesis of cancer cells (Liu et al., 2011). By upregulating p53, costunolide prevented human colorectal cancer (HCT116) cells from proliferating (Hu et al., 2018). Additionally, by activating p53 and generating ROS, costunolide caused human oesophageal carcinoma (Eca-109) cells to undergo apoptosis (Hua et al., 2016). In addition to inducing p21WAF1-related G2/M-phase arrest and Fas-mediated apoptosis, ROS production caused MDA-MB-231 cells to undergo apoptosis (Choi et al., 2012). Free costunolide reduced BCL2 in HCT116 and MDA-MB-231 cells and increased BAX in MDA-MB-231 cells, causing both cell lines to undergo apoptosis. In HCT116 cells, costunolide induced apoptosis by suppressing mammalian target of rapamycin (mTOR) phosphorylation (Hu et al., 2018) and promoting the upregulation of p53 and thioredoxin reductase 1 (TrxR1) (Zhuge et al., 2018). By producing ROS and causing cell cycle arrest, costunolide caused MDA-MB-231 to undergo apoptosis (Choi et al., 2012). It caused prostate cancer cells to undergo apoptosis by activating MAPKs and ROS production (Chen et al., 2017), and it inhibited the PI3K/Akt pathway to induce apoptosis in doxorubicin-resistant chronic myeloid leukemia (K562/ADR) cells (Cai et al., 2019).

4.2. The potential benefits of Costus speciosus for breast cancer

According to Siegel et al. (2017), approximately 30% of all new cancer diagnoses are for breast cancer, the second most lethal cancer. According to recent data, breast cancer has overtaken lung cancer as the most common cancer throughout the world. It poses a serious risk to women's health and lives due to its very high mortality rate. Histopathological examination is the most commonly used method to diagnose breast cancer. Automated histopathological image categorisation could expedite a diagnosis and reduce the possibility of errors in breast cancer diagnosis (Lakhani et al., 2012). A biopsy is used in histopathology to acquire pictures of the afflicted tissue (Das et al., 2021). Treatment of sickness and the prognosis depend on early identification (WHO, 2022).

According to Halimah et al. (2024), a *C. speciosus* leaf extract reduced the growth of MCF-7 cells due to the induction of apoptosis. An ethanolic extract induced necrosis of HeLa cells. Furthermore, diosgenin and beta-sitosterol may interact with Phe247 and Phe250 in the caspase-3 catalytic site.

C.speciosus contains secondary metabolites, including beta-sitosterol, tigogenin, diosgenin, and 5α-stigmast-9, that could be useful to treat breast cancer (Bawakid et al., 2021; Thambi and Cherian, 2023). Researchers have examined the binding mechanism and affinity of beta-sitosterol and diosgenin in the catalytic domain of cysteineaspartyl protease-3 (caspase-3) by using molecular docking simulation. Diosgenin exerts anticancer activity through a number of mechanisms. It has been shown to alter the cell cycle and to promote apoptosis. Diosgenin-exposed cells exhibited p53 activation and cell cycle arrest (Corbiere et al., 2004). Diosgenin may cause human hepatocellular carcinoma cells to undergo G2/M-phase

arrest and die (Li et al., 2015). In osteosarcoma cells (1547), diosgenin increased COX activity and led to cell cycle arrest and apoptosis (Moalic et al., 2001). Diosgenin promoted the overexpression of caspase-3 (Raju et al., 2004), caspase-8 (Li et al., 2015), and caspase-9 (Cailleteau et al., 2009). According to Srinivasan et al. (2009), diosgenin could downregulate BCL2 and BCL-xL. According to Selim and Al Jaouni (2015), diosgenin isolated from *C. speciosus* also increased the proliferation of MCF-7 cells and caspase-3 levels. Widastuti et al. (2017) found that diosgenin and taurine reduce the quantity of spermatogonia, spermatocytes, and spermatid cells that form. The combination of doxorubicin and hesperidin could increase MC-7 apoptosis and may represent a novel chemotherapeutic (Hermawan et al., 2010).

Vegetables, grains, nuts, seeds, and olive oil are rich sources of beta-sitosterol. This phytosterol reduces the viability of MCF-7 and MDA-MB-231 cells by altering the PI3K/Akt/mTOR pathway (Zhu et al., 2018). It alters the shape of human cervical cancer cells by increasing the electron density in the cell membrane and decreasing the number of organelles (Baek et al., 2017). In U937 cells, beta-sitosterol downregulated BCL2 but did not alter the expression BCL-xL or BAX, indicating a link between caspase-3 activation and BCL2 downregulation (Sharmila and Sindhu, 2017).

Dehydrocostus lactone and costunolide exert anticancer activity through a number of mechanisms: the inhibition of angiogenesis (Hao et al., 2010), the induction of apoptosis and differentiation in cancer cells (Choi and Ahn, 2009), the inhibition of invasion and metastasis (Kim et al., 2008), the reversal of multidrug resistance (Yang et al., 2011), and the inhibition of cancer cell proliferation (Liu et al., 2011) (Figure 7). Costunolide causes breast cancer cells to undergo apoptosis (Roy and Manikkam, 2015). This compound interacts with SOD, catalase, and GPx in human breast cancer cells (Rajalakshmi et al., 2014). Additionally, it worked in concert with *Rhaphidophora pinnata*, which inhibits MCF-7 cell proliferation and death (MASFRIA et al., 2013).

4.3. The potential benefits of Costus speciosus for ovarian cancer

Among the gynaecological cancers, ovarian cancer has the highest fatality rate (Kuroki and Guntupalli, 2020). Ovarian cancer is frequently referred to as a silent killer because

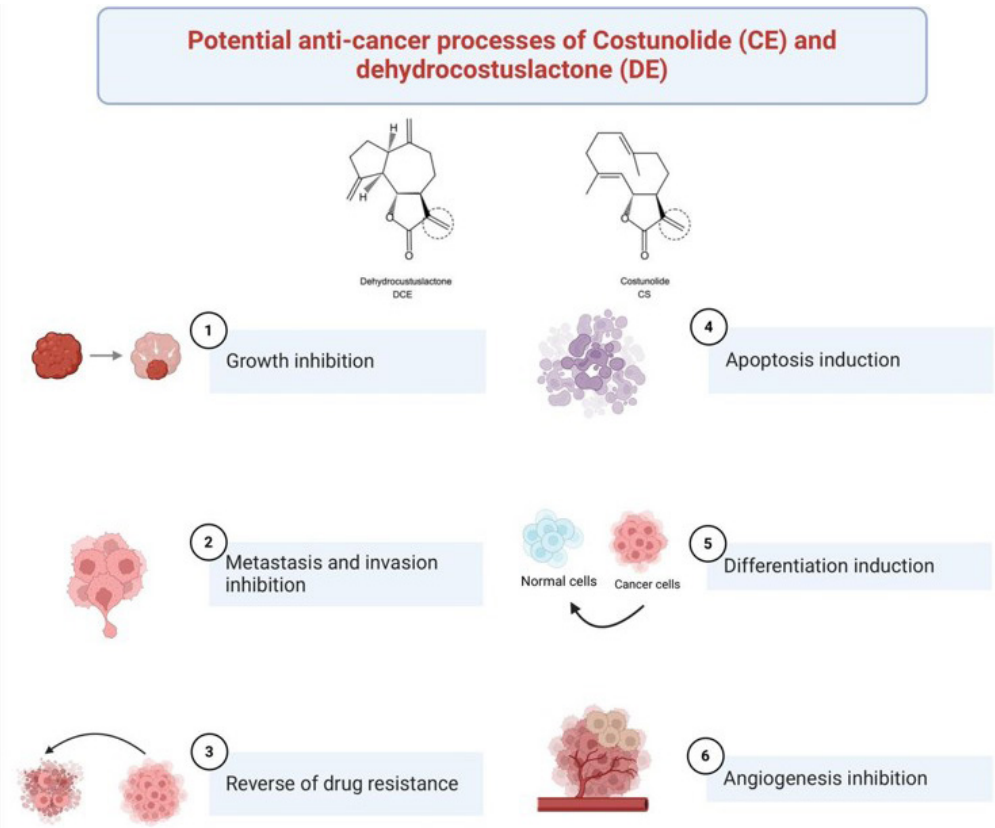

Figure 7. The chemical structures of costunolide (CE) and dehydrocostus lactone (DE) and their potential anticancer effects through six main mechanisms: growth suppression, cell cycle regulation, apoptosis induction, inhibition of angiogenesis, inhibition of invasion and metastasis, differentiation induction, and reversal of treatment resistance.
Source: Figure is designed by authors.

its symptoms are rarely detected in the early stages, so the majority of new cases are detected in advanced stages (III and IV) (Nersesian et al., 2019; Pokhriyal et al., 2019). Each year, up to 314,000 women receive an ovarian cancer diagnosis each year, and 207,000 of them die as a result of the disease. Female patients with ovarian cancer have the lowest probability of surviving a malignancy (WHO, 2020).

To make surgery easier, chemotherapy is used to reduce the tumour size. The majority of ovarian tumours respond well to platinum treatment; nevertheless, platinum resistance occurs in some of these cases, and survival is only marginally increased (Binju et al., 2019). Furthermore, 70% of those with more aggressive tumours recur 6–12 months after finishing chemotherapy (Huang et al., 2020). Cancer chemotherapy is limited by nonspecific or dose-related cellular toxicity and multidrug resistance (Harsono, 2020). Chemotherapy can induce apoptosis by increasing the levels of proapoptotic transcription factors such as p53 and BAX (Nurmaulawati, 2021).

Apoptosis happens frequently to preserve homeostatic equilibrium (Singh et al., 2019). The protein groups p53 and BCL2 are crucial in controlling apoptosis. According to Manne et al. (2021), p53 is a tumour suppressor gene, while proapoptotic BCL2 family proteins make tumours more sensitive to treatment. Apoptosis and aberrant cell proliferation may result from an imbalance between these proteins. Numerous alterations have been found in both the intrinsic and extrinsic apoptotic pathways, and cancer cells employ a variety of tactics to evade apoptotic processes (Liu et al., 2017). Whereas p53 controls BAX, an increase in BH3 alone can initiate the activation of BAX/BAKp53, which has essential roles in regulating the cell cycle and apoptosis, and preserving genomic stability (Wang et al., 2023). Activation-induced oligomerisation of BAX and BAK leads to mitochondrial outer membrane permeabilisation (MOMP) (Dadsena et al., 2021). Myeloid cell leukemia 1 (MCL1) has a lot of promise as a target for tumour treatment. Selective MCL1 inhibitors have emerged as novel anticancer medications (Wang et al., 2021).When a specific inhibitor binds to MCL1, the pro-apoptotic proteins BAX/BAK are released, and apoptosis is triggered.

A potential alternative treatment for ovarian cancer is *C. speciosus*. The rhizomes and roots contain gracilin, quinine, dioscin, dioscinprosapogenin A and B, and sitosterol-β-D-glucoside (Nafisah et al., 2022). The pharmacological properties of diosgenin mostly relate to its anticancer action based on preclinical animal models and *in vitro* experiments. According to Sethi et al. (2018), diosgenin primarily functions by altering a number of cell signalling pathways that are involved in cell cycle regulation, cell differentiation, and cell death. In SKOV-3 cells, an ovarian epithelial cell line, the ethanol extract of rhizome pacing (EP) was cytotoxic, with a notable IC_{50} of 69.143 µg/mL. Flow cytometry showed that apoptosis occurred in SKOV-3 cells treated with the extract (Hidayah et al., 2023). Diosgenin might be the reason why EP triggered apoptosis.

Molecular docking is a computational simulation that pairs a ligand receptor's active site to anticipate the binding between drugs. As seen in Figure 8, molecular docking

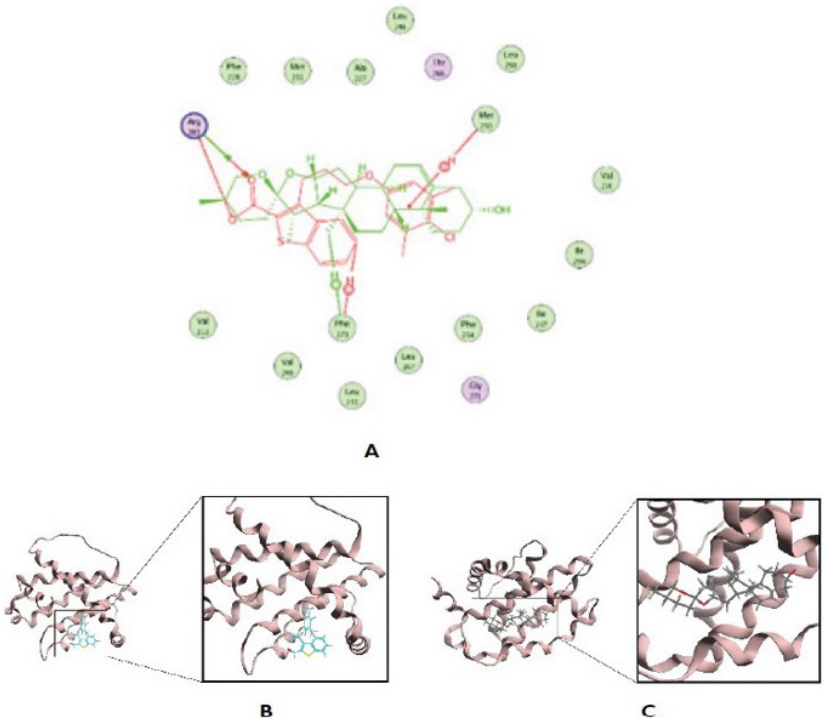

Figure 8. (A) Overlay of the diosgenin (green) and the native ligand complex; (B) and (C) three-dimensional (3D) visualisation of the native ligand and 4HW3 (Hidayah et al., 2023).

is frequently employed to identify novel medications that are more efficacious (Pratama et al., 2017). Based on molecular docking, diosgenin can bind more efficaciously to MCL1 compared with 19G, a native ligand. Of note, when binding to MCL1, diosgenin can interact with that crucial residue with which 19G interacts. Therefore, diosgenin may represent an MCL1 inhibitor.

Yang et al. (2011) stated that costunolide induced the apoptosis of platinum-resistant ovarian cancer cell lines—MPSC1(PT), A2780(PT), and SKOV3(PT)—in a time- and dose-dependent manner and suppressed tumour growth in a SKOV3(PT)-bearing mouse model through activation of caspase-3, caspase-8, and caspase-9, and downregulation of BCL2. In a xenografted tumour of human gastric adenocarcinoma BGC-823 cells, costunolide increased cleaved caspase-9, cleaved caspase-3, and Bax levels, and decreased BCL2 (Yan et al., 2019).

In SKOV-3 cells, overexpression of the BAX gene leads to MOMP and thus the release of molecules that lead to the initiation of apoptosis. Elevated p53 gene expression resulting from DNA damage can cause cancer cells to undergo apoptosis (Aubrey et al., 2017). As shown in Figure 9, increased p53 gene expression can control BAX expression and activity, further encouraging apoptosis. This anti-apoptotic protein plays a crucial role in blocking the apoptosis pathway by preventing BAX activation.

4.4. The potential benefits of Costus speciosus for uterine disorders

Lijuan et al. (2011) evaluated the influence of an ethanolic *C. specious* rhizome extract on spontaneous phasic uterine contractions. The experiment involved the use of longitudinal myometrial strips to assess isometric force. Along with a considerable increase in basal tension, the amplitude and frequency of phasic contraction also increased. By inhibiting myosin light chain kinase (MLCK) or L-type calcium channels, the force was eliminated in the presence of the extract. Fulvestrant, an oestrogen receptor blocker, had no effect on the extract's effects. The extract included a considerable amount of diosgenin, but diosgenin alone had no impact on force or even inhibited force, depending on the amount that was added. The extract produced a considerable amount of force without extracellular Ca^{2+}, which was prevented by blocking the sarcoplasmic reticulum calcium-ATPase (SERCA), while fulvestrant did not. Based on these findings, non-estrogenic actions rather than the action of diosgenin are responsible for the uterotonic effect.

Menstruation cramps can produce significant pain that impairs the quality of life of many women. Even in the absence of an underlying infection or other medically recognised illness states, severe uterine contractions are believed to cause moderate to severe pain in cases of primary dysmenorrhea, a condition associated with premenstrual

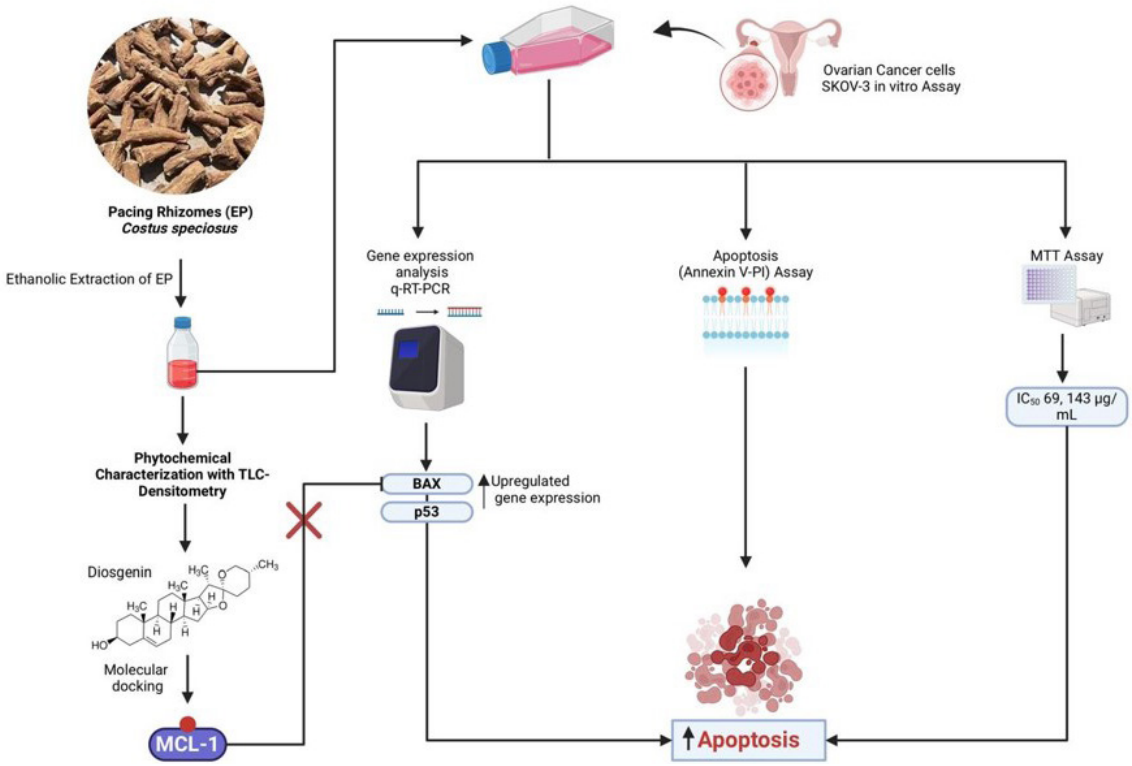

Figure 9. The mechanism by which p53 and BAX regulate the apoptosis of SKOV-3 cancer cells.
Source: Figure is designed by authors.

syndrome (PMS). The release of prostaglandins, leukotrienes, and leukocytes that typically accompany the disintegration of the endometrial lining are thought to be responsible for the associated pain and the uterine hypercontractility that is evocative of labour. According to Röhrl et al. (2016), standardised extracts of *Vitex agnus-castus* berries and *C. speciosus* are clinically useful in alleviating PMS symptoms.

Flavonoids, low-molecular-weight phenolic compounds (Middleton-Junior et al., 2000), exert antiviral, anti-inflammatory, and antioxidant properties. Flavonoid extracted from *C. speciosus* demonstrated spasmolytic effect on the rat aorta and uterus as well as the guinea pig ileum and trachea (Macêdo et al., 2011).

Our understanding of uterine pathophysiology, including embryo implantation and disorders such as dysmenorrhea and colic, which are caused by uncontrollable uterine contractions, has advanced significantly in recent years (Aguilar and Mitchell, 2010). According to Bortoleto (1995), excessive contractions cause pain that can potentially result in hypoxia, ischemia, and decreased uterine vascular flow. Certain flavonoids, including genistein, kaempferol, quercetin (Revuelta et al., 1997), and isoliquiritigenin, have demonstrated spasmolytic activity in the rat uterus. These flavonoids also demonstrated analgesic activity in mice (Shi et al., 2012), and the flavonoid galetin 3,6-dimethyl ether (Macêdo et al., 2011) demonstrated anti-inflammatory and antinociceptive properties in mice (Queiroz et al., 2010).

There has been almost no investigation regarding the mechanisms by which *C. speciosus* affects uterine cancer; thus, additional research is needed in this area.

5. Comprehensive review:

1. This study provides a thorough overview of the biological activities, chemical compositions, and potential therapeutic uses of *C. speciosus*, a critically endangered medicinal plant.
2. Diverse applications: This review highlights the wide range of pharmacological properties of *C. speciosus*, including its antimicrobial, anti-inflammatory, antioxidant, anti-cancer, antiviral, and hepatoprotective effects, demonstrating its versatility as a potential therapeutic agent.
3. Detailed analysis: This study investigated the specific bioactive compounds present in *C. speciosus*, such as costunolide, dehydrocostus lactone, and cynaropicrin, and explored their mechanisms of action and contribution to the plant's diverse biological activities.

Overall, our comprehensive study of *C. speciosus* presents a robust and informative review, highlighting the significant potential of this medicinal plant and acknowledging the need for further research, standardized methodologies, and conservation efforts to fully realize its therapeutic applications.

6. Conclusion

This review has demonstrated the diverse therapeutic potential of *C. speciosus* in many disorders, opening up new avenues for clinical investigation. Future research should identify the specific compounds present in *C. speciosus* that exert the therapeutic effects and their mechanisms of action. Moreover, safety evaluations of *C. speciosus* extracts are necessary. In the future, methanolic, ethanolic, hexane, and chloroform extracts of *C. speciosus* could be used either alone or in conjunction with pharmaceuticals to treat numerous diseases.

Future research should focus on validating the potential of *C. speciosus* in clinical settings and further investigate its biotechnological and pharmaceutical applications. Standardized research methodologies and rigorous clinical trials are vital for confirming its effectiveness and safety in various medical fields.

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Ethics and consent

Ethical approval number IRB-2020-10-052 was issued by the Institutional Review Board at Imam Abdulrahman bin Faisal University.

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