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Dolomiaea costus: an untapped mine of sesquiterpene lactones with wide magnificent biological activities

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ABSTRACT

Dolomiaea costus (Falc.) Kasana & A.K. Pandey Family Asteraceae, formerly known as *Saussurea costus* (Falc.) Lipsch contains a rich treasury of diverse bioactive compounds such as monoterpenes, sesquiterpenes, triterpenes, sterols, cardenolides, flavonoids, coumarins, lignans, phenylpropanoids and alkaloids. The sesquiterpene lactones, costunolide and dehydrocostuslactone in *D. costus*, possess unique promising *in vitro* and *in vivo* biological activities for the prevention and cure of diverse ailments like Parkinson's disease, oxidative stress, hyperpigmentation, ulcerative colitis, breast cancer, hepatocellular carcinoma, colon cancer, prostate cancer, ovarian cancer, leukemia, stomach cancer, prostate cancer, lung cancer, osteosarcoma, neuroblastoma, allergy, type 2 diabetes, hepatotoxicity, bronchitis, pulmonary fibrosis, thrombosis and various microbial infections. Costunolide and dehydrocostuslactone are potential drug candidates that could lead to the development of new medications for a variety of difficult-to-treat diseases.

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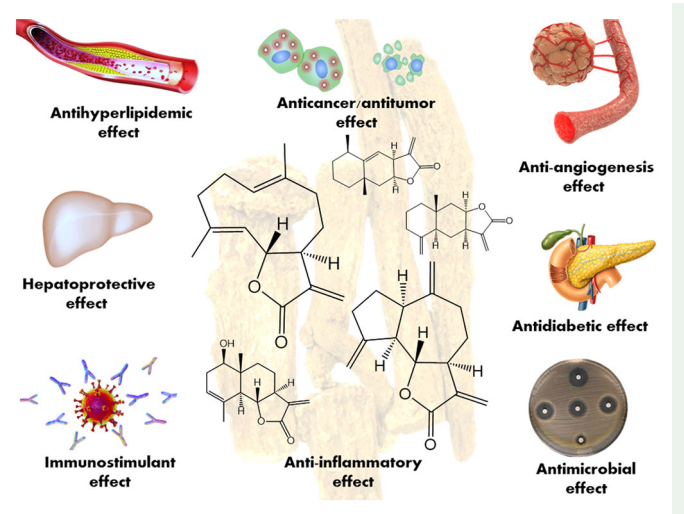

1. Introduction

Dolomiaea costus (Falc.) Kasana & A.K. Pandey is a herb belonging to the family Asteraceae (Akbar 2020; Kasana et al. 2020). The name of the genus Dolomiaea is in honor of the French geologist Déodat Graet de Dolomieu. The name of the species in Greek means 'coming from the east'. *D. costus* (Falc.) was formerly known as *Saussurea costus* (Falc.) Lipsch and as *S. lappa* (Falc.). The genus Saussurea (after the classification of Henri Louis Frédéric de Saussure) contains a group of about 400 species (Vijayalakshmi et al. 2022). Costus root has an aromatic odour due to the presence of essential oils (Abdelwahab et al. 2021). Sesquiterpene lactones are the main constituent group in the roots of *D. costus* (Okubo et al. 2021).

The roots of *D. costus* have a large number of traditional and folkloric uses in India and China. Costus root is well known for its huge therapeutic beneficial effects. These effects are listed in Table 1.

D. costus roots contain many diverse chemical groups of natural compounds. Of these multiple groups, monoterpenes like terpinen-4-ol (Chang and Kim 2008), Sesquiterpenes like elemol and γ-costol (Kumar and Agnihotri 2022), sesquiterpene lactones like costunolide, dehydrocostuslactone, alantolactone and isoalantolactone (Nadda et al. 2020) (Figure 1), triterpenes (Singh et al. 2017), sterols like β-sitosterol (Hassan and Masoodi 2020), flavonoids like luteolin-7-O-β-D-glucoside, rutin and apigenin-7-O-β-D-glucoside (Chang et al. 2012; Alaagib and Ayoub 2015), coumarins (Naseer et al. 2022), lignans (Hassan and Masoodi 2020), phenylpropanoids (Jeong et al. 2002) and alkaloids (Chandur et al. 2011). The two bioactive compounds, costunolide and dehydrocostoslactone are the main sesquiterpene lactones in the costus root oil and the root extract (Okubo et al. 2021; Moustafa et al. 2022).

Table 1. Traditional uses of costus root.

Traditional use	Reference
Aphrodisiac	Saleem et al. (2013)
Astringent	Madhavi et al. (2012)
Tonic in nervine and brain disorders	Ansari (2021)
Diuretic	Yaeesh et al. (2010)
Nephroprotective	Kadhem (2019)
Sedative	Akbar (2020)
Rubefacient	Ansari (2021)
Antihypertensive and vasodilator	Zhao et al. (2008)
Stomachic and healing for stomach ulcers	Singh et al. (2017)
Carminative	Madhuri et al. (2012)
Tonic	Abd Eldaim et al. (2019)
Anti-asthmatic	Singh et al. (2017)
Antirheumatic	Amara et al. (2017)
Emmenagogue	Akbar (2020)
Cough suppressant	Zahara et al. (2014)
Treatment of common cold	Zahara et al. (2014)
Anti-epileptic	Ambavade et al. (2009)
Treatment of polyuria	Ansari (2021)
Treatment of bronchitis	Gautam and Asrani (2018)
Anti-cholera	Ansari (2021)
Chronic ulcer	Sutar et al. (2011)
Treatment of jaundice	Ansari, Maaz, et al. (2021)
Treatment of dyspepsia	Sutar et al. (2011)
Expectorant	Chopra (1928); Pyun et al. (2018)
Anti-oedemata	Chandur et al. (2011)
Treatment of ascites	Elgharabawy et al. (2021)
Treatment of splenomegaly	Wang et al. (2020)
Treatment of leprosy	Zahara et al. (2014)

2. Methodology

Many scientific records were explored to get basic studies on *Dolomiaea costus* (*Saussurea costus*). Authors searched the literature using many literature databases including the web of science, Google Scholar, EBSCO Information Services, ProQuest, the Egyptian knowledge bank databases, Science Direct and PubMed. The present review encloses references, novel research studies, review articles and book references. Original studies with study design and literature focusing on participants of age 18–70 years were included. Articles that were excluded were ones that either did not mention the place of the participants, did not report the particular outcome of interest or were non-peer-reviewed articles.

3. Evidence-based pharmacological activities of *D. costus*

Many research articles are confirming enormous number of strong pharmacological properties for costus root. Of these therapeutic effects, the roots of the costus are proven to show anti-angiogenesis (Li et al. 2020; Alotaibi et al. 2021), anti-cholinergic and calcium channel blocker (Gilani et al. 2007), anti-hyperlipidemic (Anbu et al. 2011), anticancer/antitumor (Li et al. 2020; Mohsen et al. 2022), anticonvulsant (Gupta Pushpraj et al. 2009), antidiabetic (Lammari et al. 2021), antidiarrheal (Negi et al. 2013), antiepileptic (Ambavade et al. 2009), tyrosinase inhibitory (Choodej et al. 2019), thrombolytic (Chaudhary et al. 2015), anti-inflammatory (Tag et al. 2016), antimicrobial (Abdelwahab et al. 2021), antioxidant (Butturini et al. 2011; Singh and Chahal 2018),

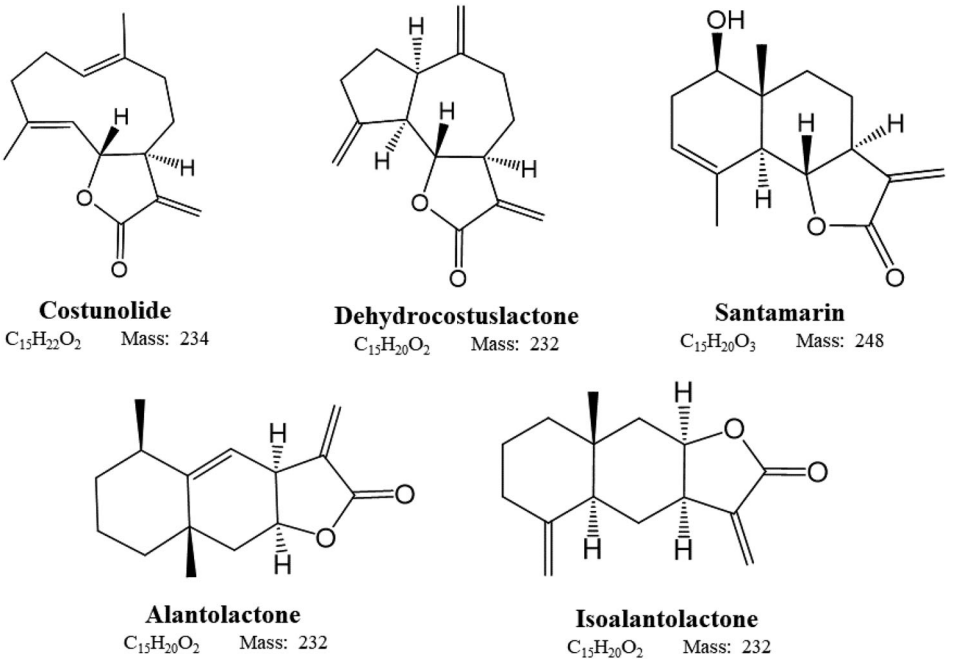

Figure 1. Representative examples of sesquiterpene lactones from *Dolomiaea costus* (*Saussurea lappa*).

antiparasitic (Zahara et al. 2014), anti-ulcer (Singh et al. 2017), bronchitis healing (Ansari 2021), cardioprotective (Saleem et al. 2013), hepatoprotective (Ansari, Hasan, et al. 2021), immunostimulant (Zahara et al. 2014), spasmolytic (Kamalpreet et al. 2019), analgesic (Tejaswi et al. 2018), anti-Parkinson's (Kim and Choi 2019) effects.

4. Costunolide, a prodigious sesquiterpene lactone drug lead

Costunolide belongs to the germacranolide sesquiterpene lactones subclass (El-Feraly and Chan 1978). It is a colorless crystalline powder with a molecular formula of $C_{15}H_{20}O_2$ and molecular weight of 232 (Kim and Choi 2019). It represents the second major compound in *D. costus* root oil 9.26% w/w (Ali and Venkatesalu 2022). The biosynthesis of costunolide occurs mainly through mevalonate pathway, yielding farnesyl diphosphate (FDP) which is the precursor for sesquiterpenes biosynthesis.

There are nine major genes involved in costunolide biosynthesis from acetyl CoA (Majeed and Rehman 2022). The biosynthetic gene was expressed and transformed into yeast and nicotiana plants (Liu et al. 2011). The biological activity of costunolide is mediated by its functional unit, α-methylene-γ-lactone, which can react with the cysteine sulfhydryl groups of various proteins to alter the intracellular redox balance (Rasul et al. 2012). Costunolide exerted a potent neuroprotective activity (Peng et al. 2019).

It significantly decreased glycosylated hemoglobin (HbA1c), serum total cholesterol, triglyceride, LDL cholesterol, while markedly increasing plasma insulin, tissue glycogen, HDL cholesterol and serum protein (Kim and Choi 2019). Costunolide caused a

significant reduction in tissue thiobarbituric acid reactive substances TBARS level and a significant increase in GSH content along with increased enzymatic activities of SOD, CAT and GPx in the treated rats when compared to untreated diabetic rats (Eliza et al. 2010).

Costunolide also significantly decreased glycosylated hemoglobin (HbA1c), serum total cholesterol, triglyceride, LDL cholesterol, markedly increased plasma insulin, tissue glycogen, HDL cholesterol and serum protein (Eliza et al. 2009). This sesquiterpene lactone significantly attenuated liver pathologic changes, as well as alanine aminotransferase and aspartate aminotransferase levels in serum splenomegaly (Wang et al. 2017). Meanwhile, costunolide inhibited the expressions of interleukin (IL-1β) and tumor necrosis factor (TNF-α) in liver tissues in a dose-dependent manner (Wang et al. 2017).

Furthermore, costunolide dose-dependently inhibited LPS/D-Gale induced NF-kB activation, so it might be a potential therapeutic reagent for liver injury (Wang et al. 2017). It inhibited the histopathologic changes, leading to decreased ALT and AST levels in the serum (Wang et al. 2017). Besides, the data showed that it inhibited the levels of IL-1β and TNF-α in the liver tissues, as well as attenuated the activation of NF-kB pathway (Wang et al. 2017). Costunolide has hepatoprotective effects against lipopolysaccharide (LPS) and D-galactosamine-induced acute liver injury (Mao et al. 2018).

Moreover, it significantly decreased the protein expression of pro-inflammatory cytokines including Interleukin 1 beta (IL-1β) and interleukin-6 (Pae et al. 2007). This interesting compound can be introduced as a lead compound for phytoestrogen agents that can offer estrogenic activity as well as treatment of postmenopausal symptoms, osteoporosis and other cardiovascular diseases (Lee and Choi 2011).

Costunolide ameliorated lipoteichoic acid (LTA)-induced acute lung injury (ALI) (Chen et al. 2018). It is a promising agent for the treatment of gram-positive bacteria-mediated pneumonia (*Staphylococcus aureus* and *Streptococcus pneumonia*) (Chen et al. 2018). Costunolide inhibits osteosarcoma growth and metastasis *in vitro* and *in vivo* by impairing STAT3 signal pathway (Jin et al. 2020). It can increase ROS levels and activate p38 and JNK to induce apoptosis in prostate cancer (Chen et al. 2017). It significantly improved the disease activity index (DAI) in the colon of mice with colitis, rescued the reduction in colon length, downregulated myeloperoxidase (MPO) activity, ameliorated pathological changes and decreased the levels of pro-inflammatory cytokines in the colon (Xie et al. 2020).

Costunolide mediated the induction of mineralization, suggesting that the induction of mineralization is associated with increased activation of ER and PI3K (Lee and Choi 2011). It significantly decreased glycosylated hemoglobin (HbA1c), serum total cholesterol, triglyceride, LDL cholesterol, markedly increased plasma insulin, tissue glycogen, HDL cholesterol and serum protein (Eliza et al. 2009). Microbial and chemical transformation of costunolide were achieved to increase the solubility and bioactivity (Zheng et al. 2007).

5. Dehydrocostuslactone, a formidable pharmacophore

Dehydrocostuslactone is a guaianolide sesquiterpene lactone (Joel et al. 2011), Dehydrocostuslactone represents the major compound in *Dolomiaea costus* root oil

46.75% w/w (Benedetto et al. 2019). It is a white powder with a molecular formula of $C_{15}H_{18}O_2$ and molecular weight of 230. Dehydrocostuslactone possesses strong cytotoxicity and holds exciting potential as a novel therapeutic agent in ovarian cancer through the modulation of DNA methylation through the inhibition of DNMTs (Fadayomi et al. 2022).

Dehydrocostuslactone can induce mitochondria-mediated apoptosis in prostate cancer by promoting the release of cytochrome-C into cytosol activating caspase signaling pathway (Wang et al. 2017). It also has a trypanocide activity, antineoplastic effect, a cyclooxygenase-2 inhibitory activity and anti-mycobacterial activity (Maya et al. 2007).

6. Common pharmacological effects shared by costunolide and dehydrocostuslactone

Costunolide and dehydrocostuslactone in *D. costus* demonstrated the potentiation of hexobarbital in its sleeping time and exhibited anti-nociceptive effects (Butturini et al. 2014). Both compounds exert their anti-pulmonary fibrosis effect by inhibiting the early inflammatory response by downregulating the JNK/p38 MAPK-mediated NF-κB signaling pathway to suppress macrophage activation (Yu et al. 2022).

They have the potential to be used for treating inflammatory skin disorders by suppressing chemokine expression (Seo et al. 2015). They have been shown to induce cell cycle arrest in breast cancer cell lines (MCF-7 cells). Both of them showed strong cytotoxic activities against cancer cell lines through cell cycle regulation, apoptosis induction, telomerase activity inhibition, anti-metastasis and invasion, anti-angiogenesis, and multidrug resistance reversion activities (Li et al. 2020).

7. Quantification of costunolide and dehydrocostuslactone

It is easy to estimate quantitatively costunolide and dehydrocostuslactone in any preparation containing *Dolomiaea costus* root extract. Many scientific research articles proved the simultaneous quantitative determination of the two compounds by HPLC, UPLC–MS/MS, ^{13}CNMR, thin-layer chromatography and high-speed countercurrent chromatography (Ferrari et al. 2005; Vijayakannan et al. 2006; Zhang et al. 2014).

8. Conclusions

Dolomiaea costus root can be considered a rich source of bioactive compounds and has not been exploited yet. Modern scientific research articles confirm the existence of an arsenal of different invaluable chemical compounds in costus root, the most important of which are the two sesquiterpene lactone compounds, costunolide and dehydrocostuslactone. These two compounds have diverse therapeutic effects with interesting pharmacological mechanisms. The two compounds proved to have extraordinary apoptotic activities on cancer cells, such as prostate cancer, liver cancer, ovarian cancer, breast cancer, osteosarcoma and lung cancer. They also showed high efficacy in the treatment of diabetes type 2, postmenopausal symptoms, osteoporosis, cardiovascular diseases, pneumonia, anxiety, Parkinsonism, peptic ulcers, ulcerative colitis,

skin hyperpigmentation and different types of inflammation. Costunolide and dehydrocostuslactone deserve to be drug motives that can lead to the development of new effective medicines for many diverse diseases, difficult to be treated.

9. Recommendations and future prospective

Continuous plant cell suspension culture stations can be constructed to produce the pharmacologically active compounds costunolide and dehydrocostulactone on a large scale. Elicitation can be attempted to enhance the biotechnological production of the two compounds in the cell suspension culture. Isolation of the two bioactive compounds' biosynthetic gene clusters and expressing them to obtain transgenic *E. coli*, yeast, nicotiana and soybean plants for large scale *in vitro* production is proposed. To know the mechanism of action of the two biologically active molecules, molecular docking is strongly proposed to predict the binding affinity to target proteins (Sabry et al. 2021). Many research articles say that *Dolomiaea costus* is an endangered medicinal plant. To prevent this problem from recurring, the above-mentioned steps can be taken urgently.

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