Current Drug Discovery Technologies, 2016, *13*, 123-143

REVIEW ARTICLE

Possible Anticancer Mechanisms of Some *Costus speciosus* Active Ingredients Concerning Drug Discovery

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ARTICLE HISTORY

Received: May 30, 2016
Revised: July 18, 2016
Accepted: July 26, 2016

DOI: 10.2174/1570163813666160802154403

Abstract: *Costus speciosus* is native to South East Asia, especially found in India, Srilanka, Indonesia and Malaysia. *C. speciosus* have numerous therapeutic potentials against a wide variety of complains. The therapeutic properties of *C. speciosus* are attributed to the presence of various ingredients such as alkaloids, flavonoids, glycosides, phenols, saponins, sterols and sesquiterpenes. This review presented the past, present, and the future status of *C. speciosus* active ingredients to propose a future use as a potential anticancer agent. All possible up-regulation of cellular apoptotic molecules as p53, p21, p27, caspases, reactive oxygen species (ROS) generation and others attribute to the anticancer activity of *C. speciosus* along the down-regulation of anti-apoptotic agents such as Akt, Bcl2, NFκB, STAT3, JAK, MMPs, actin, surviving and vimentin. Eventually, we recommend further investigation of different *C. speciosus* extracts, using some active ingredients and evaluate the anticancer effect of these chemicals against different cancers.

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Keywords: *Costus speciosus,* anticancer mechanisms, future vision.

INTRODUCTION

Plant active principles are important task for developing therapeutic agents. Herbal products are greatly safe in comparison to the synthetics. Herbal natural products are a components of different parts of medicinal herb [1]. From the important medicinal plant families is the *Zingiberaceae* that distributed throughout tropical Africa, Asia, Americas and Indo-Malayan region, Sri Lanka and in India. It is commonly grown along road sides and streams [2]. The rhizomes and roots are ascribed to have an anthelmintic, expectorant, tonic, aphrodisiac, flatulence, anti-inflammatory, antidiabetic, hepatoprotective, antihyperlipidemic, antispasmodic and antimicrobial activities [3]. Indeed, leaf extract of *C. speciosus* shows potential *in vitro* anticancer activity toward liver cancer [4]. *C. speciosus* serves as an important source of numerous compounds owning many pharmacological benefits as diosgenin, tigogenin, saponins and β-sitosterol; diosgenin, 5α-stigmast-9 (11)-en-3β-ol, β-sitosterol-β-D-glucoside, dioscin, prosapogenins A and B of dioscin, gracillin, α-tocopherol; diosgenone, cycloartanol, 25-en-cycloartenol and octacosanoic acid [5]. The major compounds *C. speciosus* oils such as α-humulene, zerumbone, camphene, α-amyrin stearate, β-amyrin, costunolide and lupeol have been isolated from its rhizomes and their structural formula are illustrated in Fig. **1** [6,7].

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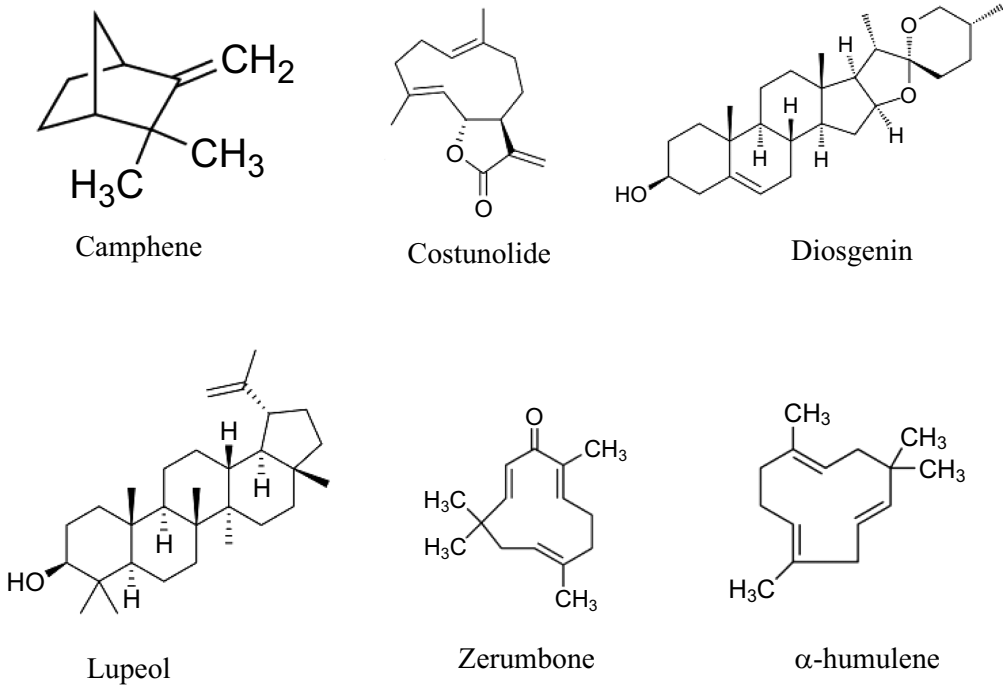

Fig. (1). Shows the structural formulae of some active ingredients present in *C. speciosus.*

Anticancer Activity Evaluation and Mechanism of *Costus speciosus* Active Ingredients

In Vitro Anticancer Activity

Up-Regulation of p53, p21 and p27

The tumor suppressor p53 is a transcription factor that responds to diverse cases of cellular stress. It is recognized as the guardian of the genome [8]. P53 promotes growth arrest genes as p21. The p21 is a tumor suppressor able to suppress cancer cell proliferation [9]. The pro-apoptotic gene products such as the PUMA, Noxa, BAX and p53AIP1 localize to the mitochondria and promote the loss of mitochondrial membrane potential and cytochrome c release. Moreover, Fas or DR5/KILLER, the components of the extrinsic pathway of apoptosis were regulated by p53. Finally, p53 induces in reactive oxygen species (ROS) production that damage the mitochondria, leading to apoptosis [10].

Cyclin-dependent kinase inhibitor 1B (p27Kip1) is an enzyme inhibitor that binds to and inhibits the activation of cyclin E-CDK2 and cyclin D-CDK4 complexes, and thus induces G1 phase arrest that may be stop or slow down the cancer cell growth [11]. The up-regulation of p53, p21 and p27 by *C. speciosus* active ingredients in different cancer cells is illustrated in Table **1**.

Up-Regulation of Caspases

Caspases are endo-proteases that accomplish their activity by hydrolysing cell protein peptide bonds. The apoptotic caspases have been sub-classified by their mechanism of action into initiator caspases (caspase-8 and -9) or executioner caspases (caspase-3, -6, and -7) [12]. They are activated in both main apoptotic pathways: extrinsic, mediated by death receptors, and intrinsic, where mitochondria play a central role. The mitochondrial pathway activates caspase-9, which, when activated, forms an apoptosome in the cytosol, together with cytochrome c, Apaf-1 and deoxyadenosine triphosphate (dATP). The apoptosome activates caspase-3 [13]. Whereas, the extrinsic death receptor Fas pathway is activated by Fas ligand interaction with Fas complexes those activate caspase 3 and induce apoptosis [14]. The up-regulation of apoptotic initiators and executioner caspases by *C. speciosus* active ingredients in numerous cancer cells are illustrated in Table **2**.

Calcium Overload Induce Apoptosis

Variation in cytosolic calcium concentration promotes numerous cellular functions as contraction of myofilaments, secretion of hormonal secretion and metabolic regulation [15]. However, it has become clear that cellular Ca^{2+} overload can cause cytotoxicity and trigger apoptosis [16]. The up-regulation of intracellular Ca^{2+} by *C. speciosus* active ingredients presented in Table **3**.

Table 1. Up-regulation of p53, p21 and p27 by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Up-regulation of p53	Diosgenin	Human osteosarcoma (1547)	[21]
		Cervix carcinoma (HEp-2)	
		Human melanoma (M4Beu)	
		Human osteosarcoma (1547)	[22]
			[23]
	Zerumbone	Human lung cancer (NSCLC)	[24]
		Human pancreatic carcinoma (PANC-1)	[25]
Up-regulation of p21	Costunolide	Human prostate cancer (PC-3)	[26]
		Breast cancer (MDA-MB-231)	[27]
	Diosgenin	Human hepatoma (Bel-7402)	[28]
		Human hepatocellular carcinoma (HepG2)	
		Human hepatoma cells (SMMC-7721)	
		Human osteosarcoma (1547)	[23]
		Human erythromyeloblastoid leukemia (K562)	[29]
		Human colon carcinoma (HCT-116)	[30]
	Lupeol	Human osteosarcoma cells (MNNG/HOS)	[31]
		Human osteosarcoma cells (MG-63)	
		Human pancreatic cancer (PCNA-1)	[32]
		Melanoma (451Lu)	[33]
	Zerumbone	Human pancreatic carcinoma (PANC-1)	[25]
Up-regulation of p27	Diosgenin	Human hepatoma (Bel-7402)	[28]
		Human hepatocellular carcinoma (HepG2)	
		Human hepatoma cells (SMMC-7721)	
	Lupeol	Human osteosarcoma cells (MNNG/HOS)	[31]
		Human osteosarcoma cells (MG-63)	
		Human pancreatic cancer (PCNA-1)	[32]

Table 2. Up-regulation of caspases by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Up-regulation of caspase-3	Camphene	Murine melanoma cell (B16F10-Nex2)	[34]
		Human pancreatic carcinoma (MIA PaCa-2)	[35]
		Human hepatocellular carcinoma (HepG2)	
		Human colon adenocarcinoma (SW-480)	
	Costunolide	Human promyelocytic leukemia (HL-60)	[36]
		Breast cancer (MDA-MB-231)	[27]

Table 2. contd….

		Human bladder carcinoma (T24)	[6]
		Ovarian cancer (MPSC1)	[37]
		Human ovarian carcinoma (A2780)	
		Human ovarian carcinoma (SKOV3)	
		Human breast adenocarcinoma (MCF-7)	[38]
		Breast cancer (MDA-MB-231)	
	Diosgenin	Human erythromyeloblastoid leukemia (K562)	[39]
		Human promyelocytic leukemia (HL-60)	
		Human osteosarcoma (1547)	[21]
		Cervix carcinoma (HEp-2)	
		Human melanoma (M4Beu)	
		Human lung carcinoma (A549)	[40]
		Human erythroleukemia (HEL)	[41]
		Human hepatocellular carcinoma (HepG2)	[42]
		Human breast adenocarcinoma (MCF-7)	
		Human hepatoma (Bel-7402)	[28]
		Human hepatocellular carcinoma (HepG2)	
		Human hepatoma cells (SMMC-7721)	
		Human epidermoid carcinoma (A431)	[43]
		Human hepatocellular carcinoma (Hep2)	
		Human erythroleukemia (HEL)	[44]
		Human erythromyeloblastoid leukemia (K562)	[29]
		Human colon adenocarcinoma (HT-29)	[45]
Up-regulation of caspase-3	Lupeol	Melanoma (451Lu)	[33]
		Head and neck squamous cell carcinoma (HNSCC)	[46]
		Human hepatoma cells (SMMC-7721)	[47]
		Human hepatocellular carcinoma (HepG2)	
	Zerumbone	Acute promyelocytic leukemia (NB4)	[48]
		Chronic myeloid leukemia (CML)	[49]
		Human erythromyeloblastoid leukemia (K562)	
		Human T-cell (Jurkat)	[50]
		Human lung cancer (NSCLC)	[24]
		Human renal carcinoma (786-0)	[51]
		Human renal carcinoma (769-P)	
		Human brain malignant glioma (GBM8401)	[52]
		Human pancreatic carcinoma (PANC-1)	[25]
		Human epithelioid cervical carcinoma (HeLa)	[53]
	leaves methanol extract	Human hepatocellular carcinoma (HepG2)	[4]

Table 2. contd….

Up-regulation of caspase-7	Camphene	Human pancreatic carcinoma (MIA PaCa-2)	[35]
		Human hepatocellular carcinoma (HepG2)	
		Human colon adenocarcinoma (SW-480)	
	Costunolide	Human promyelocytic leukemia (HL-60)	[36]
		Human neuroblastoma (IMR-32)	[54]
		Human neuroblastoma (NB-39)	
		Human neuroblastoma (SK-N-SH)	
		Human neuroblastoma (LA-N-1)	
Up-regulation of caspase-6	Costunolide	Human promyelocytic leukemia (HL-60)	[36]
Up-regulation of caspase-8	Costunolide	Breast cancer (MDA-MB-231)	[27]
		Ovarian cancer (MPSC1)	[37]
		Human ovarian carcinoma (A2780)	
		Human ovarian carcinoma (SKOV3)	
	Diosgenin	Human lung carcinoma (A549)	[40]
		Human erythroleukemia (HEL)	[41]
		Human hepatoma (Bel-7402)	[28]
		Human hepatocellular carcinoma (HepG2)	
		Human hepatoma cells (SMMC-7721)	
	Lupeol	Pancreatic cancer (PaCa)	[55]
	Zerumbone	Acute promyelocytic leukemia (NB4)	[48]
Up-regulation of caspase-9	Costunolide	Ovarian cancer (MPSC1)	[37]
		Human ovarian carcinoma (A2780)	
		Human ovarian carcinoma (SKOV3)	
		Human breast adenocarcinoma (MCF-7)	[38]
		Breast cancer (MDA-MB-231)	
	Diosgenin	Human lung carcinoma (A549)	[40]
		Human erythroleukemia (HEL)	[41]
		Human erythromyeloblastoid leukemia (K562)	[39]
		Human promyelocytic leukemia (HL-60)	
		Human hepatoma (Bel-7402)	[28]
		Human hepatocellular carcinoma (HepG2)	
		Human hepatoma cells (SMMC-7721)	
	Lupeol	Human hepatoma cells (SMMC-7721)	[56]
	Zerumbone	Chronic myeloid leukemia (CML)	[49]
		Human erythromyeloblastoid leukemia (K562)	
		Human T-cell (Jurkat)	[50]
		Human lung cancer (NSCLC)	[24]
		Human renal carcinoma (786-0)	[51]
		Human renal carcinoma (769-P)	
		Acute promyelocytic leukemia (NB4)	[48]

Table 3. Up-regulation of Bax by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Up-regulation of Bax	Costunolide	Human bladder carcinoma (T24)	[6]
	Diosgenin	Human erythromyeloblastoid leukemia (K562)	[29]
		Human erythroleukemia (HEL)	[57]
		Human lung carcinoma (A549)	[40]
		Human epidermoid carcinoma (A431)	[43]
		Human hepatocellular carcinoma (Hep2)	
		Human erythroleukemia (HEL)	[41]
	Lupeol	Human epidermoid carcinoma (A431)	[58]
		Melanoma (451Lu)	[33]
		Head and neck squamous cell carcinoma (HNSCC)	[46]
	Zerumbone	Human lung cancer (NSCLC)	[24]
		Human hepatocellular carcinoma (HepG2)	[59]
Intracellular Ca^{2+} increase	Camphene	Murine melanoma cell (B16F10-Nex2)	[34]
	Zerumbone	Human prostate cancer (PC-3)	[60]
		Human prostate cancer (DU-145)	
		Chronic myeloid leukemia (CML)	[49]
		Human erythromyeloblastoid leukemia (K562)	
Overload of nuclear Ca^{2+}	Costunolide	Human prostate cancer (PC-3)	[26]
		Human prostate cancer (DU-145)	
		Human prostate adenocarcinoma (LNCaP)	

Up-regulation of ROS Generation

Nitric oxide synthase (nNOS) is a Ca^{2+}-dependent cytosolic enzyme that forms nitric oxide (NO) from l-arginine, and NO reacts with the free superoxide radical ($O2^{-}$) to form the toxic free peroxynitrite radical ($ONOO^{-}$). These free radicals predispose the damage of cellular membranes and intracellular proteins, enzymes and DNA. COX-2-dependent reactions generate ROS during the conversion of arachidonic acid to prostaglandin G2, causing direct oxidative damage to DNA and favour apoptosis [17]. The ROS generation in cancer cells and the antioxidant status augmentation of cancer bearing animal by *C. speciosus* active ingredients are tabulated in Table **4**.

Induction of Apoptosis and Oppose Metastasis

The up-regulation of the following mentioned apoptotic molecules by *C. speciosus* active ingredients is illustrated in Table **5**. In which, the apoptosis inducing factor (AIF) is a mitochondrial intermembrane flavoprotein that induce chromatin condensation and DNA cleavage. AIF can also participate in the regulation of apoptosis by means of mitochondrial membrane permeabilization [18].

E-cadherin plays important roles in cell-cell adhesion. Cancer cell metastasis include loss of cell-cell adhesion that leads to increased invasiveness, entry into the circulation, dispersion to distant anatomic sites, extravasation and colonization. Therefore, down-regulation of E-cadherin facilitates metastasis. The combination of diosgenin and HIF-1α silencing RNAs can enhance the expression of E-cadherin [19]. Phosphatase and tensin homolog (PTEN) inhibits p-Akt and mouse double minute 2 homolog (MDM2), and then increases the level of p53, thereby inducing G1 phase arrest and apoptosis. PTEN functions by dephosphorylation of

Table 4. Up-regulation of antioxidant status by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Intracellular thiols depletion	Costunolide	Human prostate cancer (PC-3)	[26]
		Human prostate cancer (DU-145)	
		Human prostate adenocarcinoma (LNCaP)	
Up-regulation of 5-LOX	Diosgenin	Human colon carcinoma (HCT-116)	[61]
		Human colon adenocarcinoma (HT-29)	
Up-regulation of COX-2	Diosgenin	Human colon adenocarcinoma (HT-29)	[61]
		Human colon carcinoma (HCT-116)	
		Human colon carcinoma (HCT-116)	[62]
		Human colon adenocarcinoma (HT-29)	
ROS generation	Costunolide	Breast cancer (MDA-MB-231)	[27]
		Human promyelocytic leukemia (HL-60)	[36]
		Human bladder carcinoma (T24)	[6]
		Ovarian cancer (MPSC1)	[37]
		Human ovarian carcinoma (A2780)	
		Human ovarian carcinoma (SKOV3)	
	Diosgenin	Human erythromyeloblastoid leukemia (K562)	[29]
	Lupeol	Human prostate adenocarcinoma (LNCaP)	[63]
		Human epidermoid carcinoma (A431)	[58]
	Zerumbone	Human lung cancer (NSCLC)	[24]
		Chronic myeloid leukemia (CML)	[49]
		Human erythromyeloblastoid leukemia (K562)	
		Human colon carcinoma (HCT116)	[64]
		Human pancreatic carcinoma (PANC-1)	[25]
	α-Humulene	Human colon carcinoma (CaCo-2)	[65]
	β-amyrin	Human bladder carcinoma (NTUB1)	[66]

Table 5. Up-regulation of some apoptotic molecules by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Up-regulation of Apaf1	Lupeol	Human epidermoid carcinoma (A431)	[58]
Up-regulation of AIF	Diosgenin	Human osteosarcoma (1547)	[21]
		Cervix carcinoma (HEp-2)	
		Human melanoma (M4Beu)	
Up-regulation of ATF3	Zerumbone	Human colon carcinoma (HCT116)	[67]
		Human colon adenocarcinoma (SW-480)	
Up-regulation of E-cadherin	Diosgenin	Human gastric cancer (BGC-823)	[68]
Up-regulation of FADD	Lupeol	Human hepatoma cells (SMMC-7721)	[69]

Table 5. contd….

Up-regulation of Fas	Costunolide	Breast cancer (MDA-MB-231)	[27]
	Zerumbone	Acute promyelocytic leukemia (NB4)	[48]
Up-regulation of integrin α5	Diosgenin	Human gastric cancer (BGC-823)	[68]
Up-regulation of integrin β6.	Diosgenin	Human gastric cancer (BGC-823)	[68]
Up-regulation of Notch2	Zerumbone	Human breast adenocarcinoma (MCF-7)	[70]
		Breast cancer (MDA-MB-231)	[70]
Up-regulation of PTEN	Lupeol	Hepatocellular carcinoma (MHCC-LM3 HCC)	[71]
Up-regulation of Rab27a	Lupeol	Mouse melanoma (B16 2F2)	[72]
Up-regulation of thromboxane synthase	Diosgenin	Human erythroleukemia (HEL)	[41]
Up-regulation of DR4	Zerumbone	Human colon carcinoma (HCT116)	[64]

phosphatidyl inositol 3-phosphate (PIP3) and negatively regulating survival signalling mediated by protein kinase B/Akt (PKB/Akt) [20].

Down-Regulation of Akt

Akt is a serine-threonine kinase which regulates cell growth, survival and proliferation**.** The phosphatidylinositol 3-kinase/Akt pathway plays a key role in cancer cell survival [73]**.** Foxo inhibits tumor growth in breast cancer, and cytoplasmic localization of Foxo interrelated with poorer cancer cell survival. Phosphorylation of Foxos by Akt inhibits transcriptional functions of Foxos and contributes to cell survival, growth and proliferation [73]. The cell survival encouraged by Akt was diminished by *C. speciosus* active ingredients (Table **6**).

Cell Cycle Arrest

The cell cycle starts by G1 phase, during which cytoplasmic organelles are replicated. Afterward, the cell enters into the S phase where the DNA is replicated. After which cell reaches the second phase, G2 where proteins and other cellular elements are synthesized. Eventually, the cell enters M phase where it splits into two daughter cells [74]. Cell cycle progression is forcefully regulated by interaction between cyclin-dependent kinases (Cdk1, 2, 4, or 6) and regulatory cyclin subunits (cyclin A, B, Ds, or E). The cell arrest is accompanied by micro-nucleation resulting from chromosome fragments [75]. This cycle arrest was accomplished by *C. speciosus* active ingredients in different cell cycle phases as presented in Table **7**.

Down-Regulation of BCL2

B cell lymphoma-2 (BCL2) family proteins are key regulators of the apoptotic process and classified into three subgroups anti-apoptotic (BCL2, BCL-XL, and BCL2L10), pro-apoptotic (e.g. BAX, BAK, and BOK) and BH3-only pro-apoptotic members (e.g. BID, BAD, and BIM) [76]. BCL2 and the BCL2-associated X protein gene (BAX) are an oncogene and a cancer suppressor gene, respectively. Overexpression of BCL2 promotes cell survival *in vitro* and *in vivo*. When Bax is overexpressed, cell apoptosis will be hastened. Hence, the ratio BCL2/Bax governs the cell survival or death [77]. Moreover, NF-κB p65/p52 signalling mediated the effects of Glial-cell-line-derived neurotrophic factor (GDNF) on BCL2 and BCL2-w expressions [78]. The up-regulation of Bax by *C. speciosus* active ingredients in different cancer cells is illustrated in Table **3**. Whereas BCL2 down-regulations is presented in Table **8**.

Down-Regulation of NFκB

Nuclear factor κB (NFκB) is a transcription factor that activates its own inhibitor (IκB) as well as groups of pro-apoptotic and anti-apoptotic genes [79]. NFκB activates the inhibitor of apoptosis protein (IAP) gene transcription and down-regulate the activity of the caspase cascade.

Table 6. Down-regulation of PI3-kinase/Akt by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Down-regulation of PI3-kinase/Akt	Lupeol	Human hepatocellular carcinoma (HepG2)	[86]
		Human hepatoma cells (SMMC-7721)	
	Diosgenin	Human prostate cancer (PC-3)	[87]
Down-regulation of Akt	Diosgenin	Human erythroleukemia (HEL)	[88]
		Mouse melanoma (B16)	[89]
		Human prostate cancer (DU145)	[90]
		Human epidermoid carcinoma (A431)	[43]
		Human hepatocellular carcinoma (Hep2)	
		Breast cancer (HER2)	[91]
		Human breast carcinoma (BCa)	[92]
		Human breast carcinoma (BCa)	
	Lupeol	Human epidermoid carcinoma (A431)	[58]
	Zerumbone	Human colon carcinoma (HCT116)	[93]
		Human brain malignant glioma (GBM8401)	[52]
		Non-Small Cell Lung Cancer (A549)	[94]
Down-regulation of (p-PI3K)	Lupeol	Human osteosarcoma cells (MNNG/HOS)	[31]
		Human osteosarcoma cells (MG-63)	
		Human pancreatic cancer (PCNA-1)	[32]
Down-regulation of p-AKT	Lupeol	Gallbladder carcinoma (GBC-SD)	[95]
		Human osteosarcoma cells (MNNG/HOS)	[31]
		Human osteosarcoma cells (MG-63)	
		Human pancreatic cancer (PCNA-1)	[32]

Table 7. Down-regulation of cell cycle components by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Down-regulation of cdc25B	Lupeol	Human prostate cancer (PC-3)	[96]
	Zerumbone	Human prostate cancer (PC-3)	[60]
		Human prostate cancer (DU-145)	
		Human breast adenocarcinoma (MCF-7)	[97]
		Breast cancer (MDA-MB-231)	
		Human breast adenocarcinoma (MCF-7)	
		Breast cancer (MDA-MB-231)	
Down-regulation of cdc42	Diosgenin	Breast cancer (MDA-MB-231)	[98]
Down-regulation of cdk 1	Zerumbone	Human breast adenocarcinoma (MCF-7)	[97]
		Breast cancer (MDA-MB-231)	

Table 7. contd….

Down-regulation of cdk 2	Diosgenin	Human breast carcinoma (BCa)	[92]
	Lupeol	Melanoma (451Lu)	[33]
		Human prostate adenocarcinoma (LNCaP)	[99]
		Human prostate cancer (DU145)	
Down-regulation of cdk 4	Diosgenin	Human breast carcinoma (BCa)	[92]
Down-regulation of cyclin A	Lupeol	Human prostate adenocarcinoma (LNCaP)	[99]
		Human prostate cancer (DU145)	
Down-regulation of cyclin B	Lupeol	Swiss albino mice	[100]
		Human prostate cancer (PC-3)	[96]
Down-regulation of cyclin B1	Diosgenin	Human erythromyeloblastoid leukemia (K562)	[29]
	Lupeol	Human prostate adenocarcinoma (LNCaP)	[99]
		Human prostate cancer (DU145)	
	Zerumbone	Human breast adenocarcinoma (MCF-7)	[97]
		Breast cancer (MDA-MB-231)	
		Acute promyelocytic leukemia (NB4)	[48]
Down-regulation of cyclin D1	Diosgenin	Human breast carcinoma (BCa)	[92]
	Lupeol	Melanoma (451Lu)	[33]
		Human prostate adenocarcinoma (LNCaP)	[99]
		Human prostate cancer (DU145)	
		Human osteosarcoma cells (MNNG/HOS)	[31]
		Human osteosarcoma cells (MG-63)	
		Human pancreatic cancer (PCNA-1)	[32]
Down-regulation of cyclin D2	Lupeol	Melanoma (451Lu)	[33]
		Human prostate adenocarcinoma (LNCaP)	[99]
		Human prostate cancer (DU145)	
		Human prostate adenocarcinoma (LNCaP)	
		Human prostate cancer (DU145)	
G0/G1 phase arrest	Lupeol	Human osteosarcoma cells (MG-63)	[31]
		Human osteosarcoma cells (MNNG/HOS)	
		Human pancreatic cancer (PCNA-1)	[32]
	Zerumbone	Human prostate cancer (DU145)	[101]
		Human prostate cancer (PC-3)	
		Human colon adenocarcinoma (HT-29)	[102]
G1 phase arrest	Costunolide	Human prostate cancer (PC-3)	[26]
		Human prostate cancer (DU-145)	
		Human prostate adenocarcinoma (LNCaP)	
	Diosgenin	Human erythroleukemia (HEL)	[103]
		Human osteosarcoma (1547)	[23]
		Human breast carcinoma (BCa)	[92]

Table 7. contd….

G1/S phase arrest	Lupeol	Melanoma (451Lu)	[33]
G2/M phase arrest	Costunolide	Breast cancer (MDA-MB-231)	[27]
		Human bladder carcinoma (T24)	[6]
		Human breast adenocarcinoma (MCF-7)	[38]
		Breast cancer (MDA-MB-231)	
	Diosgenin	Human erythroleukemia (HEL)	[57]
		Human hepatoma (Bel-7402)	[28]
		Human hepatocellular carcinoma (HepG2)	
		Human hepatoma cells (SMMC-7721)	
		Human erythromyeloblastoid leukemia (K562)	[39]
		Human promyelocytic leukemia (HL-60)	
		Human erythromyeloblastoid leukemia (K562)	[29]
	Lupeol	Human prostate cancer (PC-3)	[96]
	Zerumbone	Human ovarian cancer (Caov-3)	[104]
		Human epithelioid cervical carcinoma (HeLa)	[104]
		Human colorectal cancer (CRC)	[105]
		Human colon adenocarcinoma (HT-29)	[102]
		Human breast adenocarcinoma (MCF-7)	[97]
		Breast cancer (MDA-MB-231)	
		Acute promyelocytic leukemia (NB4)	[48]

Table 8. Down-regulation of Bcl-2 and Bcl-xL by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Down-regulation of Bcl-2	Costunolide	Human bladder carcinoma (T24)	[6]
		Human ovarian carcinoma (SKOV3)	[37]
		Human ovarian carcinoma (A2780)	
		Human ovarian carcinoma (SKOV3)	
	Diosgenin	Human lung carcinoma (A549)	[40]
		Human epidermoid carcinoma (A431)	[43]
		Human hepatocellular carcinoma (Hep2)	
		Human erythroleukemia (HEL)	[41]
		Human breast carcinoma (BCa)	[92]
		Human erythromyeloblastoid leukemia (K562)	[29]
		Human colon adenocarcinoma (HT-29)	[45]
		Human erythroleukemia (HEL)	[57]
		Human erythromyeloblastoid leukemia (K562)	[39]
		Human promyelocytic leukemia (HL-60)	
	Lupeol	Human epidermoid carcinoma (A431)	[58]

Table 8. contd….

		Human breast adenocarcinoma (MCF-7)	[106]
		Melanoma (451Lu)	[33]
		Head and neck squamous cell carcinoma (HNSCC)	[46]
	Zerumbone	Human renal carcinoma (786-0)	[51]
		Human renal carcinoma (769-P)	
		Human hepatocellular carcinoma (HepG2)	[59]
Down-regulation of Bcl-xL	Diosgenin	Human erythroleukemia (HEL)	[44]
		Human erythromyeloblastoid leukemia (K562)	[29]
	Lupeol	Human breast adenocarcinoma (MCF-7)	[106]
	Zerumbone	Human prostate cancer (PC-3)	[60]
		Human prostate cancer (DU-145)	
		Human colon carcinoma (HCT116)	[93]

Following stimulation of the cell by a variety of agents, IκB is degraded, allowing NF-κB to translocate to the nucleus and bind to the promoter regions of its multiple target genes to promote cell survival [80,81]. The cell survival induced by NF-κB was down-regulated by *C. speciosus* active ingredients (Table **9**).

PARP Cleavage

DNA damage activates nuclear poly (ADP-ribose) polymerase-1 (PARP-1) to repair DNA. The activated PARP-1 uses NAD^+ to form polymers of ADP-ribose that amend PARP-1 and DNA repair proteins [82]. PARP-1 was cleaved by *C. speciosus* active ingredients that inhibit DNA repair of cancer cells apoptosis (Table **10**).

Down-Regulation of STAT3, JAK and MMPs

Signal transducer and activator of transcription 3 (STAT3) is a transcription factor which in humans is encoded by the STAT3 gene. The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway regulate signals for development and homeostasis. JAK activation stimulates cell proliferation, differentiation, cell migration and apoptosis [83]. The down-regulation of STAT3 and JAKs by *C. speciosus* active ingredients was presented in Table **10**.

The expression of matrix metalloproteinases (MMPs) correlates with the extracellular matrix degradation and tumor metastasis. The expression of MMP-2 and MMP-9 is associated with metastasis of numerous human cancers because they play an important role in the degradation of type IV collagen, which is a major component of the basement membrane [84]. Therefore, MMP-2, -3 and -9 may be involved in the process of metastasis of breast cancer to the brain. MMPs were down-regulated by *C. speciosus* active ingredients that inhibit DNA repair of cancer cells apoptosis (Table **10**).

Down-Regulation of p38 MAPK

The p38 is a member of Ser/Thr kinases family called the mitogen-activated protein kinase (MAPKs) (Table **12**). The p38 MAPK signalling coordinates cellular responses during erythropoiesis in which the proliferation and differentiation of erythroid progenitors are controlled by erythropoietin through the p38 (Table **11**) and Jun N-terminal kinase (JNK) (Table **9**) signalling cascades [85].

Down-Regulation of Cell Survival and Angiogenesis Molecules

The down-regulation of numerous anti-apoptotic molecules such as actin, survivin, vimentin and others by *C. speciosus* active ingredients is illustrated in Tables (**12**).

In Vivo Anticancer Activity

The *in vivo* anticancer activity of diosgenin, lupeol and zerumbone was conducted by up-

Table 9. Down-regulation of NF-κB, JAKs and JNK by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Down-regulation of NF-κB	Costunolide	Breast cancer (MDA-MB-231)	[107]
	Diosgenin	Human prostate cancer (PC-3)	[87]
		Human erythroleukemia (HEL)	[44]
		Human breast carcinoma (BCa)	[92]
	Lupeol	Head and neck squamous cell carcinoma (HNSCC)	[46]
		human pancreatic adenocarcinoma cells (AsPC-1)	[108]
	Zerumbone	Pancreatic cancer (PaCa)	[109]
		Breast cancer (HER2)	[110]
		Breast cancer (MDA-MB-231)	[111]
		Human gastric carcinoma (AGS)	[112]
Down-regulation of JAK1	Diosgenin	hepatocellular carcinoma (HCC)	[113]
Down-regulation of JAK2	Diosgenin	hepatocellular carcinoma (HCC)	[113]
	Zerumbone	Human prostate cancer (DU145)	[101]
		Human prostate cancer (PC-3)	
Down-regulation of JAKs	Lupeol	Human hepatocellular carcinoma (HepG2)	[56]
		Human liver hepatoma (PLC/PRF5)	
		Human hepatoma-derived (C3A)	
		Hepatocarcinoma (HUH-7)	
		Human hepatoma (Hep3B)	
Down-regulation of JNK	Diosgenin	Breast cancer (HER2)	[91]
		Human prostate cancer (PC-3)	[87]
		Human epidermoid carcinoma (A431)	[43]
		Human hepatocellular carcinoma (Hep2)	

Table 10. Down-regulation of PARP, STAT3 and MMPs by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
PARP cleavage	Costunolide	Breast cancer (MDA-MB-231)	[27]
		Human bladder carcinoma (T24)	[6]
		Human neuroblastoma (IMR-32)	[54]
	Diosgenin	Human erythroleukemia (HEL)	[44]
		Human lung carcinoma (A549)	[40]
	Lupeol	Human hepatoma cells (SMMC-7721)	[47]
		Human hepatocellular carcinoma (HepG2)	

Table 10. contd….

		Pancreatic cancer (PaCa)	[55]
		Human epidermoid carcinoma (A431)	[58]
		Human prostate cancer (CWR22Rnu1)	[108]
		Melanoma (451Lu)	[33]
	Zerumbone	Chronic myeloid leukemia (CML)	[49]
		Human erythromyeloblastoid leukemia (K562)	
		Human renal carcinoma (786-0)	[51]
		Human renal carcinoma (769-P)	
		Acute promyelocytic leukemia (NB4)	[48]
Down-regulation of STAT3	Diosgenin	hepatocellular carcinoma (HCC)	[113]
	Lupeol	Human hepatocellular carcinoma (HepG2)	[56]
		Human liver hepatoma (PLC/PRF5)	
		Human hepatoma-derived (C3A)	
		Hepatocarcinoma (HUH-7)	
		Human hepatoma (Hep3B)	
	Zerumbone	Human prostate cancer (DU145)	[101]
		Breast cancer cells	[114]
Down-regulation of MMP-2	Diosgenin	Human prostate cancer (PC-3)	[87]
	Lupeol	Prostate cancer (CaP)	[115]
Down-regulation of MMP-3	Zerumbone	Breast cancer (Hs578T)	[116]
		Breast cancer (MDA-MB-231)	
Down-regulation of MMP-9	Costunolide	Breast cancer (MDA-MB-231)	[27]
	Diosgenin	Human prostate cancer (PC-3)	[87]
	Lupeol	Gallbladder carcinoma (GBC-SD)	[95]

Table 11. Down-regulation of CXCR4, CXCL12, p52, p65, p70S6K and p100 by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Down-regulation of C-X-C chemokine receptor type 4 (CXCR-4)	Zerumbone	Breast cancer (HER2)	[110]
		Chronic Myelogenous Leukemia (KBM-5)	
		Human myeloma (U266)	
		Human squamous carcinoma (SCC4)	
		Human embryonic kidney (A293)	
		Human non-small cell lung carcinoma (H1299)	
		Human pancreatic carcinoma (PANC-1)	
		Pancreatic carcinoma (PANC-28)	
		Human pancreatic carcinoma (MIA PaCa-2)	
Down-regulation of C-X-C motif chemokine 12 (CXCL12)	Zerumbone	Breast cancer (HER2)	[110]
		Human pancreatic carcinoma (PANC-1)	
		Pancreatic carcinoma (PANC-28)	

Table 11. contd….

		Human pancreatic carcinoma (MIA PaCa-2)	
Down-regulation of p38	Diosgenin	Human esophageal cancer (Eca109)	[117]
		Human erythroleukemia (HEL)	[44]
Down-regulation of p52	Costunolide	Breast cancer (MDA-MB-231)	[107]
Down-regulation of p65	Costunolide	Breast cancer (MDA-MB-231)	
Down-regulation of p70S6K	Lupeol	human osteosarcoma cells (MG-63)	[31]
		human pancreatic cancer (PCNA-1)	[32]
Down-regulation of p100	Costunolide	Breast cancer (MDA-MB-231)	[107]

Table 12. Down-regulation of some anti-apoptotic molecules by *C. speciosus* active ingredients.

Mechanism	Ingredients	Cell	References
Down-regulation of actin	Diosgenin	Breast cancer (MDA-MB-231)	[98]
Down-regulation of β-catenin	Diosgenin	Human colon carcinoma (HCT-116)	[30]
	Lupeol	Prostate cancer (CaP)	[115]
Down-regulation of FADD-like IL-1β-converting enzyme)-inhibitory protein (c-FLIP)	Lupeol	Pancreatic cancer (PaCa)	[55]
Down-regulation of c-Src	Diosgenin	Hepatocellular carcinoma (HCC)	[113]
Down-regulation of epidermal growth factor receptor (EGFR)	Lupeol	Gallbladder carcinoma (GBC-SD)	[95]
Down-regulation of extracellular signal-regulated kinase (ERK)	Diosgenin	Human prostate cancer (PC-3)	[87]
		Human erythroleukemia (HEL)	[118]
Down-regulation of GLI	Diosgenin	Human erythroleukemia (HEL)	[118]
Down-regulation of Gli-1	Zerumbone	Human renal carcinoma (786-0)	[51]
		Human renal carcinoma (769-P)	
Down-regulation of glycogen synthase kinase-3 (GSK3beta)	Diosgenin	Mouse melanoma (B16)	[89]
Down-regulation of Hepatocyte growth factor (HGF)	Diosgenin	Human prostate cancer (DU145)	[90]
Down-regulation of hypoxia-inducible factor 1 (HIF-1α)	Diosgenin	Human gastric cancer (BGC-823)	[68]
		Gastric carcinoma (NCI-N87)	
		Human gastric adenocarcinoma (MGC80-3)	
		Human gastric cancer (SGC-7901)	
Down-regulation of human telomerase reverse transcriptase (hTERT)	Diosgenin	Human lung carcinoma (A549)	[119]
		Human lung carcinoma (A549)	[120]
Down-regulation of myeloid leukemia cell differentiation protein (Mcl-1)	Zerumbone	Human prostate cancer (PC-3)	[60]
		Human prostate cancer (DU-145)	

Table 12. contd….

Down-regulation of mouse double minute 2 homolog (Mdm2)	Diosgenin	Human prostate cancer (DU145)	[90]
Down-regulation of MAPKs	Zerumbone	Human colon carcinoma (CaCo-2)	[121]
		Human colon carcinoma (Colo320DM)	
		Human colon adenocarcinoma (HT-29)	
Down-regulation of mammalian target of rapamycin (mTOR)	Diosgenin	Human prostate cancer (DU145)	[90]
		Breast cancer (HER2)	[91]
Down-regulation of Polo-like kinase 1 (PLK-1)	Lupeol	Human prostate cancer (PC-3)	[96]
Down-regulation of Smoothened (SMO)	Diosgenin	Human erythroleukemia (HEL)	[118]
Down-regulation of survivin	Costunolide	Human bladder carcinoma (T24)	[6]
	Diosgenin	Human breast carcinoma (BCa)	[92]
	Lupeol	Prostate cancer (CaP)	[99]
	Zerumbone	Human colon carcinoma (HCT116)	[93]
Down-regulation of tumor necrosis factor-alpha (TNF-α)	Costunolide	Breast cancer (MDA-MB-231)	[122]
Down-regulation of vascular endothelial growth factor (VEGF)	Zerumbone	Human gastric carcinoma (AGS)	[112]
Down-regulation of Vav2	Diosgenin	Breast cancer (MDA-MB-231)	[98]
Down-regulation of vimentin	Diosgenin	Human prostate cancer (DU145)	[90]
Down-regulation of Wnt	Lupeol	Human Melanoma (Mel 928)	[123]
Down-regulation of X-linked inhibitor of apoptosis	Diosgenin	Human breast carcinoma (BCa)	[92]
	Zerumbone	Human colon carcinoma (HCT116)	[93]

regulation of caspase, Bax, antioxidant potential and PTEN. In contrary, they induce down-regulation of cyclin B, G2/M phase, Bcl-2, NF-κB and surviving as presented in Table **13**.

CONCLUSION AND RECOMENDATIONS

Chemical ingredients of *C. speciosus* have been described as potent anticancer therapy through induction of cancer cell apoptosis and weaken the cell survival through various mechanisms as illustrated in Fig. **2**. From the data of this review we can propose research suggestions as a future plan outline that include:

- Study the preclinical novel angiogenesis inhibitor of *C. speciosus*
- Study the critical component of multiple signalling pathways that regulate proliferation, survival, metastasis, and angiogenesis especially Myeloid leukemia.
- Study the possible use of some *C. speciosus* ingredients as adjuvant therapy in chemoresistant cancer; especially hepatocellular carcinoma, breast cancer, and colorectal cancer.
- Study the possible use of some *C. speciosus* ingredients as anti-RAGE, the receptor for advanced glycation end products therapy.
- Study the change of the common regimen for treatment of cancer on a basis to improve the efficacy and reduce the common serious side effects.

Table 13. ***In vivo*** **anticancer activity of** ***C. speciosus*** **active ingredients.**

Mechanism	Ingredients	Animal	References
Up-regulation of caspase-3	Lupeol	Hamster buccal pouch carcinogenesis	[124]
		Skin of Swiss albino mice	[100]
Up-regulation of caspase-9	Lupeol	Hamster buccal pouch carcinogenesis	[124]
Up-regulation of Bax	Lupeol	Hamster buccal pouch carcinogenesis	[124]
		Skin of Swiss albino mice	[100]
	Zerumbone	Hepatocarcinogenesis in rat	[125]
Antioxidant activity	Diosgenin	Breast carcinoma in female rats	[126]
		Mouse colon carcinogenesis	[127]
		Hamster buccal pouch carcinogenesis	[128]
	Lupeol	Oral carcinogenesis	[128]
	Zerumbone	Hepatocarcinogenesis in rat	[125]
Up-regulation of PTEN	Lupeol	Bladder carcinogenesis in rats	[129]
Down-regulation of cyclin B	Lupeol	Skin of Swiss albino mice	[100]
G2/M phase arrest	Lupeol	Skin of Swiss albino mice	[100]
Down-regulation of Bcl-2	Lupeol	Hamster buccal pouch carcinogenesis	[124]
		Skin of Swiss albino mice	[100]
	Zerumbone	Hepatocarcinogenesis in rat	[125]
Down-regulation of NF-κB	Lupeol	Skin cancer in CD-1 mice	[130]
	Zerumbone	Colonic adenocarcinomas in mice	[131]
		Lung adenomas in mice	[131]
Down-regulation of survivin	Lupeol	Skin of Swiss albino mice	[100]

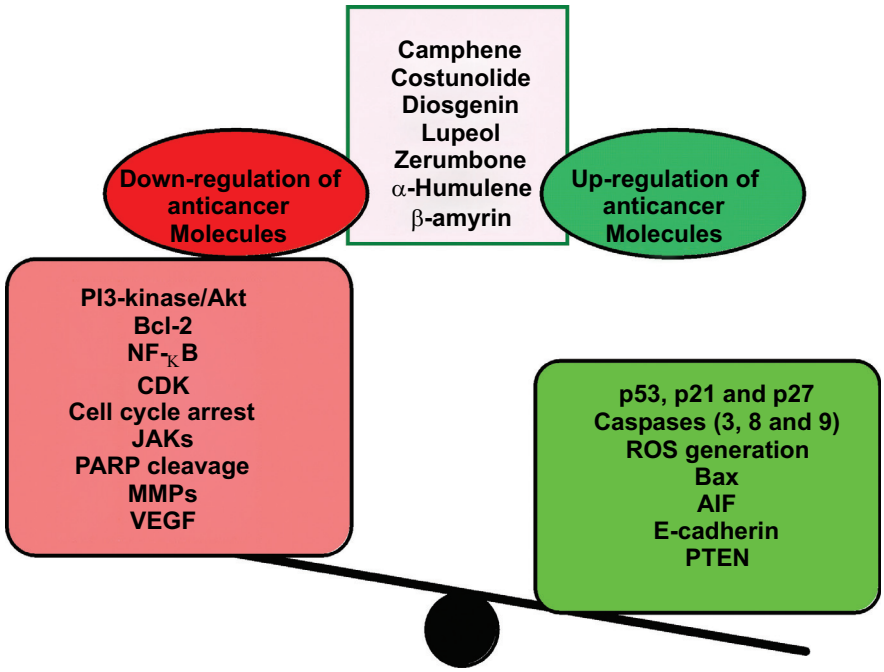

Fig. (2). Summarizes the anticancer effect of *Costus speciosus* active ingredients.

- Studies the dose-dependent antiproliferative activity in the human breast cancer MCF-7 cells as a microtubule-interacting agent. These studies demonstrated that costunolide can be related to an interaction with microtubules and inhibits the proliferation of breast cancer cells.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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