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Review

Saussurea costus: Botanical, chemical and pharmacological review of an ayurvedic medicinal plant

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Abstract

Saussurea costus (Falc.) Lipschitz, syn *Saussurea lappa* C.B. Clarke is a well known and important medicinal plant widely used in several indigenous systems of medicine for the treatment of various ailments, viz. asthma, inflammatory diseases, ulcer and stomach problems. Sesquiterpene lactones have been reported as the major phytoconstituents of this species. Different pharmacological experiments in a number of *in vitro* and *in vivo* models have convincingly demonstrated the ability of *Saussurea costus* to exhibit anti-inflammatory, anti-ulcer, anticancer and hepatoprotective activities, lending support to the rationale behind several of its traditional uses. Costunolide, dehydrocostus lactone and cynaropicrin, isolated from this plant, have been identified to have potential to be developed as bioactive molecules. Due to the remarkable biological activity of *Saussurea costus* and its constituents it will be appropriate to develop them as a medicine. The present review is an up-to-date and comprehensive analysis of the botany, chemistry, pharmacology and traditional and folkloric uses of *Saussurea costus*.

Keywords: *Saussurea costus*; *Saussurea lappa*; Sesquiterpene lactones; Pharmacology

Contents

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1. Introduction

The Asteraceae family comprises approximately 1000 genera and 30,000 species, distributed more or less throughout the globe, of which approximately 177 genera and 1052 species are found in India (Rao et al., 1988). The genus *Saussurea* DC. of the same family comprises about 300 species in the world (Bremer, 1994) of which about 61 species exist in India (Hajra, 1988; Hajra et al., 1995). Some common, ethnomedicinally important species of this genus found in India (Jain, 1991) have been listed in Table 1. *Saussurea costus* (Falc.) Lipschitz, syn *Saussurea lappa* C.B. Clarke, one of the best-known species within this genus, is commonly known as costus in English and has different vernacular names in India like, Kut (Gujrati), Kur (Bengali), Postkhai (Kashmiri), Sepuddy (Malayalam), Kot (Punjabi), Kushta (Sanskrit), Kostum (Tamil), Kustam (Telgu), Kushta (Marathi), Koshta (Kannada) and Kuth (Hindi) (Kirtikar and Basu, 2001). *Saussurea costus* (root oil and roots) has become an important drug in the international market.

In India this plant is endemic in the sub alpine regions of Jammu and Kashmir, Himachal Pradesh and Uttaranchal, from an altitude of 3200–3800 m (Fig. 1). Availability of this important plant in the wild is decreasing day by day due to over-exploitation for different medicinal and commercial purposes. This critically endangered medicinal species is enlisted in Appendix I of Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) and is one of the 37 Himalayan endangered medicinal plants that have been prioritized for in situ and ex situ conservation (Kuniyal et al., 2005). Due to a resource base bottleneck, the Ministry of Commerce, Government of India, has prohibited export of 29 medicinal and aromatic species, including *Saussurea costus*, either in crude form or in processed products (Anonymous, 2000). The Planning Commission and the National Medicinal Plants Board (NMPB) of the Government of India have prepared a policy document on the promotional and commercial aspects of the medicinal plants sector. According to the Planning Commission, Government of India, quantity of *Saussurea costus* required is to the tune of 0.43 tonnes per annum. The NMPB has prioritized 32 and Planning Commission has enlisted 24 medicinal plant species for research and development in order to meet the desired aim of the medicinal plant sector and both these lists include *Saussurea costus*. (Kala et al., 2006).

Hagers Handbuch der Pharmazeutischen Praxis (Bruchhausen et al., 1994) includes a monograph on *Saussurea costus* which describes the botany, chemical constituents, pharmacological properties and uses of *Saussurea costus.* Also there has been a tremendous interest in this plant as evidenced by the voluminous work carried out by different researchers in the recent past. Therefore, we aimed to compile an up-to-date and comprehensive review of *Saussurea costus* that covers its traditional and folkmedicinal uses, botanical characters, phytochemistry and pharmacology.

2. Botany (morphology and microscopy)

The major contributions to the family Asteraceae in Indian regions have been primarily made by two British botanists C.B. Clarke (1876) and Sir J.D. Hooker (1881). Hooker (1881) in his monumental Flora of British India has dealt with the taxonomic account of about 608 species of Asteraceae. Besides, several workers (Gupta, 1964; Sarin, 1967; Hajra, 1988; Hajra et al., 1995; Srivastava and Kapahi, 1995; Chaudhary and Rao, 2000) have significantly contributed towards the morphological

Table 1
Some common, ethnomedicinally important Indian species of genus *Saussurea*

Name	Uses	Distribution
Saussurea auriculata (Spreng. ex DC.) Sch.-Bip.	Leaf edible, used as vegetable	Himalayas on open slopes and amidst shrubs, 2000–4300 m. Jammu and Kashmir, Himachal Pradesh and Uttaranchal
Saussurea bracteata Decne.	Whole plant used in cold, cough and fever	Himalayas on open slopes, alpine meadows, 3500–5600 m. Jammu and Kashmir, Himachal Pradesh and Uttaranchal
Saussurea ceratocarpa Decne.	Whole plant used in colic, headache, lumbar pain, menorrhagia, renal pain	Western Himalayas 3000–5000 m. Jammu and Kashmir and Himachal Pradesh
Saussurea costus (Falc.) Lipsch.	Roots used in asthma, dysentery, rheumatism, stomachache, ulcer and toothache; used as incense. Leaves edible	Himalayas, in subalpine regions, 3200–5000 m. Jammu and Kashmir, Himachal Pradesh and Uttaranchal
Saussurea gossypiphora D. Don	Whole plant considered to be sacred	Himalayas, in open places, 3500–5700 m. Jammu and Kashmir, Himachal Pradesh, Uttaranchal and Sikkim
Saussurea heteromalla (Don) Hand.-mazz.	Seeds carminative, used in horse bite	In wastelands, dry hill slopes, 550–4000 m. Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Bihar and Sikkim
Saussurea obvallata (DC.) Edgew.	Roots used in bruises and cuts. Whole plant considered to be sacred	Himalayas, in morain on rocky slopes, 3800–4600 m. Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Sikkim and Arunachal Pradesh
Saussurea simpsoniana (Field. & Gard.) Lipsch.	Inflorescence used in fever, snakebite	Himalayas, in the alpine regions, 4400–5600 m. Jammu and Kashmir, Himachal Pradesh, Uttaranchal and Sikkim

characterization of the genus *Saussurea* in India, including *Saussurea costus.* Macromorphological parameters like habit, size of plants, size and shape of leaves and capitula and the nature of phyllaries in *Saussurea costus* have been described by all the above workers.

Saussurea costus is an erect, robust, pubescent, perennial herb, with a stout simple stem 1–2 m high. Leaves membranous, scaberulous above, glabrate beneath, auricled at base, irregularly toothed; basal ones very large, 0.50–1.25 m long, with a long winged petiole; upper leaves smaller, subsessile or shortly petioled; two small lobes at the base of these leaves almost clasping the stem. Flower heads stalkless, bluish-purple to almost black, hard, rounded, 2.4–3.9 cm across, often 2–5 clustered together in the axils of leaves or terminal. Involucral bracts many, ovate-lanceolate, long pointed, purple, rigid, hairless. Receptacle bristles very long. Corolla about 2 cm long, tubular, blue-purple or almost black. Anther tails fimbriate. Achenes curved, compressed *ca.* 8 mm long, tip narrowed, with one rib on each face. Pappus brown, double feathery. Roots are stout, dark brown or grey, up to 40 cm long (Hajra et al., 1995). Bruchhausen et al. (1994) and Upadhyay et al. (1993) have described the macro and microscopical characters of the roots of *Saussurea costus* while Saklani et al. (2000) have reported its achene morphology.

Fig. 1. Map of India showing distribution of *Saussurea costus*. 1. Jammu & Kashmir; 2. Himachal Pradesh; 3. Uttaranchal.

3. Ethnobotany

In the Indian systems of medicine (*Ayurveda, Siddha,* and *Unani*) *Saussurea costus* is used either as a single drug or in combination with other drugs. Its roots are used mainly as an antispasmodic in asthma, cough and also in treatment of cholera, chronic skin diseases and rheumatism (Chopra et al., 1956; Dhar et al., 1984). Its different preparations are also used by Ayurvedic physicians for the treatment of various ailments like cough and cold, quartan malaria, leprosy, persistant hiccups, rheumatism, hair-wash, stomachache, toothache, typhoid fever, etc. (Table 2). It is an important medicine for gout, erysipelas and promotes spermatogenesis. *Saussurea costus* has been used by different people and ethnic tribes of the Northern parts of India for the treatment of various ailments. Table 2 gives the region-wise ethnomedical uses of *Saussurea costus* while Table 3 summarises the different methods of using it. The root is also used in Tibetan medicine where it is considered to have an acrid, sweet and bitter taste with a neutral potency. Several traditional Tibetan formulae that are used for chronic inflammation of the lungs, cough, chest congestion eg Hippophae 5 and Eliminator of Lung Inflammation contain *Saussurea* as one of the important ingredients (Tsarong, 1994).

4. Chemistry

Salooja et al. (1950) characterized a basic fraction from the roots of *Saussurea lappa.* Subsequently, a new crystalline lactone—saussurea lactone ($C_{15}H_{20}O_2$) (Rao and Verma, 1951) and costunolide were isolated from costus (*Saussurea lappa*) root oil (Rao et al., 1960). Costunolide, dehydrocostuslactone, costic, palmitic, linoleic acids, β-sitosterol, α-cyclocostunolide, alantolactone, β-cyclocostunolide, isoalantolactone (Govindan and Bhattacharaya, 1977), isodehydrocostus lactone, isozaluzanin-C, guiainolides (Kalsi et al., 1983, 1984; Chhabra et

Table 2
Region-wise ethnomedical uses of *Saussurea costus*

Part	Ethno medical uses	Region	Reference
Root	Dysentery, ulcer, stomachache	Trans Himalayan region	Kala and Manjerkar (1999)
Decoction of roots	Cough and cold	Kullu region	Singh (1999)
Root/root powder	Quartan malaria, leprosy, persistant hiccups, rheumatism Hair-wash, astringent stimulant	Hakims and vaidyas of North India	Kapoor (2001)
Decoction of root	Stomachache, toothache, typhoid fever	Tolcha tribes of Nanda devi region of Uttaranchal	Nautiyal et al. (2003)
Root	Used to protect clothes from insect	Mountain regions of north India	Mittre (1981)
Root	Asthma, dysentery, skin disorders, toothache	Northern mountain region of India	Shah (1982)
Root	Rheumatism	Ambala Haryana region	Jain (1984)
Root	Stomachache	Kumaon region of Uttaranchal	Rawat and Pangtey (1987)
Root	Ulcer	Kashmir region	Kaul (1941)
Leaves	Chewed/edible, Snake repellent, used as incense	Lahul region of Himachal Pradesh	Koelz (1979)

Table 3
Traditional methods of application of *Saussurea costus*

Conditions	Method of applications	Reference
Stomachache	Root powder is taken with water. Decoction of root is taken. Root powder is roasted in mustard oil and the paste is applied on stomach	Kumar and Kumar (1989)
Headache	Oil heated with root is applied	
Cough and cold	Root powder is taken with warm water	
Throat infection	Root is chewed	
Backache and chest pain	Root powder is taken with milk/decoction of root powder. Oil heated with root is massaged the affected area	
Rheumatism and painful joints	Root is roasted in ghee/butter, powdered and taken with milk. The above mentioned ghee/butter is rubbed on the affected area and bandaged to keep warm.	
Scanty urination	Jaggery is mixed in the decoction of root powder which is then taken. Paste of root powder is applied on the stomach below the naval.	
Skin rashes formed after insect bite	Root powder is roasted in ghee/butter and the ghee/butter is applied on the affected area	
Exhaustion	Pieces of root are burnt in hookah and the smoke inhaled	
Lustre and growth of hair	Hair is washed with decoction. Mustard oil is heated with root powder and the oil used as topical application on hair	
Pustules	Fine root powder is dusted on the wound. Mustard oil is heated with root powder and the oil is applied and bandaged	
Fainting spells	Root is rubbed in water and the water is used a nasal drops Fine powder of root is used for sneezing.	
General weakness fatigue	Root is boiled in milk and the milk is taken twice daily	
Piles	Root are taken along with the 'Vacha' (*Acorus calamus*) roots	Bapalal (1998)
Epilepsy	The roots are taken with honey	
Headache	Paste of the root is applied	
General weakness (as *Rasayana*)	Root powder ingested with cow's milk and cow's ghee	
Scalp scabies	Essential oil of root is applied	

al., 1998a), 12-methoxydihydrodehydrocostuslactone (Dhillon et al., 1987), 4β-methoxydehydrocostus lactone (Singh et al., 1992), saussurealdehyde, isodehydrocostus-lactone-15-aldehyde (Kumar et al., 1995), sesquiterpene lactones (Kalsi et al., 1995; Ha et al., 1997), 11,13-epoxydehydrocostus-lactone, 11,13-epoxy-isozazulanin C, 11,13-epoxydehydroisozaluzamine (Chhabra et al., 1997), 11,13-epoxy-3-keto dehydrocostus–lactone (Chhabra et al., 1998b), cynaropicrin, reynosin, santamarine (Cho et al., 1998), 6,10-dimethyl-9-methyleneunused-S-E-en-2-one (Stepanov and Veselovsky, 1999), (+)-germacrene A, germacra-1(10),4,11(13)-trien-12-al, germacra-1(10), 4,11(13)-trien-12-al, and germacra-1(10), 4,11(13)-trine-12-oic acid (Kraker et al., 2001) were also isolated.

22-Dihydrostigmasterol (Jain and Banks, 1968) and sesquiterpenoides (Maurer and Grieder, 1977) were reported from costus root oil. Saussureal (a sesquiterpenoid) (Talwar et al., 1991), steroids, pregnenolone, β-sitosterol, daucosterol, a phenylpropanoid glycoside, syrine, a lignan glycoside, 1-hydroxypinoresinol-1-β-D-glucopyranoside, 12-octadecadienoic acid, (Z,Z)-9,12-octadienoic acid-2-hydroxy-1,3-propanedinyl ester (Yang et al., 1997c), seven noncytotoxic compounds including two novel sesquiterpenes, a guaianolide-type with a C17 skeleton, lappalone and 1β, 6α-dihydroxycostic acid ethyl ester were isolated (Sun et al., 2003). Subsequently, Jung et al. (1998) investigated shikokiols, the cytotoxic components of crude extract of *Saussurea lappa* root.

Five new amino acid-sesquiterpene adducts, viz. Saussureamines A, B, C, D and E, were isolated together with a lignan glycoside (−)-massoniresinol 4″-*O*-β-D-glucopyranoside (Yoshikawa et al., 1993), Subsequently, all these compounds were synthesized by Matsuda et al. (2000a,b). Costunolide, dihydrocostunolide (Kang et al., 1999; Saxena and Dixit, 1993), a new sesquiterpene aldehyde, baccharane type triterpene, 3-β-acetoxy-9(11)-baccharene and α-amyrin (Yang et al., 1997a,b) were also isolated. Chlorogenic acid (Pandey et al., 2004) and saussurine (Lalla et al., 2002) were identified by HPTLC and HPLC from the root of *Saussurea costus*.

Two new sesquiterpene lactones with the unusual sulfonic acid group, 13-sulfo-dihydrosantamarine and 13-sulfo-dihydroreynosin, were isolated and their structures, including the absolute configurations, were elucidated by spectroscopic methods (Yin et al., 2005).

Singh et al. (1957) reported that the oil can be obtained from the roots by a number of methods. Further, Bose et al. (1961) have reported the chemical analysis of *Saussurea costus* and discussed the presence of reducing sugars, tannins, resins, essential oil (1.39%) and alkaloids (0.05 %). Namboodiripad et al. (1968) isolated taraxasterol, and its acetate from the leaves of costus. Subsequently, Shoji et al. (1986) isolated the pharmacologically active compounds (costunolide and dehydrocostus lactone) from methanolic extract of crude drug *Saussurea costus*. Viswanathan and Kulkarni (1995) also reported *Saussurea costus* (Kuth) as a new source of inulin.

5. Pharmacology

Several workers have reported on the different biological activities of *Saussurea costus* in various *in vitro* and *in vivo* test models. Different extracts of this plant have been

found to exhibit anti-inflammatory, hepatoprotective, anti-ulcer, anticancer, immunomodulatory and pesticidal activities. These have been described in greater detail in the following sections.

5.1. General pharmacology

Experiments were performed to investigate the general pharmacological actions of the delactonized oil and different lactone fractions isolated from the root oil of *Saussurea costus.* Delactonized oil and lactone fractions exhibited antispasmodic activity of variable degrees when tested against spasms produced by acetylcholine chloride, histamine biophosphate and barium chloride on guinea pig ileum and dog and guinea pig trachea. No apparent stimulant or depressant effect on central nervous system was exhibited by any fraction. All the fractions exhibited varying degrees of hypotensive effect in anaesthetized dogs. Delactonized oil and 12-methoxy dihydrocostunolide were more potent than other fractions. The mechanism of hypotensive action seems to be due to direct peripheral vasodilation and cardiac depression. Different fractions protected guinea pigs to a varying degree against the experimentally produced bronchospasm induced by histamine and acetylcholine aerosols and this may explain the claimed therapeutic effect of the plant in asthma (Gupta and Ghatak, 1967).

Costunolide from roots of *Saussurea costus* inhibited contractions of the rabbit-isolated aorta induced by KCl (Potassium chloride), but exerted considerably less effect on those induced by norepinephrine, indicating the possible calcium antagonistic action of costunolide. Dehydrocostuslactone caused similar inhibitory effects on the aorta, but its specificity to potassium chloride induced contractions appeared to be less than that observed with costunolide (Shoji et al., 1986).

5.2. Anti-inflammatory

Saussurea costus is frequently used in Korean traditional prescriptions for inflammatory diseases. Its total methanol extract at 0.1 mg/ml as a final concentration exhibited more than 50% of inhibition on the cytokine induced neutrophil chemotactic factor (CINC) induction (Lee et al., 1995).

A sesquiterpene lactone isolated from the methanolic extract of *Saussurea costus* exhibited dose dependent inhibition on the CINC-1 induction of LPS (lipopolysaccharide) stimulated NRK-52-E cells of rat kidney (Ha et al., 1997).

Dehydrocostus lactone isolated from *Saussurea costus*, inhibited the production of nitric oxide in LPS activated RAW 264.7 cells by suppressing inducible nitric oxide synthase enzyme expression (Lee et al., 1999). The preventive effects of dehydrocostus lactone from *Saussurea costus* on NF-kappa B activation in LPS treated RAW 264.7 macrophages and U937 human monocytic cells were examined to elucidate the molecular mechanism for the suppression of LPS-induced nitric oxide (NO) production. The results showed that the suppression of NO production is mediated by the inhibitory action on the inducible nitric oxide synthase (iNOS) gene expression through the inactivation of NF-kappa B and these lactones can act as pharmacological inhibitors of the NF-kappa B activation (Jin et al., 2000).

The total ethanol extract of *Saussurea costus,* frequently used in Korean traditional prescriptions for inflammatory diseases, exhibited more than 50% of inhibition on tumor necrosis factor (TNF)-alpha production in LPS-stimulated RAW 264.7 cells (Cho et al., 1999).

Total methanol extract of *Saussurea costus* showed potent inhibitory effect on the production of TNF-alpha, a pro-inflammatory cytokine, in murine macrophage-like cell (RAW 264.7 cells). The activity-guided purification resulted in the isolation of three sesquiterpene lactones, cynaropicrin, reynosin, and santamarine, which inhibited TNF-alpha production in a dose-dependent manner. The molar concentrations of cynaropicrin, reynosin, and santamarine producing 50% inhibition (IC_{50}) of TNF-alpha production were 2.86 μg/ml (8.24 μM), 21.7 μg/ml (87.4 μM), and 26.2 μg/ml (105 μM), respectively. However, treatment with sulfydryl (SH) compounds such as L-cysteine, dithiothreitol, and 2-mercaptoethanol abrogated the inhibitory effect of cynaropicrin on TNF-alpha production. Therefore, it was concluded that the principal inhibitory component of *Saussurea costus* is cynaropicrin and its inhibitory effect is mediated through conjugation with SH-groups of target proteins (Cho et al., 1998).

In vitro anti-inflammatory effect of cynaropicrin, on TNF-alpha and nitric oxide release, and lymphocyte proliferation was investigated. Cynaropicrin strongly inhibited TNF-alpha release from LPS-stimulated murine macrophage, RAW 264.7 cells, and differentiated human macrophage, U937 cells, known to produce notable amount of TNF-alpha. It also potently attenuated the accumulation of NO released from lipopolysaccharide and interferon-gamma stimulated RAW 264.7 cells in a dose-dependent manner. The results showed that cynaropicrin may participate in the inflammatory response by inhibiting the production of inflammatory mediators and the proliferation of lymphocytes and its inhibitory effect is mediated through conjugation with sulfydryl groups of target protein(s) (Cho et al., 2000).

The methanolic extract of the roots of *Saussurea costus* was found to inhibit nitric oxide production in lipopolysaccharide activated mouse peritoneal macrophages. Saussureamines A and B in addition to costunolide and dehydrocostus lactone did not inhibit inducible NO synthase (iNOS) enzyme activity, but they inhibited both induction of iNOS and activation of NF-kappa B in accordance with induction of heat shock protein 72 (Matsuda et al., 2003).

The sesquiterpene lactone fraction of *Saussurea costus* roots was evaluated for its effect on the transudative, exudative and proliferative phases of inflammation using the cotton pellet granuloma assay in rats. The fraction (25–100 mg/kg, p.o.) showed significant dose-dependent inhibition of the increase in wet weight of the cotton pellet at 3 h (transudative phase). The studies suggested that the anti-inflammatory activity of the sesquiterpene lactone fraction of *Saussurea costus* may, in part, be due to stabilization of lysosomal membranes and an antiproliferative effect (Damre et al., 2003).

The inhibitory effects of costunolide (isolated from the root of *Saussurea costus*) on the protein and mRNA expression of interleukin-1β (IL-1β) in LPS-stimulated RAW 264.7 cells were examined. Results showed that costunolide inhibited the activity of AP-1 transcription factor, and the phosphorylation of mitogen-activated protein kinase (MAPK), including stress-activated protein kinase/c-Jun NH2-terminal Kinase (SAPK/JNK) and p38 MAP kinase, and also inhibited IL-1β gene expression by blocking the activation of MAPKs and DNA binding of AP-1 in LPS-stimulated RAW 264.7 cells (Kang et al., 2004).

The ethanolic extract of *Saussurea costus* at the doses of 50, 100 and 200 mg/kg, p.o. was screened for effect on acute and chronic inflammation induced in mice and rats. *Saussurea lappa* was found to significantly inhibit paw oedema induced by carrageenan and Freund's complete adjuvant and to prevent accumulation of inflammatory cells in carrageenan-induced peritonitis at doses of 50–200 mg/kg. Results showed anti-inflammatory and anti-arthritic activity and supported the rationale behind the traditional use of this plant in inflammatory conditions (Gokhale et al., 2002).

Extract of the roots of *Saussurea costus* was found to inhibit iNOS by the decreasing iNOS protein and iNOS mRNA level. It is one of the constituents of the complex herb preparation Padma 28 and the inhibition of iNOS might contribute to the anti-inflammatory activities of Padma 28 (Moeslinger et al., 2000).

5.3. Anticancer/antitumor

Costunolide, an active compound isolated from the root of *Saussurea costus*, was investigated for its effect on the induction of apoptosis in HL-60 human leukemia cells and its putative pathways of action. Using apoptosis analysis, measurement of reactive oxygen species (ROS), and assessment of mitochondrial membrane potentials, it was shown that costunolide is a potent inducer of apoptosis, and facilitates its activity via ROS generation, thereby inducing mitochondrial permeability transition (MPT) and cytochrome C release to the cytosol. ROS production, mitochondrial alteration, and subsequent apoptotic cell death in costunolide-treated cells were blocked by the antioxidant *N*-acetylcystein (NAC). Cyclosporine A, a permeability transition inhibitor, also inhibited mitochondrial permeability transition and apoptosis. Results data indicated that costunolide induces the ROS-mediated mitochondrial permeability transition and resultant cytochrome C release. This is the first report of the mechanism of the anticancer effect of constunolide (Lee et al., 2001).

A study to understand the molecular basis underlying the antitumor effects of *Saussurea costus* was performed that analyzed the effects of this medicinal herb on proliferation and on expression of cell growth/apoptosis related molecules, using an AGS gastric cancer cell line. The treatment with *Saussurea costus* dramatically reduced cell viabilities in a dose and time-dependent manner. FACS analysis and Annexin V staining assay also showed that *Saussurea lappa* induced apoptotic cell death of AGS. Expression analyses via RT-PCR and Western blots revealed that it increased expression of the p53 and its downstream effector p21Waf1, and increased expression of apoptosis related Bax and cleavage of active caspase-3 protein. It also confirmed the translocation of Bax to mitochondria. The data demonstrated that *Saussurea costus* induced growth inhibition and apoptosis of human gastric cancer cells, and these effects were correlated with down- and up-regulation of growth-regulating apoptotic and tumor suppressor genes, respectively (Ko et al., 2004). The cytostatic effects of *Saussurea costus* root were attributed to the regulation of cyclins and pro-apoptotic molecules and suppression of anti-apoptotic molecules. The extracts of *Saussurea costus* root may thus be used for the treatment of gastric cancers either by traditional herbal therapy or by combinational therapy with conventional chemotherapy (Ko et al., 2005).

Lappadilactone and seven sesquiterpene lactones of *Saussurea costus* were examined against selected human cancer cell lines for cytotoxicity. Lappadilactone, dehydrocostuslactone and costunolide exhibited the most potent cytotoxicity with CD_{50} values in the range 1.6–3.5 μg/ml in dose- and time-dependent manners. The cytotoxicities were not specific and showed similar activities against HepG2, OVCAR-3 and HeLa cell lines. The structure–activity relationship showed that the α-methylene-γ-lactone moiety is necessary for cytotoxicity, and activity is reduced with the presence of a hydroxyl group (Sun et al., 2003).

Dehydrocostus lactone (DL), the major sesquiterpene lactone isolated from the roots of *Saussurea costus*, inhibited NF-kappa B activation by preventing TNF-alpha induced degradation and phosphorylation of its inhibitory protein I-kappa B alpha in human leukemia HL-60 cells and that DL renders HL-60 cells susceptible to TNF-alpha induced apoptosis by enhancing caspase-8 and caspase-3 activities (Oh et al., 2004).

Cynaropicrin, isolated from *Saussurea lappa*, exhibited immunomodulatory effects on cytokine release, nitric oxide production and immunosuppressive effects. Cynaropicrin potently inhibited the proliferation of leukocyte cancer cell lines, such as U937, Eol-1 and Jurkat T cells, but some other cells such as Chang liver cells and human fibroblast cell lines were not strongly suppressed by cynaropicrin treatment. The combination treatment with cysteine and *N*-acetylcysteine, reactive oxygen species scavengers, or rottlerin (1-[6-[(3-acetyl-2, 4, 6-trihydroxy-5-methylphenyl)methyl]-5,7-dihydroxy-2, 2-dimethyl-2H-1-benzopyran-8-yl]-3-phenyl-2-propen-1-one), a specific protein kinase (PK) Cδ inhibitor, abolished cynaropicrin-mediated cytotoxicity and morphological change, and that cynaropicrin-induced proteolytic cleavage of PKCδ suggests that reactive oxygen species and PKCδ may play an important role in mediating pro-apoptotic activity by cynaropicrin. It is concluded that, cynaropicrin may be a potential anticancer agent against some leukocyte cancer cells such as lymphoma or leukemia, through pro-apoptotic activity (Cho et al., 2004).

Costunolide, a sesquiterpene lactone isolated from *Saussurea lappa*, exerted an anti-angiogenic effect. This compound selectively inhibited the endothelial cell proliferation induced by vascular endothelial growth factor (VEGF). It was also found to inhibit the VEGF-induced chemotaxis of human umbilical

vein endothelial cells (HUVECs) in a dose-dependent manner. The result showed that costunolide might inhibit angiogenesis by blocking the angiogenic factor signaling pathway. VEGF interacts with its cognate receptors, KDR/Flk-1 and Flt-1, and exerts its angiogenic effect. Costunolide inhibited the autophosphorylation of KDR/Flk-1 without affecting that of Flt-1. These results suggest that costunolide may prove useful for the development of a novel angiogenesis inhibitor (Jeong et al., 2002).

C-17 polyene alcohol isolated from *Saussurea costus* exhibited moderate cytotoxicities against the human tumor cell lines A549, SK-OV3, SK-MEL-2, XF 498 and HCT 15 (Jung et al., 1998).

5.4. Hepatoprotective

Two active components, constunolide and dehydrocostus lactone showed strong suppressive effect on the expression of the hepatitis B surface antigen (HBsAg) in human hepatoma Hep 3B cells, but had little effect on the viability of the cells. Both costunolide and dehydrocostus lactone suppressed the HBsAg production by Hep3B cells in a dose-dependent manner with IC_{50} of 1.0 and 2.0 μM, respectively. Northern blotting analysis showed that the suppression of HBsAg gene expression by both, costunolide and dehydrocostus lactone, was mainly at the mRNA level. Furthermore, the suppressive effect of costunolide on replication of human liver cells, was also observed in another human hepatoma cell line Hep A2 which was derived from Hep G2 cells by transfecting a tandemly repeat hepatitis B virus DNA. Similarly, the mRNA of HBsAg in HepA2 cells was also suppressed by these two compounds. The findings suggested that costunolide and dehydrocostus lactone had the potential to be developed as specific anti-HBV drugs in the future (Chen et al., 1995).

5.5. Anti-ulcer and cholagogic

The acetone extract from *Saussurea costus* and costunolide, exhibited both cholagogic effect and inhibitory effect on the formation of gastric ulcer (induced by restraint in water) in mice (Yamahara et al., 1985). The variation in gastric acidity output, serum gastrin and plasma somatostatin concentration were observed during *Saussurea costus* decoction perfusion into the stomach of patients with chronic superficial gastritis. It revealed that decoction could accelerate the gastric emptying and increase the endogenous motilin release (Chen et al., 1994). *Saussurea costus* is one of the major ingredients in a formulation UL-409, which possesses anti-ulcer activity (Venkataranganna et al., 1998) and the observed activity may be due to the modulation of defensive factors by improvement in gastric cytoprotection (Mitra et al., 1996).

The amino acid–sesquiterpene adducts, saussureamines A, B and C, isolated from the dried root of Chinese *Saussurea costus* showed anti-ulcer effect on HCl/ethanol-induced lesion in rats. Saussureamine A also exhibited inhibitory activity on stress induced ulcer formation in mice (Yoshikawa et al., 1993). Saussureamines and the related amino acid–sesquiterpene conjugates from the methanolic extract of the dried roots of *Saussurea lappa* were synthesized using a Michael type addition reaction of amino acid to the α-methylene-γ-lactone moiety of sesquiterpenes. Besides the saussureamines, costunolide and dehydrocostus lactone also showed a gastroprotective effect on acidified ethanol-induced gastric mucosal lesions in rats (Matsuda et al., 2000a,b).

Infection by *Helicobacter pylori* has been ascertained to be an important etiologic impetus leading usually to chronic active gastritis and gastric ulcer with growing incidences worldwide. Utilizing as the test pathogen a standard and five clinical strains of *Helicobacter pylori*, the antibacterial action was assessed *in vitro* with ethanol extract of *Saussurea lappa* which has been prescribed since ancient times in the Chinese herbal medicine for treating gastritis-like disorders (Yang et al., 2005). It was found to be strongly inhibitory to all test strains (MIC: 40 μg/ml).

5.6. Imunomodulator

Costunolide and dehydrocostus lactone were isolated from an extract of *Saussurea costus* as inhibitors of killing activity of cytotoxic T lymphocytes (CTL). Constunolide inhibited the killing activity of CTL through preventing the increase in tyrosine phosphorylation in response to the crossslinking of T cell receptors (Taniguchi et al., 1995).

Mokko lactone, dehydrocostus lactone from *Saussurea costus* and other guaianolides were examined for their structure activity relationship as inhibitors of the killing function of CTL and the induction of intercellular adhesion molecule-1 (ICAM-1). It was observed that the guaianolides possessing an α-methylene-γ-lactone moiety exhibited significant inhibitory activity towards the killing function of CTL and the induction of ICAM-1 (Yuuya et al., 1999).

5.7. Bronchitis

Experiments were conducted to study the effect of different extracts of *Saussurea costus* against chronic bronchitis and asthma (Dutta et al., 1960; Sastry and Dutta, 1961). The alkaloidal fraction was found to be non-toxic and had little effect on the blood pressure and respiration of the cat and rabbit. It exhibited marked spasmolytic effect on the smooth (intestinal) and tracheal muscle of the guinea pig when stimulated by histamine and antispasmodic effect on the perfused isolated guinea pig lungs (Dutta et al., 1960). Studies were also carried out on Tincture Saussurea, petroleum ether extract, Tincture Saussurea prepared from defatted roots and extracts obtained by successive extraction of the roots of *Saussurea costus*. The results showed that Tincture Saussurea and petroleum ether extract produced broncho-constriction in guinea pigs while Tincture Saussurea prepared from defatted roots and other extracts produced no such effect thereby suggesting that Tincture Saussurea devoid of the petroleum ether soluble fraction would be a useful drug for chronic bronchitis and asthma (Sastry and Dutta, 1961). The preliminary experiments, thus, seemed to justify the reputation of the drug as a useful remedy against chronic bronchitis and asthma.

5.8. Miscellaneous

5.8.1. Hypolipidaemic

Aqueous extract of *Saussurea costus* orally administered to twenty seven rabbits at a dose of 2 mg/kg body weight showed hypolipidaemic effect. Reduction in serum cholesterol and serum triglycerides was found to be significant (Upadhyay et al., 1994).

5.8.2. Hypoglycaemic

Saussurea costus was found most effective for obese diabetes when a detailed survey and clinical study on potent hypoglycaemic plants of different regions from India was undertaken to find antidiabetic plants used in Indian folklore and by different tribes (Upadhyay et al., 1996).

5.8.3. Antimicrobial

The inhibitory effects of the ethanol extract of *Saussurea lappa* on the growth, acid production, adherence, and water-insoluble glucan synthesis of *Streptococcus mutans* were examined (Yu et al., 2006). The growth and acid production of *Streptococcus mutans* were significantly inhibited by the presence of ethanol extract of *Saussurea lappa* (0.5–4 mg/ml). The ethanol extract of *Saussurea lappa* (0.25–4 mg/ml) also significantly lowered the adherence of *Streptococcus mutans* in a dose dependent manner. In water-insoluble glucan synthesis assay, 2–4 mg/ml of the ethanol extract of *Saussurea lappa* significantly inhibited the formation of water-insoluble glucan. *Saussurea lappa* is known to have therapeutic effects on oral diseases such as halitosis, dental caries, and periodontal disease (Lee, 1986; Kim et al., 1991). These results provided some scientific rationales for its use in the treatment of dental diseases and suggested that *Saussurea lappa* may inhibit the caries-inducing properties of *Streptococcus mutans*.

5.8.4. Antiparasitic

The antiparasitic activity of *Saussurea costus* was evaluated against *Clonorchis sinensis*, *Trypanosoma cruzi* and some nematodal infections. Decoction of *Saussurea costus*, when administered orally into rabbits infected with *Clonorchis sinensis*, to study its *in vivo* clonorchicidal activity, was found to be somewhat effective by observing the suppression effects of the egg laying capacity from rabbits (Rhee et al., 1985). The antinematodal efficacy of *Saussurea costus* was studied on the basis of percentage reductions in the faecal eggs per gram (EPG) counts in the children infected naturally with the respective worms. It contained active principles effective against nematodes and did not produce adverse side effects in the doses tested (Akhtar and Riffat, 1991). *Saussurea lappa* methanolic extract was tested *in vitro* with the epimastigote form of *Trypanosoma cruzi*, clone Bra C15 C2, at 27 °C in F-29 medium at a concentration of 100 μg/ml in axenic cultures. Allopurinol was used as reference drug. *Saussurea lappa* extract exhibited inhibitory activity of 100% (Lirussi et al., 2004).

5.8.5. Antifeedant

The rhizomes of *Saussurea lappa* showed significant repellent activity against *Tribolium castaneum* (Herbst) and antifeedant activity against *Rhyzopertha dominica* F. (Malik and Naqvi, 1984). The essential oil of *Saussurea costus* was also studied for food repellency against adult and growth inhibitory effects against larvae of *Tribolium castaneum*. At 0.1 and 0.5% concentrations it exhibited promising repellency (85.25 and 85.71%, respectively) after 24 h, while after 48 h it was found to be highly effective (85.22 and 88.10% repellency at 0.1 and 0.5% concentrations, respectively). However, when tested for growth inhibitory effect, it did not show reduction in adult emergence (Naik et al., 1995).

5.8.6. CNS depressant

Dehydrocostus lactone and costunolide from *Saussurea costus* increased hexobarbital induced sleeping time and decreased body temperature, nociception spontaneous locomotor activity thus exhibiting CNS depressant activity (Okugawa et al., 1996).

Besides the above-mentioned biological activities there are some other reports also for *Saussurea costus.* Inhalation of the essential oil of *Saussurea costus* by women in labour minimized the symptoms related to pain during the course of labour. The drug allayed anxiety, apprehension and related symptoms, produced mild sedation and no adverse effect on mother and foetus (Huntose et al., 1999). The total plant extract of *Saussurea costus* as well as its Ayurvedic preparations, ‘Asava’ and ‘Arishta’, were screened for antimicrobial activity (Farooq and Pathak, 1998). Sesquiterpene lactones are important cause of allergic plant contact dermatitis. Costus oil, used in perfumery, being rich in sesquiterpene lactones, is responsible for numerous cases of allergic contact dermatitis (Cheminat et al., 1981).

6. Conclusion

Saussurea costus is a well-known medicinal plant that is frequently prescribed in various indigenous systems of medicines especially those of India, Tibet, China and Korea. Its most widespread traditional uses have been for the treatment of inflammation of the lungs, cough, cold, ulcer and rheumatism (Tsarong, 1994; Singh, 1999; Kapoor, 2001; Nautiyal et al., 2003; Jain, 1984; Rawat and Pangtey, 1987; Kaul, 1941). It is a major ingredient of the ‘Brahmyadi Ghana vati’ which is used for hypertensive control (Rath et al., 1999).

The preliminary experiments carried out by Dutta et al. (1960) and Sastry and Dutta (1961), justify the reputation of the drug as a useful remedy against chronic bronchitis and asthma. The results of the different studies have empirically indicated that *Saussurea costus* is effective as an anti-inflammatory agent. Total methanol extract of *Saussurea costus* showed potent inhibitory effect on the production of TNF-alpha, a pro-inflammatory cytokine, in murine macrophage-like cell (RAW 264.7 cells). The activity-guided purification resulted in the isolation of three sesquiterpene lactones, cynaropicrin, reynosin, and santamarine, which inhibited TNF-alpha production in a dose-dependent manner (Cho et al., 1998). Inflammation has been closely related to rheumatism (Palmer, 1914) and thus the

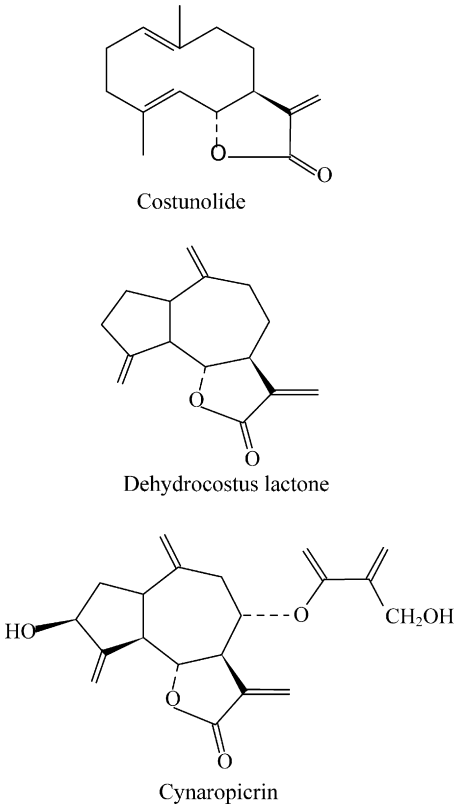

Fig. 2. Some bioactive molecules from *Saussurea costus*.

anti-inflammatory properties of *Saussurea costus* may be the reason for its ethnomedical use in rheumatism. Another traditional use of *Saussurea costus* has been in ulcer and gastritis like disorders. The recent findings tend to support this ethnomedicinal use of *Saussurea costus* as experiments have shown that it exerts an inhibitory effect on gastric ulcer formation and its ethanol extract showed strong inhibition of several strains of *Helicobacter pylori* (Yang et al., 2005). Modern science has, therefore, lent support to the rationale behind the traditional uses of *Saussurea costus*.

A few of its chemical constituents too have been found to have the potential to be developed as bioactive molecules (Fig. 2). Cynaropicrin has been identified as the principal inhibitor of TNF-alpha (Cho et al., 1998). Cynaropicrin and costunolide have been identified as potential anticancer agents (Cho et al., 2004; Jeong et al., 2002). Costunolide and dehydrocostus lactone have been reported to exhibit strong suppressive effect on the expression of HBsAg in human hepatoma Hep 3β cells and therefore have the potential to be developed as anti-HBV drugs (Chen et al., 1995). Besides, there are several other reports also which indicate it to possess antidiabetic, hypolipidaemic, CNS depressant and antiparasitic activities. But these pharmacological activities need to be studied in sufficient detail before they be attributed to *Saussurea costus* with confidence.

A potential source for NF-K B inhibitors (or stimulators) are medicinal plants used in indigenous medical systems. Nuclear factor kappa B (NF-Kappa B) plays a crucial role in acute and chronic inflammatory conditions, induced and adaptive immunity, apoptosis and induced cell proliferation and has attracted intense research interest throughout the world (Bremner and Heinrich, 2005; Dale et al., 2006; Bork et al., 1997; Hehner et al., 1999; Li et al., 2005). Plants like *Tanacetum parthenium* and *Arnica montana* that are rich in sesquiterpene lactones, and are used as anti-inflammatory remedies, too exhibit inhibitory effect on NF-K B activation. Parthenolide, a sesquiterpene lactone from *Tanacetum parthenium*, has become a model compound for studying NF-Kappa B modulation as well as a compound of pharmaceutical relevance. Modulators of NF-Kappa B can, therefore, be used to study numerous disease conditions within which NF-Kappa B plays a regulatory role. *Saussurea costus* being rich in sesquiterpene lactones and exhibiting modulatory activity can be used as a lead for developing new pharmaceuticals for the treatment of acute and chronic inflammation eg Crohn's disease or chronic arthritis. However, some doubts about the clinical relevance of sesquiterpenes as a class have been raised due to their toxicity profiling and need to be addressed to (Schmidt, 1999). Although the published evidence to date supports the safety and perhaps the effectiveness of *Saussurea costus* the quality of the evidence is limited; active constituents, bioavailability, pharmacokinetics, physiological pathways, and importance to human health are not known with sufficient detail or confidence. The ethnobotanical approach, if combined with biochemical or physiological methods, would provide useful pharmacological leads.

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