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Mini-review article

Biological applications and secondary metabolites of *Saussurea costus* (Falc.) Lipsch.

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ABSTRACT

Saussurea costus (Falc.) Lipsch. (Compositae), popularly known as Kuth in Ayurveda, is useful for gastrointestinal disorders in the form of a digestive agent, anti-gastric agent or an appetizer. Its roots have been used in respiratory problems like cough and asthma. The plant is also used in various other traditional medicinal systems including Unani. A number of scientific reports have proved its therapeutic importance as anti-gastric, anti-asthmatic, antispasmodic, antimicrobial and anti-inflammatory agent. A variety of secondary metabolites including sesquiterpenoid lactones, lignins, and phytosterols have been identified as bioactive principles from the roots of this plant. Today, many healthcare products are available in the market those contain *S. costus* roots as single or in the form of a polyherbal formulation. According to the IUCN Red List, *S. lappa* is under the threatened category and due to its high demand in the market, it is becoming extinct very fast from its natural habitat. Hence, there is an urgent need to protect the plant by promoting its cultivation on a large scale.

INTRODUCTION

Saussurea costus (Falc.) Lipsch. (Syn. *Saussurea lappa* (Decne.) Sch.Bip.) belongs to Compositae family. The genus *Saussurea* comprises 433 species (The Plant List, 2013), out of which, 61 species have been found in India. Due to overexploitation of this plant for various medicinal purposes and lack of protection, this herb has been kept in the list of rare and endangered species (Madhuri et al., 2012). Efforts are being made to conserve and protect this medicinal plant. *Saussurea lappa* (SL) has a wide distribution throughout Asia, North American and various parts of Europe. It typically grows in moist and alpine habitats. It also grows in arctic regions and alpine habitats. The size of the plant varies depending upon the altitude at which it grows.

In India, this plant is distributed at an altitude of 2,500 to 3,000 m throughout the higher altitude of Himalayas, Kashmir, Jammu, Western Ghats and Kishenganga valley. SL is known by different vernacular names such as Amaya, Pakala (Sanskrit), Kud, Kur (Assam), Kudo (Bengali), Costus (English), Kutha (Hindi), Kuth (Kashmiri), Kottam (Malayalam), Upleta, Kustha (Marathi), Kudha (Oriya), Kuth (Punjabi), Goshtam, Kostham, Kottam (Tamil), Changalva Koshtu (Teluga), Qust (Urdu). It is now cultivated in Tamilnaidu, and various parts of Uttar Pradesh (Kokate et al., 2002).

BOTANICAL DESCRIPTION

S. costus (*S. lappa*) is a tall perennial herb of 1-2 m height. Leaves are about 1 m long, lobate, and stalked one. Flowers are arranged in clusters (Fig. 1). The flower heads are about 3–5 cm in diameter, stalk-less, hard, round, varies from dark bluish to blackish in appearance. Its flowering time extends in between July to August. Its Fruit is about 3 mm long, curved, cupped and compressed. The root is 60 cm in length having a strong, characteristic aromatic odour. The dried roots are slightly bitter in taste. The roots are collected in September and October (Anonymous, 1985).

ETHNOBOTANY

S. lappa is used in the treatment of various ailments like asthma, inflammatory diseases, ulcer and stomach problems. The roots are used for normalising tridosha, improving complexion, cures of leucoderma, itching, ringworm, vomiting, scabies, headache, epilepsy and hysteria.

Fig. 1. *Saussurea costus* plant with blooming flower

It is also used as carminative, aphrodisiac and anthelmintic. The phytochemicals present in the root stimulate the brain, cure various diseases associated with blood, liver, and kidney as documented in the Unani system of medicine (Kritikar and Basu, 1987). Chemical extracts from this herb have antispasmodic, bronchodilatory, and blood-pressure-lowering effects. It has been found to be effective in curing cough, asthma, cholera, jaundice, leprosy and rheumatism. The root powder is applied as an ointment to wounds, skin diseases and tumours. Roots are aromatic, contains essential oil, which is used as tonic, stimulant and antiseptic. Its roots are frequently used in hair tonic, perfumeries, and the preparation of incenses. It also has a significant role in the treatment of swelling and fullness of the stomach. It serves as a cardiac stimulant and relaxes the involuntary muscle (Madhuri et al., 2012).

MARKETED PRODUCTS

Saussurea costus as a single herb or in the form of one of the active ingredients of a formulation has been used in several medicinal products which are already available in the market. A list of selected popular market products together with the name of their manufactures is given in Table 1.

Table 1. Commercial products of costus available in market

Product Name	**Key ingredients**	**Manufacturer/ Supplier**	**Use**
Biotique Bio Costus Foot Cream	Costus roots; *Taraxacum officinale*; *Mesua ferrea* and *Mentha piperita*	Biotique Botanicals, Bio Veda Action Research Pvt. Ltd.	Soften hard skin and relax tired feet
Biotique Color Lipstick	Costus roots	Biotique Botanicals, Bio Veda Action Research Pvt. Ltd.	Keeps lips smooth and soft, also useful for cracked lips
Costus Ecoessence	Resinoids, aplotaxene, costus acid, costol, costus lactone, β-selinene, γ-ionone	La- Whiff Fragrances	Woody, erogenic, somewhat balsamic, sweet-like, animal-note; used in perfumery
Costus Root Oil		Katyani Exports	It has antispasmodic, antiviral, antiseptic, bactericidal, digestive, carminative, expectorant, stimulant, febrifuge, stomachic and tonic properties. Fascinating notes in oriental type perfumes; a fixative and perfume component; a flavour in drinks and confectionery; as incense
		Kanta Enterprises Private Limited	
		Aromex Industry	
		India Essential Oils	
		People's Chemical Agency	
		The Perfumers	
		Natural Biotech Products	
		Total Herbal	
		Proderna	
		Gangotri Essential Oils Private Limited	
		Naturae'S Riches	
		Ruchi Menthol Private Limited	
		Sant Bhama Enterprises	
		Green Leaf Extractions Private Limited	
		Komal Exotic Spices Private Limited	
		Fiducia Essential Oil & Biotech Industries	
		Blue Planet Minerals Pvt. Ltd.	
		Prakash Chemicals	
		Natural Essentials	
		Kapco International Limited	

		Lala Jagdish Prasad & Co.	
		Expo Essential oils	
Costus root absolute		Essential Oil Bazaar	
Costus root essential oil		Nanda Medicinal Plants Exports	
Qust al-Hindi (Costus/Qust Shirin)	Costus roots	Sunnah Remedies	It is a good tonic for all organs of the body, a good carminative, an anti-inflammatory and effective against pleurisy; externally used for arthritic pain and back pain
Costus Indien	Costus roots	Maher Shop	used for Sexual weakness, erection problem, Gonorrhea, Gastric disorders, Thrombus, Diseases of the kidneys and the liver (hepatitis), Cancer of the mouth, Asthma and tuberculosis, Migraine, Case the Sourcery
Pipalyadyasavaya	Downy Grislea, *Woodfordia fruticosa*, Sandalwood, Costus, Jata Mansha	Beam Chemicals Pvt Ltd	Improves appetite; digestive disorders; effective for cough, bronchial asthma, catarrh and piles
Costus root essential oil	Costus lactone, β-selinene, aplotaxene, γ-ionone, costus acid	Oshadhi Ltd.	Used for aromatherapy

PHARMACOLOGICAL ACTIVITIES

S. costus has been evaluated for various pharmacological activities. The root, which is used in traditional medicine, showed activity against cancer, microbial infections, inflammation, ulcer, etc. The detail biological applications of the plant are given in following heads.

Anti-inflammatory property

The anti-inflammatory activity of SL is mainly expressed as the inhibitory effect of its active ingredients on pro-inflammatory cytokines. Ethanolic extract inhibits acute and chronic inflammation in mice & rats at a dose range of 50-200 mg/kg (Gokhale et al., 2002). It prevents the accumulation of infected cells at doses of 50-200 mg/kg of body weight and causes a reduction in mRNA level and production of inflammatory chemokines and cytokine, including thymus-activation-regulated chemokine (TARC), macrophage-derived chemokine (MDC). Normal T-cell expressed and secreted interleukin-8 (IL-8) in tumour necrosis factor and reduction in histamine production in MC/9 cells (Lim et al., 2014). Isolated compounds like costunolide, dehydrocostus lactone, cynaropicrin, saussureamine A, B and santamarin have been found to exhibit anti-inflammatory activities. Cynaropicrin inhibits the production of inflammatory factors and proliferation of lymphocytes (Cho et al., 2000). Costunolide suppressed TNFα-induced NF-κB signalling activation, resulting in reduced expression of MMP-9, which is a commonly known NF-κB-dependent gene to intervene in breast tumour cell growth and metastases (Choi et al., 2012). The alkaloid, saussurine found active against asthma studied by means of a reserved-phase TLC method (Lalla et al., 2004). SL roots in homoeopathic dilutions have been considered as a potential candidate for therapeutic support in autoimmune and chronic inflammatory disorders. The concentration of 2 μM has been shown to exert maximum leukocyte phagocytic activity to clear the soluble immune complexes, which causes chronic inflammatory injury of tissue. Inhibition of lymphocyte proliferation and IFN-gamma by SL may contribute to suppressing immune-mediated inflammatory reactions possibly through a cell-mediated cytokine pathway (Sarwar and Enbergs, 2007).

Wound healing property

The alcoholic extract of SL roots at a dose concentration of 500 mg/kg post oral, in rats has shown significant increase in rate wound healing activity in excision, incision and dead space wound models in rats as compared to control group (Ganachari et al., 2005).

Immuno-stimulatory activity

Hydroalcoholic extract of *S. lappa* causes an increase in white blood cell count, the weight of spleen, phagocytic activity and antibody-secreting cells when applied at a dose of 100 and 200 mg/kg body weight (Pandey et al., 2012). They also cause a reduction in the anaphylactic features in animals. Thus extract shows a dose-dependent humoral as well as cell-mediated effect. When this extract is applied at low doses (100 mg/kg), the humoral immune responses remain unaffected, however, 200 mg/kg concentration has been found to exhibit higher antibodies titer. Polyfructoscan, insulin extracted from dried roots shows immunostimulant activity with increased total WBCs and potentiate the delayed-type hypersensitivity response to SRBC (Kulkarni et al., 2001).

Antioxidant activity

The phenolics and flavonoids contents were examined under the Folin-Ciocalteu's colourimetric and the aluminium nitrate methods. The n-butanol soluble fractionates of SL (1000 ppm) showed the strongest inhibitory potential on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical with reducing power at 92.98% and 0.38, respectively, thus showing their ant oxidative effectiveness (Chang et al., 2012). Aqueous extract of root induces oxidative myocardial injury against isoproterenol (Mohamed Saleem et al., 2013).

Hepatoprotective and choleretic activity

Pre-treatment of mice with different doses of aqueous-methanolic SL extracts (150- 600 mg/kg) have been found to prevent D-GalN and LPS-induced rise in plasma levels of liver functioned enzymes (ALT and AST) in a dose-dependent manner. The histopathology of the tissue (liver), showed improved architecture, absence of parenchyma congestion, decreased cellular swelling in treatment groups as compared to the negative control group of animals (Yaeesh et al., 2010).

Costunolide and dehydrocostus lactone suppress the activity of hepatitis B surface antigen production by Hep3B cells in a dose-dependent manner (Pandey et al., 2007). The acetone extract and costunolide inhibit ulcer and shows a choleretic effect in mice (Yaeesh et al., 2010). The ethanolic extract increases bile flow, before and after rat medication (Shao et al., 2005).

Antiulcerogenic activity

Ethyl acetate extract of the *S. lappa* root exhibits antiulcer activity, studied in different models of gastric and duodenal ulceration in rats. The extract was provided at a dose of 200 and 400 mg/kg orally, before 30 min to ulcer induction. Its 400 mg/kg concentration has been found to show gastric acid, free acid and total acid inhibition to 53.54%, 52.55% and 30.30%, respectively (Sutar et al., 2011).

Anti-bacterial activity

The antibacterial activity of SL was done by both agar disc diffusion method and agar well diffusion method against five bacterial strains, viz., *Bacillus cereus, Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli, Pseudomonas pseudoalcaligenes*. The plant material was extracted with distilled water and methanol. The preliminary screening experiment revealed that methanol extracts were more potent than the aqueous extracts. The plant extracts were more active against gram-positive bacteria than gram-negative bacteria. The most susceptible bacteria were *K. pneumoniae* and the most resistant bacteria were *E. coli* (Parekh et al., 2006). The antibacterial activity of the plant is mainly due to the presence of volatile oils. Costus oil gives minimum inhibition concentration (MIC) ranging from 0.15 to 0.16 µl/mL on virulence-associated exoprotein in *Staphylococcus aureus* through Western blot, haemolytic, TNF release and real-time RT-PCR assays. The ethanolic extract shows an inhibitory effect on growth, production and water-soluble synthesis of *Streptococcus mutans* and also lowers its adherence at a dose of 2-4 mg/ml (Yu et al., 2007). Ethanolic extract of *S. lappa* was studied for its antimicrobial activity using *S. mutans.* The extract showed significant inhibition on the growth, acid production and the formation of water-insoluble glucan. They are also helpful in lowering the adherence of *S. mutans* in water-soluble glucan synthesis assay about 2-4 mg/mL (Yu et al., 2007) and with agar dilution test they show microbial inhibition at the concentration of 2-12 µg/µL (Hasson et al., 2013). Phenolic and flavonoid extract also shows antimicrobial activity. The ethanolic extract fractionated into various solvents like n-hexane, chloroform and n-butanol which shows inhibition concentration (IC_{50}) value 62.5, 250 and 500 ppm, against *L. monocytogenes*, *B. cereus* and *B. subtilis,* respectively, when examined by disc-diffusion and microdilution susceptibility assays (Chang et al., 2011).

Anti-viral activity

The root extract obtained from *Saussurea lappa* was examined for their activity against *Hepatitis B* virus. Costunolide and dehydrocostus lactone were found to suppress the expression of *Hepatitis B* surface antigen (HbsAG) against human hepatoma Hap3B cells (Chen et al., 1995).

Larvicidal activity

A number of essential oils have been isolated from SL roots which were analysed by hydrodistillation and gas chromatography. The major oils are dehydrocostus lactone (46.75%), costunolide (9.26%), 8-cedren-13-ol (5.06%), sesquiterpenoids (79.80%), monoterpenes (13.25% and α-curcumene (4.33%). The study shows that costunolide and dehydrocostus lactone exhibited strong larvicidal activity with LC_{50} values of 2.34 and 2.26 μg/mL, against *A. albopictus* while other essential oils had an LC_{50} value of 12.41 μg/mL (Liu et al., 2012).

Antiangiogenesis effect

Costunolide, a sesquiterpene lactone from *S. lappa,* inhibited the endothelial cell proliferation induced by vascular endothelial growth factor (VEGF). VEGF interacts with its cognate receptors, KDR/Flk-1 and Flt-1, by blocking the angiogenic factor signalling pathway through auto-phosphorylation of KDR/Flk-1 without affecting that of Flt-1 (Jeong et al., 2002).

PTP1B inhibitory activity

The methanolic extract of *S. lappa* was found to show *in vitro* protein tyrosine phosphatase 1B (PTP1B) inhibitory activity by 61% at 30 μg/mL. Betulinic acid, betulinic acid methyl ester, mokko lactone and dehydrocostus lactone isolated from this extract were found to inhibit PTP1B activity at the minimum concentrations of 0.70, 0.93, 1.41, and 6.51 μg/mL, respectively (Choi et al., 2009).

Gastro-protective effect

Methanolic extract like saussureamines A, B, C, costunolide and dehydrococtus lactone in a dose-dependent manner (5 and 10 mg/kg) shows the gastroprotective effect on acidified ethanol-induced gastric mucosal lesions in rats (Matsuda et al., 2003).

Cardiotonic activity

Heart rate, contractility and coronary flow were determined in the presence of different concentrations of methanolic extract of *S. lappa*. The extract was administered at a dose of 0.5/μg, 2.5/μg and 5.0/μg (Akhtar et al., 2013). The aqueous extract of the root of *S. lappa* was investigated for the cardioprotective effect against s myocardial injury at a dose of 85 mg/kg (Mohamed Saleem et al., 2013). SL helps in reducing blood pressure, prevents blood coagulation and dilates blood vessels. The volatile oils dehydrocostus lactone, and costunolide ingredients inhibit ADP-induced platelet coagulation. The presence of tannins, triterpenes, alkaloids, insulin-like compounds and oils in roots helps in decreasing the level of cholesterol and triglycerides in the blood (Anbu et al., 2011).

Anticancer activity

SL has been found to exert anticancerous activity in divergent cancerous cells. Methanolic extract of SL has been found to be effective against oral cancer (KB) cell with an IC_{50} value of 30 μg/ml by inhibiting cell proliferation through apoptosis pathway (Moon et al., 2013). Isolated active compound costunolide has been found to be effective in the treatment of various types of cancer, which includes breast, oral, gastric, prostate, ovarian and colon cancer respectively (Ko et al., 2005). It inhibits TNF-induced NF-B activation, which results in the reduced expression of MMP-9 gene, which mediates breast cell growth and its metastasis (Choi et al., 2013).

Hexane extract and dehydrocostus lactone of SL inhibit the basal and EGF induced migration of prostate cancer cells in a dose-dependent manner (Kim et al., 2012). The study measured by electrophoretic mobility shift assay shows that costunolide suppress the transcriptional activity of IL-1B promoter, AP-1 factor and phosphorylation of MAPKs (Kang et al., 2004). Cynaropicrin another compound has been found effective in inhibiting the proliferation of leukocyte-like cancer cells such as U937, Eol-1, and Jurkat T, but this inhibition is not shown on liver cells and human fibroblast cells. (Sun et al., 2003). At different concentrations (0-5 μg/ml) the hexane extract of roots hinders the growth of human colon cancer cells HT-29 (Kim et al., 2008) and human prostate cancer cells LNCaP (Park et al., 2008).

Cytotoxicity activity

Dehydrocostus lactone effect investigated in osteoblastic MC3T3-E1 cells found to protect mitochondrial membrane potential dissipation, complex IV inactivation, ATP loss, cytochrome c release, intracellular calcium elevation, potassium ions loss and reactive oxygen species production against antimycin A through improved mitochondrial function (Choi et al., 2009). The cytotoxic effect of cynaropicrin using U937 cells inhibits the proliferation of leukocyte cancer cell lines such as U937, Eol-1, Jurkat T cells studied under flow-cytometric and DNA fragmentation method (Cho et al., 2004). Sesquiterpenoid lactones show cytotoxicity with IC_{50} values of 1.6-3.5 μg/ml in a dose-dependent manner, studied by bioassay-directed fractionation (Sun et al., 2003).

SECONDARY METABOLITES

Phytochemical analysis of *S. costus* shows the presence of various secondary metabolites like alkaloids, terpenes, flavonoids, tannins and sesquiterpenes (Ambavade et al., 2009). The first phytochemical report on *S. lappa* was documented in 1914 by Semmler and Feldstein followed by another supplementary study in the same year (Semmler and Feldstein, 1914a,b). They isolated two lactones, had molecular formulae $C_{15}H_{22}O_2$ and $C_{15}H_{20}O_2$, from the roots oil. However, the proper identification and structure elucidation of these lactones could not be established. The plant is rich in terpenes and sesquiterpenoid lactones like compounds, which include costunolide and dehydrocostus lactone (Robinson et al., 2008). A new sesquiterpenoid with modified form and an uncommon group of sulfonic acid is also isolated from roots named 13-sulfo-dihydrodehydro-costuslactone (Yin et al., 2007). Sesquiterpene lactones are active constituents derived from a variety of medicinal plants used traditionally for the treatment of inflammatory diseases (Cho et al., 2000). The crude extract of roots contains gut stimulatory as well as inhibitory constituents which show lethality to larvae of brine shrimp (Jung et al., 1998; Gilani et al., 2007). The petroleum extract isolated from roots contains lappadilactone, germacrenes, 4β-methoxy-dehydrocostus lactone (De Kraker et al., 2001). Methanolic extract of the roots produced saussuramines A-E, lignin glycoside (-)-massoniresinol 4″-O-β-D-glucopyranoside, betulinic acid methyl ester and mokko lactone (Matsuda et al., 2000). Santamarin is another component isolated from roots which inhibit nitric oxide synthase protein (iNOS), suppressed COX-2 protein and reduced murine peritoneal macrophages (Choi et al., 2012). β-Cyclocostunolide and dihydrocostunolide have isolated from hexane roots extract (Robinson et al., 2008). Two phytosterols, lappasterol and 3-epi-lappasterol have been obtained from the roots (Singh et al., 2004).

Li et al. (2004) identified costunolide, β-costic acid, reynosin, arbuscalin A, 4-allyl-2,6-dimethoxyphenyl glucoside, syringin, costunolid-15-β-D-glucopyranoside, lactone and chlorogenic acid from the roots. Fresh costus roots contain germacrenes (De Kraker et al., 2001). A total of sixty-three aromatic compounds including thirteen alcohols, twenty-six hydrocarbons, four aldehydes, eleven ketones, one oxide, and one carboxylic acid were analysed by GCMS. A linear insulin-type fructofuranosese and oligomeric glucofructans have also been isolated from the roots (Olennikov et al., 2011). Selected phytochemicals isolated from the roots of *S. lappa* are given in Fig. 2.

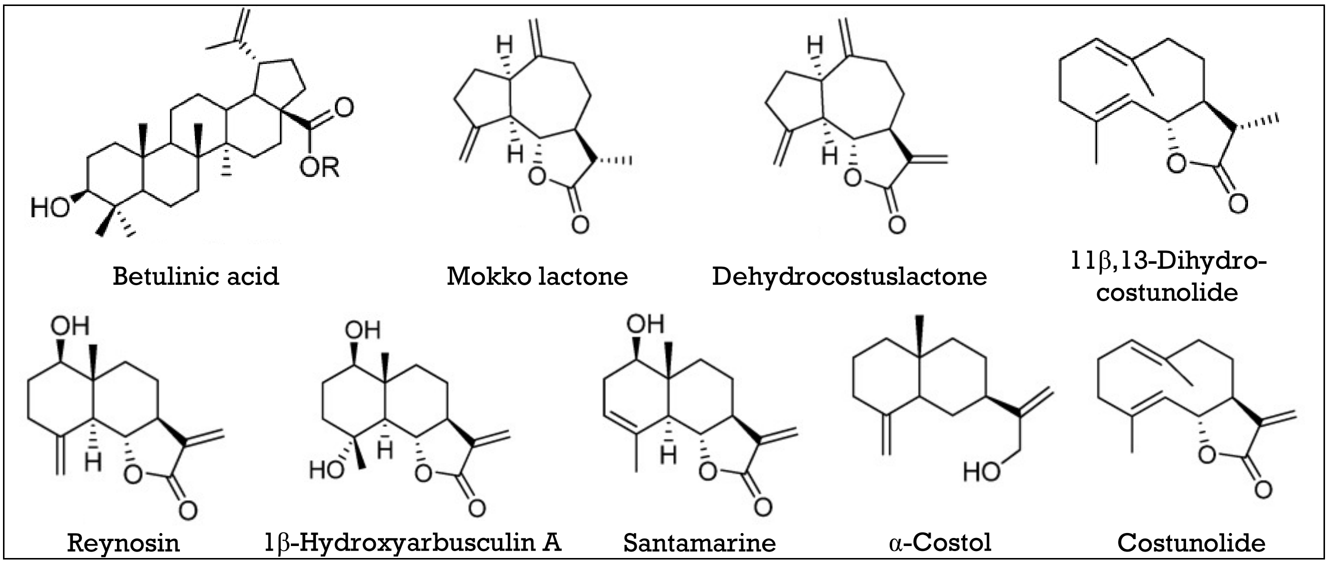

Fig. 2. Selected bioactive constituents isolated from the root of *S. costus*

CONCLUSION

This review concludes that *S. costus* has the potential to treat many human ailments including respiratory, gastrointestinal and various metabolic disorders. Various secondary metabolites such as phytosterols and sesquiterpenoid lactones have been isolated from this plant. These phytochemicals were found to be responsible for the biological activities of *S. costus*.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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