A review of therapeutic potential of *Saussurea lappa*—An endangered plant from Himalaya

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1. Introduction

1.1. Geographical distribution

*Saussurea lappa* (*S. lappa*) is indigenous to India, Pakistan and China, where it grows in the Himalaya region at 2500–3500 m altitude[1].

1.2. Morphological description of *S. lappa* (Decne.) C.B. Clarke plant

*S. lappa* C.B. Clarke, syn. *Saussurea costus* (Falc.) Lipsch belonging to family Asteraceae (Table 1), commonly known as *Costus* which is a tall, perennial herb that grows to a height of 1–2 m; stem is upright, stout and fibrous while root is a long stout of approximately 60 cm with a characteristic odour; leaves are lobate, stalked, membranous, irregularly toothed; upper leaves are small while basal leaves are large with long lobately winged stalks. Flowers are stalkless, dark purple to black in colour and are arranged in terminal and axillary heads (Figure 1). Pappas is approximately 1.7 cm long, fluffy, feathery giving an inquisitive appearance to the fruiting flower heads. Fruit of *S. lappa* is cupped, curved, compressed and hairy[2].

2. Active constituents of *S. lappa*

Studies on the chemical ingredients of *S. lappa* could be traced back to 1950s. Until now, many compounds have been isolated. Its active constituents are mainly terpenes, but it also contains anthraquinones, alkaloids and flavonoids. Plant has various terpenes that mainly have antitumor properties and anti-inflammatory, such as costunolide, dihydrocostunolide, 12-methoxydihydrocostunolide, dihydrocostus lactone, dehydrocostus lactone[3], α-hydroxydehydrocostus lactone, β-hydroxydehydrocostus lactone, lappadilactone[4], mokko lactone, betulinic acid, betulinic acid methyl ester[5], cynaropicrin, reynosin, santamarine[6], saussureamines A–C[7], α-cyclocostunolide, alantolactone, isoalantolactone[8], isodihydrocostunolide, β-cyclocostunolide[9], 1β-hydroxy arbuseculin A[5],
S. lappa has three anthraquinone compounds, namely, aloeemodin-8-O-β-d-glucopyranoside, rhein-8-O-β-d-glucopyranoside, and chrysophanol. Four flavonoid glycosides have antibacterial function[12]. Shikokiol has antitumor activity[13], whereas chlorogenic acid prevents oxidization.

### 3. Costus oil

The oil extracted from the roots of S. lappa is known as costus oil, which is used in the preparation of hair oil and in high quality perfumes. Costus oil is pale yellow to brownish in color and is also said to be valuable in treating leprosy.

In a recent study, 39 components have been identified from the essential oil of S. lappa roots. The chief compounds were dehydrocostus lactone (46.75%), costunolide (9.26%), 8-cedren-13-ol (5.06%) and α-curcumene (4.33%). However, β-cotost (13.55%) and δ-elemene (12.69%), α-selinene (5.02%), β-selinene (4.47%), α-costol (4.02%), 4-terpinol (3.58%), elemol (3.21%), α-ionone (3.13%), β-elemene (3.00%), (−)-γ-elemene (2.08%), p-cymene (1.96%) and 2-β-pinene (1.57%), (−)-α-selinene, (+)-selina-4, 11-diene, (−)-α-trans-bergamotene, (−)-α-costol, (−)-γ-costol, (−)-eleva-1,3,11 (13)-trien-12-ol, (−)-α-costal, (−)-γ-costal, (−)-eleva-1,3,11(13)-trien-12-al, (−)-E-trans-bergamota-2,12-dien-14-al, (−)-ar-curcumene, (−)-caryophyllene oxide and 12-m ethoxydihydrodehydrocostuslactone were also reported[14,15]. However, in the other reported studies, the proportion of all these compounds greatly differs. Existing variations in the composition of S. lappa essential oil may be due to various factors related to ecotype, phenophases, chemotype and variations in environment conditions such as relative humidity, temperature, photoperiod and irradiance. Furthermore, the chemistry of secondary metabolites of plants may also be affected by genetic background[16].

### 4. Pharmacology

S. lappa is a medicinally important plant. Various active compounds isolated from plant are reported to have medicinal properties e.g. the major components are sesquiterpene lactones such as costunolide and dehydrocostus lactone. S. lappa possesses various bioactivities such as antifungal[17], antidiabetic[18], antihelminthic[19], antitumor[20], antiulcer[21], antimicrobial[22], immunostimulant[23], antiinflammatory[24] and antihepatotoxic[25].

#### 4.1. Anticancer/antitumor

Costunolide (isolated from root of S. lappa) was studied for its effect and supposed pathways of action on the induction of apoptosis in HL-60 human leukemia cells. Using apoptosis analysis, evaluation of mitochondrial membrane potentials and measurement of reactive oxygen species (ROS), it was proved that costunolide was a potent apoptosis inducer, and by ROS generation aiding its activity, it induced mitochondrial permeability transition and released cytochrome C to the cytosol. In cells treated with costunolide, an antioxidant N-acetylcystein is responsible for blocking the mitochondrial alteration, ROS production, and consequent apoptotic cell death. Costunolide stimulates the ROS–mediated mitochondrial permeability transition and resultant cytochromes C release[26].

The hexane extract of S. lappa was investigated for the chemo preventive potential in autonomous androgen prostate cancer and apoptosis induction in DU145 cells. Results of this study showed that dehydrocostus lactone isolated from the hexane extract of S. lappa induced apoptosis in cell lines of DU145 human autonomous androgen prostate cancer and inhibited the cell growth[27].

Cynaropicrin isolated from S. lappa was assessed for its immunomodulatory effects on cytokine release, immunosuppressive effects, and nitric oxide production.
Cynaropicrin repressed Jurkat T, Eol−1 and U937 cell lines in a dose−dependent manner with IC\textsubscript{50} values of 2.36, 10.90 and 3.11 μmol/L respectively. Further, by means of DNA disintegration, cell cycle arrest and morphological analysis via U937 cells, its cytotoxic effect is studied. When cynaropicrin is treated in combination with ROS scavengers’ rottlerin, N-acetyl-L-cysteine or L-cysteine repressed the cynaropicrin mediated cytotoxicity. The results showed that cynaropicrin was more cytotoxic toward leukocyte derived cancer cells than fibroblasts[28].

Costunolide is a sesquiterpene lactone isolated from S. lappa proved to have effect on carcinogenesis via reporter gene assay, persuaded by a tumor endorsing phorbol ester 12−O−tetradecanoylphorpyl−13−acetate at cellular level. The activity of nitric oxide synthase is amplified by tumor promoting phorbol ester 12−O−tetradecanoylphorpyl−13−acetate which consecutively repressed by costunolide with the IC\textsubscript{50} value of 2 μmol/L[29].

In another study, the effect of costunolide on telomerase inhibitory activity was investigated on MDA−MB−231, MCF−7 cells which confirmed the hindering activity[30]. Dehydrocostus lactone is another sesquiterpene lactone isolated from S. lappa and investigated for anticancer potential for non lung cancer cell lines, for example A549, NCI−H460 and NCI−H520 and its activity have been confirmed[31].

Ethanolic extract of S. lappa showed that apoptosis followed in a dose and time dependent manner such as 80 μg/mL and 48 h which gives confirmation for the treatment of gastric cancer by S. lappa[32].

Hepatocellular carcinoma activity of dehydrocostus lactone was evaluated by in vitro assays, such as cell proliferation assay, immunoblot assay, assay for kinase activity, apoptosis and caspase activity assay. By using transmission electron microscopy, the in vivo analysis was done. The results proved its anticancer activity at the IC\textsubscript{50} values 16.7 and 18.8 μmol/L[32].

Costunolide and dehydrocostus lactone had been isolated from different extracts of S. lappa. Costunolide and dehydrocostus lactone confirmed the cytolytic activity at ID\textsubscript{50} of 3.6−10 μmol/L. At 13.6 μmol/L, costunolide completely inhibited the granule exocytosis in a dose−dependent manner and even repressed the amplification in the tyrosine phosphorylation at different concentrations. Therefore, results disclosed that the costunolide performed in a mechanistic means by preventing the increase in the phosphorylation of tyrosine[33].

Costunolide inhibits the vascular endothelial growth factor (VEGF)−induced chemotaxis of human umbilical vein endothelial cells in a dose−dependent manner. It was also found to selectively inhibit the endothelial cell proliferation induced by VEGF. The result of this study showed that by blocking the angiogenic factor signaling pathway, costunolide might inhibit angiogenesis. VEGF interacts with its cognate receptors, KDR/Flk−1 and Flt−1, and exerts its angiogenic effect. Costunolide is found to inhibit the autophosphorylation of KDR/Flk−1 without affecting that of Flt−1. These results suggest that costunolide may prove to be useful for the development of a new angiogenesis inhibitor[34]. C−17 polyene alcohol isolated from S. lappa exhibited moderate cytotoxicities against the human tumor cell lines A549, SK−MEL−2, SK−OV3, HCT 15 and XF 498[13].

4.2. Anti−inflammatory activity

In Korean traditional prescriptions, S. lappa is frequently used for inflammatory diseases. Methanol extract of S. lappa was investigated. It was observed that at 0.1 mg/mL concentration, it exhibited more than 50% of inhibition on the cytokine induced neutrophil chemotactic factor induction[35].

Ethanolic extract of S. lappa was studied at a dose range of 50−200 mg/kg, for the acute and chronic inflammation induced in both mice and rats. The result of this study revealed that the extract showed considerable values for anti−inflammatory activity through carrageenan induced paw edema and peritonitis animal models[36]. Costunolide was investigated for anti−inflammatory activity and it was observed that costunolide hindered the protein and mRNA expression of interleukin−1β. By means of an electrophoretic mobility shift assay, it was confirmed that it also concealed the AP−1 transcription activity. So, all these activities proved the anti−inflammatory activity of costunolide[37].

The potential of dehydrocostus lactone for the oxidative osteoblast damage was investigated and showed considerable increase in the osteoblast growth and hydrogen peroxide. At 0.4−2 μg/mL of dose, the factors for example calcium deposition, collagen and alkaline phosphatase were improved. These results confirmed that dehydrocostus lactone compound had potential to be used against oxidative osteoblast damage[5].

At the doses of 50, 100 and 200 mg/kg, the ethanolic extracts of S. lappa were assessed for their action on acute and chronic inflammation and at 50−200 mg/kg it showed considerable inhibition on carrageenan induced paw edema[36].

4.3. Hepatoprotective

Costunolide and dehydrocostus lactone (isolated from S. lappa) had little effect on the viability of the cells. However, they showed inhibitory effect on human hepatoma Hep3B cells, and on the expression of the hepatitis B surface antigen (HBsAg). It is proved that these compounds inhibit the HBsAg production by Hep3B cells with IC\textsubscript{50} of 1.0 and 2.0 μmol/L, respectively. Northern blotting analysis proved that they suppress (HBsAg) gene expression mainly at the mRNA level. Moreover, in another human hepatoma cell line Hep A2 (derived from Hep G2 cells) by transfecting a tandemly repeat hepatitis B virus (HBV) DNA, the inhibitory effect of costunolide on replication of human liver cells was studied. Results showed that both costunolide and dehydrocostus lactone had the tendency to be developed as potent anti HBV drugs in the future[38].

4.4. Anti−ulcer and cholagogic

The acetone extract of S. lappa and costunolide showed cholagogic effect and inhibitory effect on the formation of
gastro-protective effect of S. lappa decoction perfusion into the stomach of patients with chronic superficial gastritis and results revealed that the decoction could increase the endogenous motilin release and accelerate the gastric emptying[38]. S. lappa is one of the major ingredients of UL–409, a formulation which possesses anti-ulcer activity and the activity is may be due to the intonation of defensive factors by improvement in gastric cytoprotection[40,41].

Antiulcer activity of herbal formulation of S. lappa was tested in Wistar rats and male pigs. Orally 600 mg/kg drug was given. The drug showed significant effect in gastric ulceration induced by alcohol and aspirin, cold resistant induced ulcerations and duodenal ulcer models. It amplified the mucus discharge in all so it was proved to be an antiulcer agent[40].

4.5. Immunomodulator

Costunolide and dehydrocostus lactone act as inhibitors of killing activity of cytotoxic T lymphocytes (CTL). Through preventing the increase in tyrosine phosphorylation, costunolide inhibited the killing activity of CTL in response to the crosslinking of T cell receptors as inhibitors of the killing function of CTL and the induction of intercellular adhesion molecule-1, dehydrocostus lactone from S. lappa and other guaianolides were examined for their structure activity relationship[33]. It was confirmed that the guaianolides moiety exhibited considerable inhibitory effects towards the induction of intercellular adhesion molecule-1 and killing function of CTL[42].

4.6. Anticonvulsant activity

Different extracts of S. lappa root were evaluated for the anticonvulsant activity by picrotoxin-induced convulsions, pentylentetrazole and maximal electroshock tests performed in mice. It was proved that the petroleum extract of S. lappa roots showed potent anticonvulsant activity at a dose of 100 and 300 mg/kg[43].

4.7. Gastric function

Decoction of S. lappa was given to patients affected with persistent superficial gastritis and checked for difference in factors such as serum gastrin, gastric acidity and plasma somatostatin. Decoction of S. lappa was also given to five healthy volunteers. It was observed that it sped up the gastric emptying time and discharge of endogenous motilin. However, no change is observed in plasma somatostatin, acidity output and serum gastrin levels[38].

4.8. Gastro-protective effect

Costunolide, saussureamines and dehydrocostus lactone isolated from the methanolic extract of S. lappa showed the gastro-protective effect in rats on acidified ethanol induced gastric mucosal lesions in a dose dependent manner 5 and 10 mg/kg[44].

4.9. Angiogenesis effect

Endothelial cell proliferation (induced by vascular endothelia growth factor) is reported to be repressed by costunolide (isolated from S. lappa root). Studies proved that the chemotaxis induced by vascular endothelia growth factor of human umbilical vein endothelial cells was noticeably inhibited at IC50 of 3.4 µmol/L. Similarly by in vitro method the neo-vascularisation of mouse corneal stimulated by vascular endothelia growth factor is reported to be inhibited at a dosage of 100 mg/kg/day. Inhibition of vascular endothelia growth factor on VEGFR KDR/Flk–1 was also proved through signaling pathway[34].

4.10. Hypoglycaemic

When a comprehensive examination and clinical study on potent hypoglycemic plants of different regions from India was undertaken, S. lappa was found effective for obese diabetes[18].

4.11. Spasmolytic activity

From studies, it was proved that S. lappa was significantly able to relax the contraction induced by carbachol (30 µmol/ L). S. lappa has been reported to have antiperoxidative effects possibly due to the presence of sesquiterpene lactones. It is known to suppress contractions in guinea-pig aorta. Sesquiterpenes are recognized to stimulate the sGC which stimulates extrusion of K+ ions and thereby reduces intrinsic Ca++ ions through activation of cGMP and PKG pathway, leading to relaxation of smooth muscles[32].

4.12. Anti-hepatotoxic activity

Aqueous and methanolic extracts of S. lappa root were investigated for hepatotoxic activity in mice against lipopolysaccharide and D-galactosamine induced hepatitis. With different doses of S. lappa, pretreatment of mice led to rise in creatinine plasma levels in a dose dependent manner and alanine transaminase, aspartate aminotransaminase, aspartate aminotransferase level as well. Whereas post treatment led to the limited progression of the hepatic damage which was induced by lipopolysaccharide and D-galactosamine. By the studies it is proved that the root extract works against hepatotoxic activity[25].

4.13. Miscellaneous

4.13.1. Antidiarrheal activity

Methanol extract of S. lappa roots was investigated for antidiarrheal activity on Wistar rats and it was observed that administration of 100, 300 and 500 mg/kg body weight of dose showed 26.33, 32.28 and 66.77% inhibition of diarrhea, respectively. The standard drug (loperamide) showed significant reduction (68.02%) in diarrheal stool at the dose of 5 mg/kg body weight. The result of this study showed that the dose of 500 mg/kg body weight showed nearly similar effect to that of standard drug loperamide in reducing diarrheal stool.
The methanol extract of *S. lappa* roots showed 32.28% inhibition of diarrhea at the dose of 300 mg/kg body weight. So, these findings clearly showed that the MeOH extract of *S. lappa* exhibited significant antidiarrheal activity.[45]

### 4.13.2. Hypolipidaemic

Aqueous extract of *S. lappa* was orally administered to twenty-seven rabbits at a dose of 2 mg/kg body weight and showed significant hypolipidaemic effect. Reduction in serum cholesterol and serum triglycerides was also found to be significant.[38, 53]

### 4.13.3. Resistance to pathogenic microorganisms

*S. lappa* or its combination with other herbs could be used clinically for the treatment of gastritis, gastric ulcer, skin diseases, reflux esophagitis, hepatitis, diarrhea and some oral cavity diseases, which may be related to its capability to improve resistance to pathogenic microorganisms.

### 4.13.4. Resistance to *Helicobacter pylori* (H. pylori)

*H. pylori* is an important pathogenic microorganism that causes many diseases, including functional diseases of the digestive tract (e.g., gastric cancer, gastritis and dyspepsia) as well as endocrine disorders and autoimmune.[46] *S. lappa* extract strongly inhibits all the strains tested with minimum inhibitory concentration value of approximately 40 mg/ml.[47–49]

Various extracts of *S. lappa* was investigated for its antibacterial potential by using five strains of *H. pylori* and it showed highest minimum inhibitory concentration at the dosage of 40 µg/mL.[50]

### 4.13.5. Resistance to *Streptococcus mutans* (S. mutans)

*S. mutans* is the most important currently recognized cariogenic bacteria,[51] traditionally used for treating oral cavity diseases such as tooth decay, had breath, and periodontitis,[27], which proposed that *S. lappa* may inhibit *S. mutans*. In another study, the effects of ethanolic extract were evaluated on the growth and acid production of *S. mutans*, as well as the synthesis and adherence of water-insoluble glucans.[52]

Their results of this study showed that ethanolic extract (0.5 mg/mL to 4 mg/mL) inhibited the growth and acid production of *S. mutans*, reduced the adherence of *S. mutans*, and inhibited the synthesis of water insoluble glucans. Results proved that *S. lappa* astonishingly inhibited the cariogenic activity of *S. mutans*.[52]

### 4.13.6. Resistance to other microorganisms

The active ingredients of *S. lappa* inhibit the transfer and binding of R plasmids in *Shigella flexneri*.[50] Moreover, they inhibit the expression of the HBsAg as well as growth of other microorganisms and pathogens.[38, 53]

Ethanolic extract of *S. lappa* was assessed for antimicrobial potential using *S. mutans*. The study showed that the ethanolic extract caused significant (*P*<0.05) inhibition on the growth. In addition, it also reduced the adherence of *S. mutans*.[52]

The compounds KSR1–KSR4 were isolated by repeated chromatography (column and high performance liquid chromatography) of a flavonoid fraction obtained by processing of an ethanolic extract of powdered, dry *S. lappa* roots. Antifungal potential of *S. lappa* was assessed. By using microdilution technique, nine fungal strains *i.e.*, *Aspergillus niger*, *Aspergillus ochraceus*, *Aspergillus versicolor*, *Aspergillus flavus*, *Penicillium ochrochloron*, *Penicillium funiculosum*, *Trichoderma viride*, *Cladosporium cladosporioides* and *Alternaria*. KSR4 possessed the highest antifungal potential, while KSR3 showed medium activity. Compounds KSR1 and KSR2, showed good activity.[12],

### 4.13.7. Antiparasitic

The activity of *S. lappa* against *Trypanosoma cruzi*, *Clonorchis sinensis*, and some nematodal infections were determined. Decoction of plant was given orally into *Clonorchis sinensis* infected rabbits and found to be effective up to some extent.[54]. In the children infected with the respective worms, the efficacy of *S. lappa* was studied on the basis of percentage reductions in the faecal egg counts. In the doses, tested *S. lappa* did not produce any adverse side effects.[55, 56]. The methanolic extract of *S. lappa* was investigated in axenic cultures with the epimastigote form of *Trypanosoma cruzi*, clone Bra C15 C2, at 27 °C in F–29 medium at a concentration of 100 mg/mL. It is proved that *S. lappa* extract exhibited antiparasitic activity.

### 4.13.8. Antiviral activity

*S. lappa* root extract was investigated for its potential against HBV in human hepatoma Hep3B cells. Active compounds isolated from *S. lappa* such as costunolide and dehydrocostus lactone suppressed the expression of HBsAg with IC₅₀ values of 1.0 and 2.0 mmol/L respectively. By northern blotting analysis, the suppression was also observed in HepA2 cell line, so it was confirmed that compounds present in *S. lappa* root extract had considerable activity against HBV.[38],

### 5. Other uses

#### 5.1. Perfumery

The fragrant oil obtained from *S. lappa* is very valuable in perfumery. Its odour slightly resembles with the oil of orris. It is also blends with other oriental perfumes in a lasting manner.[57],

#### 5.2. Pesticidal

The root, containing both the essential oil and the alkaloid, is a reliable insect repellent. In China, it is the basis of incense, made into sticks which are burned in home and in the temples for worship, and also serve through their smoke to keep gnats, mosquitoes, and other flying insects at a space. In India, the dried root yields brilliant fumigatory pastilles, which burn fairly well and as the Chinese joss–sticks, it serves the same insectifugal function.[58, 59],

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6. Traditional uses

6.1. Ethnomedicinal uses

*S. lappa* is one of the most commercially viable species among all the species of genus *Saussurea*. It is widely utilized in various indigenous systems of medicine all around the world for treating variety of disorders such as tenesmus, diarrhea, vomiting, dyspepsia, inflammation[60,61]. It is also prescribed in irregular menstruation, tenesmus and abdominal pain[20,62].

Medicinal properties of this plant are well documented in traditional Chinese medicine, ayurvedic medicine and the Tibetan system of medicine[63]. In the Handbook of Traditional Tibetan Drugs, out of the 175 formulations it was reported that *S. lappa* was one of the main ingredients in 71 formulations[64]. The roots of *S. lappa* have a strong and sweet aromatic odour with a bitter taste, and are used in controlling bronchial asthma and as an antiseptic. Preparations made from this species are also reported to cure various diseases and conditions including ophthalmic conditions, fever, cough, paralysis, asthma, deaf, tridosha, hysteria and headache[65,66].

The plant is prehistoric and well known about 2500 years ago. It is used in various ancient system of medicine such as Unani, Ayurveda and Siddha[67]. In Indian traditional systems of medicine, *S. lappa* is used either in combination with other drugs or as a single drug. The dried roots are somewhat bitter in taste and grey to yellow in colour. The essential oil obtained from roots is mostly used in medicine[68]. Its roots are mainly used in asthma, cough and also in treatment of chronic skin diseases, rheumatism and cholera[60,61]. Different preparations of roots are used by Ayurvedic physicians for the treatment of a range of ailments like cold, flatulence, pruritus, gout, epilepsy, headache, itching and leucoderma[71,72]. *S. lappa* is used as an important medicine for gout, erysipelas and promotes spermatogenesis. In Tibetan medicine, the roots are considered to have an acrid, sweet and bitter taste with a neutral potency. *S. lappa* is one of the important ingredients in several traditional Tibetan formulae that are used for chronic inflammation of the lungs, chest congestion e.g. hippophae and eliminators of lung inflammation[73]. The roots possess carminative, anthelmintic, analgesic and emmenagogic properties. It stimulates the brain and cures blood, liver and kidney disorders. Different preparations of *S. lappa* are prescribed in helminthic infestations, convulsions, gas, leprosy, cold, persistent hiccup, tuberculosis, quaran malaria, rheumatism, intestinal carcinogenesis and edema[26,74]. It is also used traditionally to cure skin diseases such as scabies, ringworm, bruises and cuts[75–77].

6.2. Ethnoveterinary uses

Locally, it is used against the heart diseases of cattle[78].

6.3. Other uses

The powdered roots are sprinkled over crops as insecticides. The roots are used as insecticide to protect woollen fabrics, and as incense. The upper parts of its plants are used as fuel and fodder and dried leaves are smoked as tobacco[43]. It is also used to improve complexion, as a hair wash to kill lice and to turn grey hair to black[62,79]. Other traditional applications of *S. lappa* are shown in Table 2.

### Table 2

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Method of applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomachache</td>
<td>Root powder is taken with water. Defection of root is taken. Root powder is roasted in mustard oil and the paste is applied on stomach</td>
</tr>
<tr>
<td>Headache</td>
<td>Oil heated with root is applied</td>
</tr>
<tr>
<td>Cough and cold</td>
<td>Root powder is taken with warm water</td>
</tr>
<tr>
<td>Throat infection</td>
<td>Root is chewed</td>
</tr>
<tr>
<td>Backache and chest pain</td>
<td>Root powder is taken with milk/decoction of root powder. Oil heated with root is massaged the affected area</td>
</tr>
<tr>
<td>Rheumatism and painful joints</td>
<td>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.</td>
</tr>
<tr>
<td>Scanty urination</td>
<td>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.</td>
</tr>
<tr>
<td>Skin rashes formed after fatigue</td>
<td>Root powder is roasted in ghee/butter and the ghee/butter is applied on the affected area</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>Pieces of root are burnt in hookah and the smoke inhaled</td>
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<tr>
<td>Lastre and growth of hair</td>
<td>Hair is washed with decoction. Mustard oil is heated with root powder and the oil used as topical application on hair</td>
</tr>
<tr>
<td>Pastules</td>
<td>Fine root powder is dusted on the wound. Mustard oil is heated with root powder and the oil is applied and bandaged</td>
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<tr>
<td>Fainting spells</td>
<td>Root is rubbed in water and the water is used a nasal drops Fine powder of root is used for sneezing.</td>
</tr>
<tr>
<td>General weakness</td>
<td>Root is boiled in milk and the milk is taken twice daily</td>
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<tr>
<td>Filaries</td>
<td>Root are taken along with the ‘Vacha’ (Acorus calamus) roots</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>The roots are taken with honey</td>
</tr>
<tr>
<td>Headache</td>
<td>Paste of the root is applied</td>
</tr>
<tr>
<td>General weakness as Rasayana</td>
<td>Root powder ingested with cow’s milk and cow’s ghee</td>
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<tr>
<td>Scalp scables</td>
<td>Essential oil of root is applied</td>
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<tr>
<td>Typhoid fever</td>
<td>Decoction of root is taken</td>
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<tr>
<td>Persistent hiccup</td>
<td>Root powder is ingested</td>
</tr>
<tr>
<td>Leprosy</td>
<td>Root powder is ingested</td>
</tr>
<tr>
<td>Cold</td>
<td>Decoction of root is taken</td>
</tr>
</tbody>
</table>
7. Trade of S. lappa

In the Himalaya along with the dominant high altitude genera for high number of endemic species, *Saussurea* is the second largest genera (35 spp.)[70]. As already mentioned *S. lappa* has great demand in pharmaceutical industry but during the last decade, the species for its threatened status has been more popularized globally. In past, due to high market demand and unchecked exploitation, the species was reported to be extinct in many pockets in the wild[75]. In order to conserve the species and to fulfill the growing trade requirements, commercial cultivation of *S. lappa* was taken up in various regions. It is now commercially grown on a extensive scale, from Kashmir to Garwhal in Uttar Pradesh (United Provinces) in the forested areas similar to where it grows naturally.

It has been introduced and cultivated in three southernmost provinces of China. Trade has been significant over a long period. For shipment to Arabia and the Red Sea ports, large amount of the root have customarily been exported from Kashmir to Bombay and Calcutta for use chiefly in perfumery and medicine. There has also been substantial movement of the product within China. Globally, China has exported a total of 1 024 tons of roots and derivates overall since 1983 to 2009 and India exported a total of 266 tons during the same period.

Presently, France is one of the leading importers of the root. Medicinally, the drug is known as radix saussureae lappae and the product has been marketed under the names costus root and costus root oil, Putchuk or Patchak (the Bengali name), and now in India as Kuth.

8. Challenges in conservation and sustainable use of S. lappa

*S. lappa* is an important plant, used widely in traditional and herbal medicine, also utilized in modern medicine. Due to high demand, most of the natural populations of the species are either have been extirpated or are under destructive harvesting, therefore availability of this important plant is decreasing in the wild day by day. *S. lappa* is endemic to a geographically limited part of the Himalayas, and grows on moist slopes at altitudes of 2 600–4 000 m[80]. Apart from the restricted distribution, the harvesting of whole plant is one of the reasons for being threatened. This critically endangered species is enlisted in Appendix I of Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). *S. lappa* is one of the 37 Himalayan endangered medicinal plants that have been prioritized for *in situ* and *ex situ* conservation[81].

Because of an endemic species to the Himalaya, the distribution of this species is fairly restricted to tremendously narrow geographical range[82], which makes it more vulnerable to extinction. Being an endangered species[83], it was enlisted in Appendix I of CITES. Trade of *S. lappa* is strictly prohibited under Foreign Trade Development Act–1992. It is first listed in Appendix II of CITES on 1.7.1975 as *S. lappa* and afterward up listed to Appendix I in 1985.

Due to the various known uses, *S. lappa* is in high demand both internationally and at the local level. It is one of the most commercially used Appendix I CITES species for various complaints in numerous indigenous systems of medicine[2,84]. *Saussurea costus* has been in high demand in the pharmaceutical industry. During the last decade, the species has been even more popularized due to its threatened status globally. Due to uncontrolled exploitation of the species and high market demand, it was reported to be extinct in many pockets in the wild.

9. The way forward

A multi–branched approach to maintain the resource base that includes *in situ* and *ex situ* conservation and selection of better–quality genotypes followed by their multiplication (by both biotechnological and conventional approaches) could well provide available solution to the problem.

9.1. Biotechnological interventions

Since the value of medicinal plants depends on the amount of the active principle present in it, it would be enviable to carry out cultivation of superior clones (recognized as ‘elite’). These elites can be acknowledged by chemoprofiling and by the use of different molecular marker techniques. Thereafter, either or both conventional methods of propagation and tissue culture techniques can be used to multiply the plant for raising commercial plantations as well as for conservation.

For the species which are difficult to regenerate by conventional methods and due to over exploitation by destructive harvesting, their populations have decreased. Micropropagation can be used as a feasible alternative. It is also useful in terms of the active principles present. There is lots of variability, and elites have been recognized based on their potential for yielding higher amount of active principle.

This technology can successfully be used to meet up the growing demand for clonally uniform elite plants of *S. lappa*. For large–scale production of plant cells from which secondary metabolites could be extracted besides micropropagation, cell suspension culture systems could be used.

Cell culture systems have numerous major advantages as it is independent of space constraints, geographical and seasonal variations and offers a defined production system ensuring an uninterrupted supply of good quality products of high yield. It also allows for preset management of cell growth and regulation of metabolite processes which in turn will improve productivity and lessen labour costs.

9.2. Cultivation practices

Cultivation has several advantages over collection from the wild. Due to environmental and genetic differences, wild harvested plants usually vary in quality and consistency which dangerously compromise economic returns. Similarly, local environmental conditions strongly control the efficacy of medicinal plants. A plant might fail to produce the active constituents of concern since temperature, day length, rainfall and soil characteristics are some of the factors that have serious effects on the potency of medicinal plants. Before arriving at suitable agro–techniques, these are some
parameters that need to be studied well. Biopesticides, better-quality planting material produced through micropropagation in combination with use of bio-fertilizers (mycorrhiza) and improved agro-techniques would enhance the yields even further and generate constantly higher financial returns to the growers.

9.3. Post–harvest handling

The quality of medicinal plants also depends on the manner of post–harvest handling. It is observed that during harvesting, handling and storage, the collectors of herbal material pay less consideration to quality of material. It has been reported that stored herbal drug samples very frequently harbour mycotoxin producing fungi.

Above the acceptable limit fixed by the World Health Organization for human consumption, such herbal drugs containing mycotoxins above would be rejected in the global market. Therefore, efforts should be made in order to encourage sustainable management of medicinal plants at the community level itself by highlighting the improvement of collection, cultivation and marketing practices.

10. Conclusion

*S. lappa* is a renowned medicinal plant that is often prescribed in various indigenous systems of medicines chiefly those of India, China, Tibet and Korea. It is used for treatment of many ailments in allopathic and herbal system of medicine such as chronic skin diseases, rheumatism, cholera, cough and cold, persistant hiccups, stomachache, toothache, typhoid fever, rheumatism, quartan malaria, leprosy etc. Various active compounds isolated from *S. lappa* are reported to have medicinal properties. The major components are sesquiterpene lactones such as costunolide and dehydrocostus lactone. It has various biological activities such as anticancer, anti-inflammatory, hepatoprotective, anti-ulcer and chologagic, anticonvulsant, immunomodulator, gastroprotective, antiangiogenesis, hypoglycaemic, spasmolytic, anti-hepatotoxic, anti diarrheal, hypolipidaemic, antiparasitic, antimicrobial and antiviral activity. It is also considered as an important plant in terms of veterinary medicine and used against the heart diseases of cattle. The oil obtained from *S. lappa* is very valuable and used in perfumery. The root is considered as a reliable insect repellant as their smoke to keep gnats, mosquitoes, and other flying insects at a space.

The preliminary experiments justify the reputation of the drug as a useful remedy against cancer[26–29]. The results of the different studies have empirically designated that *S. lappa* is effectual as an anti-inflammatory agent. Total methanol extract of *S. lappa* showed compelling inhibitory effect on the formation 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, reynosin, cynaropicrin and santamarine, which in a dose dependent manner inhibited TNF–alpha production. Inflammation has been closely related to rheumatism. Therefore, the anti-inflammatory properties of *S. lappa* may be the reason for its ethnomedical use in rheumatism. Some of the chemical constituents of *S. lappa* have been found to have the potential to be developed as bioactive molecules. Costunolide and cynaropicrin have been identified as latent anticancer agents. Similarly, cynaropicrin has been identified as the principal inhibitor of TNF–alpha. Dehydrocostus lactone and costunolide have been reported to display strong suppressive effect on the expression of HBsAg in human hepatoma Hep3B cells and therefore have the potential to be developed as anti–HBV drugs. Although the published confirmation to date supports the safety and perhaps the efficiency of *S. lappa*, the quality of the evidence is limited; active constituents, physiological pathways, pharmacokinetics, bioavailability, and importance to human health are not known with sufficient detail or assurance. Since *S. lappa* has various medicinal applications, that’s why more *in vitro*, clinical and pathological studies are required to investigate the unexplored potential of this plant.

As already mentioned, *S. lappa* has great demand in pharmaceutical industry. So due to high demand, most of the natural populations of the species are either have been extirpated or are under destructive harvesting. It is endemic to a geographically limited part of the Himalayas. This critically endangered species is enlisted in Appendix I of CITES. However, a multi–branched approach including *in situ* and *ex situ* conservation and selection of better–quality genotypes followed by their multiplication could well provide available solution to the problem.

Conflict of interest statement

We declare that we have no conflict of interest.

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