VETERINARY RESEARCH INTERNATIONAL
Journal homepage: www.jakraya.com/journal/vri

REVIEW ARTICLE

Phytochemical and Pharmacological Review of an Ethno Medicinal Plant: *Saussurea Lappa*

Hemlata Gautam and R.K. Asrani

Department of Veterinary Pathology, DGCN COVAS, CSK HPKV, Palampur - 176062 (HP).

*Corresponding Author:

R. K. Asrani

Email: asranirk@gmail.com

Received: 19/12/2017
Accepted: 11/01/2018

Abstract

Indian Himalayan region is one of the richest sources of valuable medicinal plants and herbs since antiquity due to its unique climatic conditions. *Saussurea lappa* is one of the most common prescribed herbs in indigenous systems of medicines in China, Tibet and India for treatment of various types of human ailments such as fever, bronchitis, rheumatoid arthritis, typhoid fever and chronic skin diseases. *S. lappa* produces various secondary metabolites with extraordinary biological activities which has anti-inflammatory, antibacterial, hepatoprotective, anti-tumor, anti-viral, anti-ulcerogenic, anti-epileptic and cyto-toxic properties. Costunolide and dehydrocostus lactone are major constituents that exhibits anti-inflammatory and anti-tumor activities. The present review puts an insight on the phytochemical, pharmacological and therapeutic properties of the plant as well scope of the future research for medicinal application.

Keywords: *Saussurea lappa*, Indigenous medicine, Costunolide, Anti-inflammatory, Anti-tumor, Phytochemicals, Therapeutic uses.

1. Introduction

Saussurea lappa is a potential herb belonging to family Asteraceae (Table 1). It is a long erect herb found mostly in Northern mountainous regions of Pakistan and India (Gupta *et al*., 1967). Its flowers are dark purple or black in color, occupying terminal and axillary heads. Pappas is long, fluffy, feathery and fruit is cupped, curved, compressed and hairy (Fig 1). Leaves are radical with long lobately winged stalks. Roots (Fig 2) are stout, carrot like, 60cm long, possessing a characteristic penetrating sweet aromatic odour along with bitter taste (Jain *et al*., 1984; Nayar *et al*., 1987, 1988, 1990; Stainton, 1988; Samant *et al*., 1998; Pandey *et al*., 2007). It is known in different languages with various names like saw-wort, snow lotus and in Hindi: Kuth; Urdu: Minal; English: Costus; Chinese: Mu Xiang; Tamil: Kostum; Sanskrit: Amayam, Puskara; Gujrati: Upleta; German: Practige kostwurz; French: Costus elegant; Marathi: Kustha; Kannad: Changal kustha; Malyalam: Kottam; Bengali: Kudo (Chadha, 1972). Medicinal properties of *S. lappa* plant are well documented in traditional Chinese medicine, Ayurvedic medicine and Tibetan system of medicine (Singh, 1999). In the Handbook of Traditional Tibetan Drugs, out of 175 formulations *S. lappa* to be amongst the main ingredients in 71 formulations (Tasrong *et al*., 1986). Traditionally it has been used in the treatment of large number of ailments and diseases such as asthma, cough, throat infection, tuberculosis, leprosy, malaria, convulsions, fever, helminthic infestations, ophthalmic conditions, paralysis, deaf, tridosha, hysteria, headache, rheumatism, intestinal carcinogenesis, oedema and as an antispasmodic (Nadkarni *et al*., 1954; Basu *et al*., 1987; Lee *et al*.,2001; Malik *et al*., 2011).

Table 1: Taxonomic classification of *Saussurea lappa*

Kingdom	Plantae
Subphylum	Euphyllophytina
Infraphylum	Radiatopses
Subclass	Asteridae
Superorder	Asteranae
Order	Asterales
Family	Asteraceae
Genus	*Saussurea*
Species	*S. lappa*

2. Phytochemicals

Saussurea lappa contains a variety of phytochemicals of which some are identified and many more are yet to be discovered and isolated. Its main active constituent are terpenes such as costunolide, dihydrocostunolide, 12 methoxydihydro costunolide, dihydrocostus lactone, dehydrocostus lactone (Yang *et al*., 1998), α-hydroxy dehydrocostus lactone, β-

hydroxy dehydrocostus lactone, lappadilactone (Sun *et al.,* 2003), mokko lactone, betulinic acid, betulinic acid methyl esters (Choi *et al.,* 2009), cynaropicrin, reynosin, santamarine (Cho *et al.,* 1998), saussureamines A-C (Yoshikawa *et al.,* 1993), α-cyclocostunolide, alantolactone, isoalantolactone (Zhao *et al.,* 2008), isodihydrocostunolide, β-cyclocostunolide (Robinson *et al.,* 2008), β- hydroxyl arbusculin A (Choi *et al.,* 2009), arbusculin B (Julianti *et al.,* 2011), saussureal and so on (Talwar *et al.,* 1992), which have antitumor and anti-inflammatory properties**.** It also contains anthraquinones, mainly three compounds aloeemodin-8-o-β-d-glucopyranoside, rhein-8-o-β-d-glucopyranoside and chrysophanol, alkaloids and flavonoids (Zahara *et al.,* 2014). Four flavonoids glycosides have antibacterial function (Rao *et al.,* 2007). Shikokiols have antitumor activity (Jung *et al.,* 1998), whereas chlorogenic acid prevents oxidization.

Fig 1, Fig 2: Arial parts and roots of *S. lappa.*

3. Pharmacological Properties

Several researchers investigated different extracts of this plant and found the constituents exhibiting anti-inflammatory, anti-bacterial, anti-tumor, hepatoprotective, anti-ulcer and immunomodulatory activities. Till date, different biologically active ingredients of *Saussurea lappa* have been isolated and purified. Among those active compounds sesquiterpene lactones such as costunolide and dehydrocostus lactone has been reported to exhibit medicinal bioactivities.

3.1 Antitumor Property

Kanetoshi *et al.* (2005) inferred that β-peltatin and lignin derivatives from the acetone extracts of *S. lappa* inhibit human pancreatic cancer cells, lung cancer cells, and squamous cancer cells. Park *et al.* (2007) found that dehydrocostus lactone and costunolide inhibit the activity of human MCF-7 and MDA-MB-453 mammary tumor cell. 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 cells lines of DU 145 human autonomous androgen prostate cancer and inhibited the cell growth (Kim *et al.,* 2012). The effect of costunolide isolated from *Saussurea lappa* and supposed pathways of action on the induction of apoptosis in HL-60 human leukemia cells. It has been observed that costunolide stimulates the ROS-mediated permeability transition and resultant cytochrome C release. It was concluded that *Saussurea lappa* extract inhibited cell proliferation through induction of apoptosis (Lee *et al.,* 2001). Cytotoxic activity of chloroformic extract of *Saussurea lappa* on breast cancer cell lines (MDA-MB) was nearly comparable to that of the standard compound, doxorubicin (Sunkara *et al.,* 2010). Costunolide extracted from *Saussurea lappa* suppresses tumor growth and metastases of MDA-MB-231, highly metastatic human breast cancer via inhibiting TNF-α induced NF - kB activation (Youn *et al.,* 2013). *Saussurea lappa* extract inhibits cell proliferation through apoptosis pathway on κB human oral cancer cells (Moon *et al.,* 2013). Cynaropicrin, isolated from *S. lappa* for its immune modulatory effects on cytokine release, immune suppressive effects, and nitric oxide production. Cynaropicrin repressed Jukart T, Eol-1 and U937 cell lines in a dose dependent manner with IC 50 values of 2.36, 10.90 and 3.11 µmol/L respectively. The results showed that cynaropicrin was more cytotoxic toward leukocyte derived cancer cells than fibroblasts (Cho *et al.,* 2004). The ethyl acetate extract of *S. lappa* when administered orally in rats, inhibited the production of gastric acid, free acid and total acid by 53.53%, 52.55% and 30.30% respectively which gives confirmation for the treatment of gastric cancer by *S. lappa* (Niranjan *et al.,* 2011). The hepatocellular carcinoma activity of dehydrocostus lactone isolated from *Saussurea lappa* was tested by *in vitro* assays. The results proved its anticancer activity at the IC 50 values of 16.7 and 18.8µmol/L (Hsu *et al.,* 2009). Sun *et al*. (2008) obtained eight types of compounds that have cytotoxic activity on human cancer cells. Lappa dilactone, dehydrocostus lactone, and costunolide demonstrate non-specific cytotoxicity and their effects on HepG2, OVCAR-3, HeLa, and other cancer cells are similar. Studies on structure-function relationship demonstrate that α-methylene and γ-lactone are the structure necessary for cytotoxic activity, and the presence of hydroxide radical lowers this activity. Robinson *et al.* (2008) obtained dihydrocostunolide and several known antitumor compounds (costunolide, β-cyclocostunolide, dihydrocostus lactone, and dehydrocostus lactone). Iso-dihydrocostus lactone has

strong cytotoxic activity on human colon cancer (Colo-205), skin cancer (A-431), and mammary gland cancer (MCF-7) cells, and general cytotoxic activity on A549 cells. Costunolide and mokko lactone induce the apoptosis of human leukemia cells (HL-60) by triggering mitochondrial permeability transition, which induces the release of cell pigment C or damage of mitochondrial membrane potential (Lee *et al.,* 2001; Yun *et al.,* 2004). Cynaropicrin effectively inhibits the proliferation of leukocyte-like cancer cells such as U937, Eol-1, and Jurkat T, but it does not possess apparent inhibitory activity on Chang liver cells and human fibroblast cells (Cho *et al.*, 2004). Other studies have shown that dehydrocostus lactone could inhibit Rb protein and growth of cancer cells, i.e., preventing cancer cell proliferation by inhibiting CDK2 kinase activity and inducing cell apoptosis, inhibiting NF-κB activity (could induce cancer cell resistance to drugs) by preventing degradation and phosphorylation of protein I-κBα in HL-60 cells, and causing the apoptosis of cancer cells (HL-60) (Oh *et al.,* 2004; Jeon *et al.,* 2005). Dehydrocostus lactone expresses dose-dependent inhibitory role on cancer cells tested. Flow-cytometry shows that dehydrocostus lactone facilitates cell apoptosis and cell cycle arrest at the G2/M stage, thereby preventing cell proliferation (Choi *et al.,* 2010). Dehydrocostus lactone also affects cell viability, cell cycle distribution and ATP binding cassette transporter expression in soft tissue sarcoma cell lines. Furthermore, it led to caspase 3/7 activity as well as caspase-3 and PARP cleavage, which are indicators of apoptosis (Kretschemer *et al.,* 2012). Among all the antitumor compounds in *S. lappa,* dehydrocostus lactone, costunolide and cynaropicrin are the most extraordinary ones, of which the activities have been verified by extensive studies (Cho *et al.,* 2004; Choi *et al.,* 2009; Kim *et al.,* 2012; Rasul *et al.,* 2012, 2013).

3.2 Antibacterial Property

Different type of solvents extracts (e.g. methanolic, ethanolic, aqueous, petroleum ether) have been tested for the *in vitro* antibacterial activity of the *Saussurea lappa* and it is observed to be effective against variety of resistant pathogens. (Yang *et al.,* 2005) studied the in vitro effects of ethanolic extracts on five clinical *H. pylori* strains. The results showed that, *S. lappa* extract strongly inhibits all of the strains tested (the MIC was approximately 40 mg/mL). The *in vitro* antibacterial activity of methanolic extract of *Saussurea lappa* has shown some degree of antibacterial activity against the tested bacterial strains (Parekh *et al.,* 2007). Moreover, it inhibits the expression of hepatitis B surface antigen and core-related antigens (Chen *et al.,* 1995) as well as growth of other microorganisms and pathogens (Patil, 2009). The active ingredients of *S. lappa* inhibit the binding and transfer of R plasmids in *Shigella flexneri* (Li *et al.,* 2010). The *in vitro* antibacterial activity of different extracts of *Saussurea lappa* was evaluated against *E. coli, Bacillus thurigenesis* and *Cornybacterium* by disc diffusion method. It was concluded that *S. lappa* showed significant antibacterial activity against the mentioned organisms at different concentrations of plant extract (Irshad *et al.,* 2012). The antimicrobial activity of methanolic and chloroformic extracts of *Saussurea lappa* roots were tested against *Staphylococcus aureus, Pseudomonas aeruginosa, E. coli, Klebsiella pneumonia, Proteus vulgaris, Candida albicans* and *Aspergillus* through agar well diffusion method. It was found to be significantly effective against all the mentioned organisms (Thara *et al.,* 2012). The antimicrobial activity of ethanolic extract of *Saussurea lappa* was tested against multi drug resistant *Staphylococcus aureus, Pseudomonas aeruginosa, E. coli* and *Klebsiella pneumoniae* through agar well diffusion method. It was found to be effective against all mentioned bacteria with the minimum inhibitory concentration ranges from 2.0µg/µg-12.0µg/µl (Hassan *et al.,* 2013). The *in vitro* antibacterial activity of different solvent extracts of *Saussurea lappa* against *Bacillus subtilis, Staphylococcus aureus, E. coli, Pseudomonas aeruginosa* and *Klebsiella pneumonia* was studied. It was found that all the extracts showed antibacterial activity against mentioned bacteria but chloroformic extract showed the highest antibacterial activity (Alaagib *et al.,* 2015).

3.3 Anti Inflammatory Activity

The major anti-inflammatory ingredients in *S. lappa* are sesquiterpenes, which stabilize endosomal release and prevent cell proliferation (Damre *et al.,* 2003). The methanolic extract of *S. lappa* was investigated for anti-inflammatory activity. 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 (Lee *et al.,* 1995). The ethanolic extract of *S. lappa* was tested at a dose range of 50-200 mg/kg, on acute and chronic inflammation induced in both mice and rats. The result of this study revealed that the extract showed anti-inflammatory activity through carrageenan induced paw oedema and peritonitis in animal models (Gokhale *et al.,* 2002). *In vitro* anti-inflammatory activity of *Saussurea lappa* was evaluated by monitoring the TNF-α levels and nitricoxide levels in mouse macrophages cells (Damre *et al.,* 2003). Costunolide isolated from *Saussurea lappa* was analysed for anti-inflammatory activity, and it was observed that costunolide hindered the protein and mRNA expression of interleukin -1b. 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 (Kang *et al.,* 2004). The potential of dehydrocostus lactone which was isolated from *Saussurea lappa* was tested for the oxidative osteoblast damage and showed considerable increase in the osteoblast growth and hydrogen peroxide in the tissue. At 0.4-2µg/ml of dose, the factors such as calcium deposition, collagen and alkaline phosphatase were improved. These, results confirmed that dehydrocostus lactone compound had potential to be used against oxidative osteoblast damage (Choi *et al.,* 2009). Three sesquiterpene lactones (cynaropicrin, reynosin, and santamarin) were isolated through an active screening test inhibit TNF-α activity, among which, cynaropicrin is possibly the major ingredient that inhibits TNF-α in *S. lappa* (Cho *et al.,* 1998). Further experiments proved that, cynaropicrin affects inflammation by inhibiting the production of inflammatory factors and the proliferation of lymphocytes, while santamarin inhibited inducible nitric oxide synthase (iNOS) protein, reduced iNOS-derived NO, suppressed cyclo-oxyge-nase (COX)-2 protein and reduced COX-derived prostaglandin E2 production in LPS-stimulated RAW264.7 cells and murine peritoneal macrophages (Cho *et al.,* 2000; Choi *et al.,* 2012). Dehydrocostus lactone inactivates the nuclear transcription factor (NF-κB), inhibits the expression of iNOS genes, and reduces the generation of NO and TNF-α level induced by LPS (Lee *et al.,* 1999; Jin *et al.,* 2000). Saussureamines A and B effectively inhibit NO production induced by LPS and NF-κB activation (Matsuda *et al.,* 2003).

3.4 Hepatoprotective Effect

Yamahara *et al.* (1985) found that the acetone extract of *S. lappa* and costunolide have choleretic effect and could inhibit ulcer in mice. Costunolide and dehydrocostus lactone (isolated from *S. lappa*) had little effect on the viability of the cells. However, they showed inhibitory effect on human hematoma Hep3B cells and on the expression of the hepatitis B surface antigen (HBsAg). It was found that these compounds inhibit the HBs Ag production by Hep3B cells with IC50 of 1.0 and 2.0µmol/L respectively. Results showed that both costunolide and dehydrocostus lactone has the tendency to be developed as potent anti HBV drugs in the future (Chen *et al.,* 1994). The aqueous-methanolic extract of *Saussurea lappa* roots against the D-galactosamine and liposaccharide induced hepatitis in mice. Pretreatment of mice with different doses of *S. lappa* extract (150,300 and 600mg/kg) significantly prevented the rise in ALT and AST in a dose dependent manner. Post treatment with *S. lappa* (600 mg/kg) significantly restricted the progression of hepatic damage. It was further verified by histopathology where liver showed improved architectural detail, absence of parenchymal congestion, decreased cellular swelling and apoptotic cells. Hence, rationalizing the traditional uses of *S. lappa* in liver disorders (Yaeesh *et al.,* 2010). Shao *et al.* (2005) compared the effects of ethanolic extract on bile flow before and after rat medication. Their result showed that ethanolic extract increases bile flow and has a choleretic effect. Liu *et al.* (2008) examined the effects of *S. lappa* on gall bladder movement and its mechanism in dogs. The result showed that *S. lappa* solution induces gall bladder contraction in dogs, but does not affect plasma cholecystokinin.

3.5 Anti Ulcer and Cholagogic

S. lappa is one of the major ingredients of UL-409, a formulation which possesses anti-ulcer activity and the activity may be due to the intonation of defensive factors by improvement in gastric cytoprotection (Mitra *et al.,* 1996; Venkataranganna *et al.,* 1998). *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 (Chen *et al.,* 1994). The acetone extract of *S. lappa* and costunolide showed cholagogic and inhibitory effect on the formation of gastric ulcer in mice (Yamahara *et al.,* 1985). The antiulcer activity of herbal formulation of *S. lappa* was tested in Wistar rats and male pigs by oral route @ 600 mg/kg. The drug showed significant effect in gastric ulceration reduction, induced by alcohol and aspirin, cold resistant induced ulcerations and duodenal ulcer models. It amplified the mucus discharge in all, thereby proving to be an antiulcer agent (Mitra *et al.,* 1996). Ethyl acetate extract of *Saussurea lappa* was found to be effective in different model of gastric and duodenal ulceration in rats (Niranjan *et al.,* 2011). *S. lappa* extract apparently protects against acute damage to rat gastric mucosa induced by hydrochloric acid-ethanol and reserpoid (Wang *et al.,* 2004). The three active ingredients (saussureamines A, B and C) isolated from *S. lappa* remarkably protects against the gastric damage caused by hydrochloric acid and ethanol. Saussureamine A also inhibits stress-induced gastric ulcers in mice (Yoshikawa *et al.,* 1993). Aside from saussureamines A, B and C costunolide and dehydrocostus lactone remarkably improves gastric ulcers in rats (Mastuda *et al.,* 2000).

3.6 Immunomodulator

The immunomodulatory effect of hydroalcoholic *Saussurea lappa* root extract was

observed at the dose of 100 mg/kg and 200 mg/kg and it was found that 250mg/kg did not show significant effect on humoral immunity and number of antibody producing cells of spleen, reflecting *Saussurea lappa* has no effect on such responses on short term treatment. Higher doses of *Saussurea lappa* extract have shown potentiation of immunomodulatory activity in both humoral as well as cellular arms of the immune system (Pandey, 2012). Costunolide and dehydrocostus 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 cross linking of T cell receptors as inhibitors of the killing function of CTL and the induction of intercellular adhesion molecules -1, dehydrocostus lactone from *S. lappa* and other guainolides were examined for their structure activity relationship. It was confirmed that guaianolide moiety exhibited considerable inhibitory effects towards the induction of intercellular adhesion molecule-1 and killing function of CTL (Taniguchi *et al.,* 1995; Yuuya *et al.,* 1999).

4. Miscellaneous Activities

4.1 Cardio Vascular Effects

It was found that extract of *Saussurea lappa* helps in lowering of the blood pressure and prevents blood coagulation. *S. lappa* also showed vasodilatation and reduction in cholesterol and triglycerides in the blood (Upadhay *et al.,* 1994). Aqueous decoctions of *S. lappa* strengthen fibrin content of blood (Yu, 1986). The volatile oils of *S. lappa* inhibited ADP-induced platelet coagulation that was mainly due to dehydrocostus lactone and costunolide content of oil (Hou *et al.,* 2008). *S. lappa* also inhibited enzyme PTB-1B involved in insulin signal, transduction, hypertension and obesity of type 2 diabetes due to presence of the betulinic acid, betulinic acid methyl ester, mokko lactone, dehydrocostus lactone and anthraquinones in the extract (Li *et al.,* 2006; Choi *et al.,* 2009; Choi *et al*., 2012). *S. lappa* extract and costus oil also reported to exhibit hypoglycemic effect (Gupta *et al.,* 1967; Wang, 1997).

4.2 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 could be a useful drug for chronic bronchitis and asthma (Sastry and Dutta, 1961).

4.3 Anticonvulsant Activity

Petroleum ether extract of *S. lappa* roots have potent anticonvulsant activity against pentylenetrazole and picrotoxin induced convulsions in mice, by elevating the seizure threshold through GABAergic receptors (Ambavade *et al.,* 2009). The alcoholic extract of root of *Saussurea lappa* was reported to show significant anti epileptic activity (Gupta *et al.,* 2009; Harish *et al*., 2010). The different extracts of *S. lappa* root for the anticonvulsant activity by picrotoxin induced convulsion, pentylenetetrazole and maximal electroshock tests performed on 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 (Butola *et al.,* 2010).

4.4 Antiparasitic Activity

The activity of *S. lappa* was tested against Trypanosoma cruzi, *Clonorchis sinensis* and some nematode infections. Decoction of plant given orally to *Clonorchis sinensis* infected rabbits was found to be effective to some extent (Rhee *et al.,* 1985).

4.5 Antihyperlipidemic Activity

The aqueous extract of *S. lappa* orally administered to rabbits at a dose of 2 mg/kg body weight showed significant hypolipidaemic effect (Upadhya *et al.,* 1996). The ethanolic extract of *S. lappa* reduces the triglycerides level as well as it significantly increased the HDL-C level in both serum and the tissues (Anbu *et al.,* 2011).

4.6 Antidiarrheal Activity

The methanolic extract of *S. lappa* roots against antidiarrheal activity in Wistar rats was studied 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 diarrhoea, respectively. The standard drug (loperamide) showed significant reduction (68.02%) in diarrheal stool at the dose of 5mg/kg body weight. The result of this study concluded

that the dose of root extract at 500 mg/kg body weight showed effect similar to that of standard drug loperamide in reducing diarrhoea stool. The methanolic extract of *S. lappa* roots showed 32.28% inhibition of diarrhoea at the dose of 300 mg/kg body weight. So, these findings clearly showed that the MeOH extract of *S. lappa* has significant antidiarrheal activity (Hemamalini *et al*., 2011). The methanolic extract of *S. lappa* significantly protected the rats against diarrhoea evoked by castor oil in dose dependent manner (Negi *et al.,* 2013).

4.7 Angiogenesis Effect

The endothelial cell proliferation is suppressed by costunolide (isolated from *S. lappa* root). Studies proved that the chemotaxis induced by vascular endothelial growth factor of human umbilical vein endothelial cells was noticeably inhibited at IC50 of 3.4 µmol/L of *S. lappa*. Similarly, by *in vivo* method the neovascularization of mouse corneal stimulated by vascular endothelial growth factor was reported to be inhibited at a dosage of 100 mg/kg/day (Jeong *et al.,* 2002; *Thara et al.,* 2012; Mohammad *et al.,*2013).

4.8 Spasmolytic Activity

It was observed that *S. lappa* significantly able to relax the contraction induced by carbachol (30µmol/L). The antiperoxidative effects of *S. lappa* were possibly due to the presence of sesquiterpene lactones. Sesquiterpenes has been recognized to stimulate the Sgc which stimulates extrusion of K ions thereby reducing intrinsic Ca ions through activation of cyclic GMP and PKG pathways, leading to relaxation of smooth muscles (Hsu *et al.,* 2009).

4.9 Anti-Mycobacterial Activity

Herrera *et al*. (2007) investigated the in vitro anti mycobacterial activity of *S. lappa* where whole oil and its fractions and pure active compounds were determined by fluorometric Alamar Blue microassay (FMABA) and found that costunolide and dehydrocostuslactone are mainly responsible for anti-mycobacterial activity against Mycobacterium tuberculosis H37Rv with MICs of 6.25 and 12.5 mg/L, respectively. Anti-mycobacterial activity was found to be better for the mixture than for pure compounds thus both lactones presented synergistic activity.

5. Conclusion

The present review is a compilation of the research work carried out on different solvent extracts and active constituents of *Saussurea lappa*. Among these components, terpenes such as costunolide, dehydrocostus lactone and cynaropicrin have showed the major pharmacologic activities. Costunolide, cynaropicrin, beta-peltatin and lignin derivatives have been identified as effective against pancreatic, lung, mammary, prostate, leukemia, gastric and colon cancer hence, could lead to the development of anti neoplastic drug. Different extracts of *S. lappa* are effective against various multidrug resistant *Staphylococcus* spp., *E. coli*, *Klebsiella*, *Proteus* and *Bacillus thurigenesis* and antibacterial activity vary with the concentration of the plant material used. Hence, *S. lappa* root extract has certain antibiotic potential and it could be a new source of antimicrobial agents with possibly novel mechanism of action. Also, cynaropicrin, reynosin and santamarin has been identified as the principal indicator of TNF-alpha and suppressor of COX-II enzymes, hence it has anti inflammatory activity. Dehydrocostus lactone and costunolide have been reported to display strong suppressive effect on human hepatoma antigen in liver and therefore, have been the potential to develop as an antiviral or anti HBV drug. Since, *S. lappa* has tremendous medicinal applications in traditional medicine system, hence more clinical and pathological studies are required to investigate its active constituents, physiological pathway, pharmacokinetics, bioavailability and safety with detail or assurance. Furthermore, potential active compounds could help in new drug discovery and could be used to treat the neoplasm, viral, bacterial and chronic skin ailments.

References

Alaagib RM and Ayoub SM (2016). On the chemical composition and antibacterial activity of *Saussurea lappa* (Asteraceae). *The Pharma Innovation,* 4(2): 73-76.

Ambavade S, Mhetre N, Muthal A and Bodhanka S (2009). Pharmacological evaluation of anticonvulsant activity of root extract of *Saussurea lappa* in mice. *European Journal of Experimental Biology,* 2(2): 417-420.

Anbu J, Anjana A, Purushothaman K, Sumithra M, Suganya S, Bathula and Modak N (2011). Evaluation of Anti hyperlipidemic activity of ethanolic extract extract of *Saussurea lappa* in rats. *International Journal of Pharma and Bio Sciences,* 2(4): 551-556.

Basu BD and Kirtikar KR (1987). Indian medicinal plants, Derhadun: *International Book Distributors.* p. 915.

Butola JS and Samant SS (2010). *Saussurea* species in Indian Himalayan Region: diversity, distribution and indigenous uses. *International Journal of Plant Biology,* 1: 43-51.

Chadha YR (1972). The wealth of India, Vol. IX: Rh-So, CSIR, New Delhi, 196.

Chen HC, Chou CK, Lee SD, Wang JC and Yeh SF (1995). Active-compounds from *Saussurea lappa* clarke that sup-press hepatitis B virus surface antigen gene expres-sion inhuman hepatoma cells. *Antiviral Research,* 27: 99-109.

Chen SF, Li YQ and He FY (1994). Effect of *Saussurea lappa* on gastric functions, *Zhongguo Zhong Xi Yi Jie He Za Zhi*, 14: 406-408.

Cho JY, Baik KU, Jung JH and Park MH (2000). *In vitro* anti inflammatory effects of cynaropicrin, a sesquiterpene lactone, from *Saussurea lappa*. *European Journal of Pharmacology*, 398(3): 399-407.

Cho JY, Kim AR, Jung JH, Chun T, Rhee MH and Yoo ES (2004). Cytotoxic and pro-apoptotic activities of cynaropicrin, a sesquiterpene lactone, on the viability of leukocyte cancer cell lines. *European Journal of Pharmacology*, 492: 85-94.

Cho JY, Park J, Yoo ES, Baik KU, Jung JH and Lee J (1998). Inhibitory effect of sesquiterpene lactones from *Saussurea lappa* on tumor necrosis factor-alpha production in murine macrophage like cells. *Plant Medicine*, 64(7): 594-597.

Choi EJ and Kim G (2010). Evaluation of anticancer activity of dehydrocostus lactone in vitro. *Molecular Medicine Reports*, 3(1): 185-8.

Choi HG, Lee DS, Li B, Choi YH, Lee SH and Kim YC (2012). Santamarin, a sesquiterpene lactone isolated from *Saussurea lappa*, represses LPS-induced inflammatory responses via expression of heme oxygenase-1 in murine macrophage cells. *International Immunopharmacology*, 13(3): 271-9.

Choi JY, Na MK, Hwang IH, Lee SH, Bae EY and Kim BY (2009). Isolation of betulinic acid, its methyl ester and guaiane sesquiterpenoids with protein tyrosine phosphatase 1B inhibitory activity from the roots of *Saussurea lappa C. B. Clarke. Molecules*, 14(1): 266-272.

Damre AA, Damre AS and Saraf MN (2003). Evaluation of sesquiterpene lactone fraction of *Saussurea lappa* on transudative, exudative and proliferative phases of inflammation. *Phytotherapy Research*, 17: 722-725.

Dutta NK, Sastry MS and Tamhane RG (1990). Pharmacological actions of an alkaloidal fraction isolated from *Saus-surea lappa*. *Indian Journal of Pharmacy*, 22: 6-7.

Gokhale AB, Damre AS, Kulkarni KR and Saraf MN (2002). Preliminary evaluation of anti-infammatory and anti-arthritic activity of *S. lappa*. *Phytomedicine*, 9: 433-437.

Gupta OP and Ghatak BJ (1967). Pharmacological investigation on *Saussurea lappa* (Clarke). *Indian Journal of Medical Research*, 55: 1078-83.

Gupta P, Jadhav S, Ghaisas M and Deshpande A (2009). Anticonvulsant activity of *Saussurea lappa*. *Pharmacologyonline*, 3: 809-814.

Harish B, Mohana L and Saravana K (2010). A Review on Traditional System of Medicine for Treats Epilepsy. *International Journal of Biological and Pharmaceutical Research*, 1(1): 1-6.

Hasson SS, Al-Balushi MS, Al-Busaidi J, Othman MS, Said EA, Habal O, Sallam TA, Aljabri AA and AhmedIdris M (2013). Evaluation of anti-resistant activity of Auklandia (*Saussurea lappa*) root against some human pathogens. *Asian Pacific Journal of Tropical Biomedicine* 1, 3(7): 557-62.

Hemamalini K, Vasireddy U, Nagarjun GA, Harinath K, Vamshi G and Vishnu E (2011). Anti-diarrhoeal activity of leaf extracts Anogessius accuminata. *International Journal of Pharmaceutical Research and Development*, 3(6): 55-57.

Herrera J, Costa M, lez H, Rodrigues A and Castilho P (2007). Synergistic antimycobacyerial activities of sesquiterpene lactones from *Laurus* spp. *Journal of Antimicrobial Chemotherapy*, 59: 548-552.

Hou PF, Chen WX, Zhao XH, SU S, Liu H, Lu Y and Duan J (2008). Analysis of chemical composition of the essential oil from radix aucklandiae by GC-MS and the effect on platelet aggregation. *Zhongguo Shi Yan Fang Ji Xue Za Zhi*, 14(7): 26-30.

Hsu YL, Wu LY and Kuo PL (2009). Dehydrocostuslactone, a medicinal plant derived sesquiterpene lactone induces apoptosis coupled to endoplasmic reticulum stress in liver cancer cells. *Journal of Pharmacology Experimental Therapeutics*, 329: 809-819.

Irshad S, Mahmood M and Perveen F (2012). In vitro antibacterial activities of three medicinal plants using agar well diffusion method. *Reserach Journal of Biology*, 2(01): 1-8.

Jeon YJ, Lee HS, Yeon SW and Ko JM (2005). Inhibitory effects of dehydrocostuslactone isolated from Saussurea Radix on CDK2 activity. *Korean Journal of Pharmacognosy*, 36(2): 97-101.

Jeong SJ, Itokawa T, Shibuya M, Kuwano M, Ono M and Higuchi R (2002). Costunolide, a sesquiterpene lactone from *Saussurea lappa*, inhibits the VEGFR KDR/Flk-1 signaling pathway. *Cancer Letterrs*, 187: 129-133.

Jin M, Lee HJ, Ryu JH and Chung KS (2000). Inhibition of lps - Induced NO productiion abd TNF - kappaB activation by a sesquiterpene from *Saussurea lappa*. *Archives of Pharmacological Research*, 23: 54-58.

Julianti T, Hata Y, Zimmermann S, Kaiser M, Hamburger M and Adams M (2011). Antitrypanosomal sesquiterpene lactones from *Saussurea costus. Fitoterapia*, 82(7): 955-959.

Jung IH, Kim Y, Lee CO, Kang SS, Park JH and Im KS (1998). Cytotoxic constituents of *Saussurea lappa*. *Archives of Pharmacal Research*, 21: 153-156.

Kanetoshi A, Inoue S and Anetai M (2005). An in vitro screening test for anti-cancer components of wild plants in Hokkaido. *Report-Hokkaido Institute of Public Health*, 55: 49-53.

Kang JS, Yoon YD, Lee KH, Park SK and Kim HM (2004). Costunolide inhibits interleukin-1beta expression by down-regulation of AP-1 and MAPK activity in LPS-stimulated RAW 264.7 cells. *Biochemical and Biophysical Research Communications*, 313: 171-177.

Kim EJ, Hong JE, Lim SS, Kwon GT, Kim J, Kim JS, Lee KW and Park JH (2012). The hexane extract of Saussurea lappa and its active principle, dehydrocostus lactone, inhibit prostate cancer cell migration. *Journal of Medicinal Food*, 15(1): 24-32.

Kretschmer N, Rinner B, Stuendl N, Kaltenegger H, Wolf E, Kunert O, Boechzelt H, Leithner A, Bauer R and Lohberger B (2012). Effect of costunolide and dehydrocostus lactone on cell cycle, apoptosis, and

ABC transporter expression in human soft tissue sarcoma cells. *Planta Medica*, 78(16): 1749-56.

Lee GI, Ha JY, Min KR, Nakagawa H, Tsurufuji S and Chang IM (1995). Inhibitory effects of oriental herbal medicines on IL-8 induced in lipopolysacharide activated rat macrophages. *Planta Medica*, 61: 26-30.

Lee MG, Lee KT, Chi SG and Park JH (2001). Costunolide induces apoptosis by ROS-mediated mitochondrial permeability and cytochrome C release. *Biological Pharmaceutical Bulletin*, 24: 303-306.

Li S, An TY, Li J, Shen Q, Lou FC and Hu L (2006). PTP1B inhibitors from Saussurea lappa. *Journal of Asian National Products Research*, 8(3): 281-6.

Li YH, Gong T, Yang QM, Miao ZL, Cheng GQ and Huo QP (2010). *In vivo* study of the inhibition of R plasmid transfer by conjugation in rats taking extracts of Radix *aucklandiae* and *Polygonatum cyrtonema*. *Zhongguo Ji Sheng Chong Bing Fang Zhi Za Zhi*, 5(2): 108-110, 166.

Liu JJ, Zheng CQ and Zhou Z (2008). The influence of herba Lysimachiare and Radix Aucklandiae on the movement of dog gallbladder and its plasma CCK value. *Sichuan Zhong Yi*, 26(4): 31-2.

Malik AH, Khuroo AA, Dar GH and Khan ZS (2011). Ethnomedicinal uses of some plants in the Kashmir Himalaya. *Indian Journal of Traditional Knowledge*, 10(2): 362-366.

Matsuda H, Kageura T, Inoue Y, Morikawa T and Yoshikawa M (2000). Absolute stereostructures and synthesis of saus-sureaamines A and B, C, D and E, amino acid sesqui-terpene conjugates with gastro protective effect, from the roots of *Saussurea lappa. Tetrahedron*, 56: 7763-7777.

Matsuda H, Toguchida I, Ninomiya K, Kageura T, Morikawa T and Yoshikawa M (2003). Effects of sesquiterpenes and amino acidsesquiterpene conjugates from the roots of Saussurea lappa on inducible nitric oxide synthase and heat shock protein in lipopolysaccharide-activated macrophages. *Bioorganic and Medicinal Chemistry*, 11(5): 709-15.

Mitra SK, Gopumadhavan S, Hemavathi TS, Muralidhar TS and Venkataranganna MV (1996). Protective effect of UL-409, an herbal formulation against physical and chemical factor induced gastric and duodenal ulcers in experimental animals. *Journal of Ethnopharmacology*, 52: 165-169.

Mohamed S, Lokanath N, Prasanthi A, Madhavi, G Mallika M and Vishnu N (2013). Aqueous extract *of Saussurea lappa* root ameliorate oxidative myocardial injury induced by isoproterenol in rats. *Journal of Advanced Pharmaceutical Technology and Research. 2013; 4(2):94-100.*

Moon S, Yun S, Koom J, Kim H, Choi M, Park B, Kim S, Lee S, Ahn H, Chun H and Kim C (2013). Anticancer activity of *Saussurea lappa* extract by apoptotic pathway in KB human oral cancer cells. *Pharmaceutical Biology*, 51(11): 1372-1377.

Nadkarni KM (1954). In: Nadkarni KA. *Indian Materia Medica*, (2nd edition), Popular Book Depot, Bombay, India, 76-78.

Nayar MP and Shastry ARK (1987, 1988 and 1990). Red data book of Indian Plants, Published by Botanical survey of India, Vol. 1, II and III. BSI, Calcutta, 187.

Negi S, Bisht VK, Bhandari AK, Bhatt VP, Sati MK, Mohanty JP and Sundriya RC (2013). Antidiarrheal activity of methanol extract and major essential oil contents of *Saussurea lappa. African Journal of Pharmacy and Pharmacology*, 7(8): 474-477.

Niranjan S, Ranju G, Sharma U, Singh N and Roy S (2011). Antiulcerogenic activity of *Saussurea lappa* roots. *International Journal of Pharmacy and Life Science*, 2(1): 516-520.

Oh GS, Pae HO, Chung HT, Kwon JW, Lee JH, Kwon TO, Kwon SY, Chon BH and Yun YG (2004). Dehydrocostus lactone enhances tumor necrosis factor-alpha-induced apoptosis of human leukemia HL-60 cells. *Immunopharmacology and Immunotoxicology*, 26(2): 163-75.

Pandey M, Rastogi S and Rawat A (2007). *Saussurea costus*: Botanical, chemical and pharmacological review of an ayurvedic medicinal plant. *Journal of Ethnopharmacology*, 110: 379-390.

Pandey R (2012). *Saussurea lappa* extract modulates cell mediated and humoral immune response in mice. *Der Pharmacia Lettre*, 4(6): 1868-1873.

Parekh J, Jadeja D and Chanda S (2007). Efficacy of aqueous and methanol extracts of some medicinal plants for potential antibacterial activity. *Turkish Journal of Biology*, 29: 203-210.

Park H, Choi EJ, Lee YS and Kim GH (2007). Sesquiterpene lactones from *Saussurea lappa* and their cell proliferation effects on human breast cell lines. *Yakhak Hoeji*, 51(2): 145-9.

Patil SM, MB Patil, GN Sapkale and RP Umbare (2009). Antimicrobial activity of *Saussurea lappa* Clarke roots. *Research Journal Pharmacognosy and Phytochemistry*, 1: 51-53.

Rao KS, Babu GV and Ramna reddy YV (2007). Acylated flavone glycosides from the roots of *Saussurea lappa* and their antifungal activity. *Molecules*, 12(3): 328-44.

Rasul A, Parveen S and Ma T (2013). Costunolide: A novel anti-cancer sesquiterpene lactone. *Bangladesh Journal of Pharmacology 2012*, 7: 6-13.

Rasul A, Yu B, Yang L, Arshad Khan M, Ma T and Yang H (2012). Costunolide, a sesquiterpene lactone induces G2/M phase arrest and mitochondria-mediated apoptosis in human gastric adenocarcinoma SGC7901 cells. *Journal of Medicinal Plants Research*, 6(7): 1191-200.

Rhee JK, Back BK and Ahn BZ (1985). Structural investigation on the effects of the herbs on *Clonorchis sinensis* in rabbits, *American Journal of Chinese Medicine*, 13: 119-125.

Robinson A, Kumar TV, Sreedhar E, Naidub VG, Krishna SR and Babua KS (2008). A new sesquiterpene lactone from the roots of *Saussurea lappa*: structure-anticancer activity study. *Bioorganic and Medicinal Chemistry Letters*, 18(14): 4015-4017.

Samant SS, Dhar U and Palni LMS (1998). Medicinal plants of Indian Himalaya: Diversity, Distribution, Potential Values. *Himavikas Publication*, 13: 43-47.

Sastry MS and Dutta NK (1961). A method for preparing tincture *saussurea*. *Indian Journal of Pharmacy*, 23: 247-249.

Shao Y, Huang F, Wang Q and Chengguie D (2005). Anti-inflammatory and cholagogic effects of *aucklandiae*. *Jiangsu Yao Xue Yu Lin Chuang Yan Jiu*, 13(4): 5-6, 51.

Singh SK (1999). Ethnobotanical study of useful plants of Kullu districts in north western Himalayas, India. *Journal of Economic and Taxonomic Botany*, 23: 185-198.

Stainton A (1988). Flowers of the Himalaya. A Supplement. Oxford University Press, Delhi, 81-84.

Sun CM, Syu WJ, Don MJ, Lu JJ and Lee GH (2003). Cytotoxic sesquiterpene lactones from the root of *Saussurea lappa*. *Journal of Natural Products*, 66(9): 1175-1180.

Sun SX (2008). Transition and differentiation of foundation during historical evolution of *Saussurea lappa* as a medicinal plant. *Zhong Yao Cai*, 31(7): 1093-5.

Sunkara Y, Robinson A, Suresh B, Naidu K, Vishnuvardhan M, Ramakrishna M, Madhavendra S and Rao J (2010). Anti-inflammatory and cytotoxic activity of chloroform extract of roots of *Saussurea lappa*. *Journal of Pharmacy Research*, 3(8): 1775-1778.

Talwar KK, Singh IP and Kalsi PS (1992). A sesquiterpenoid with plant growth regulatory activity from *Saussurea lappa*. *Phytochemistry*, 31(1): 336-338.

Taniguchi M, Kataoka T, Suzuki H, Uramoto M, Ando M and Arao K (1995). Costunolide and dehydrocostus lactone as inhibitors of killing function of cytotoxic T lymphocytes. *Bioscience, Biotechnology and Biochemistry*, 59: 2064-2067.

Thara KM and Zuhra KF (2012). Comprehensive *In vitro* pharmacological activities of different extracts of *Saussurea lappa*. *Europian Journal of Experimental Biology*, 2(2): 417-420.

Tsarong TJ (1986). Handbook of traditional Tibetan drugs, their nomenclature, composition, use and dosage. India: *Tibetan Medical Publications*. p. 101.

Upadhyay OP, Singh RH and Dutta SK (1994). Studies on anti diabetic medicinal plants used in Indian folklore. *Ayurvaidyan*, 9: 159-167.

Venkataranganna MV, Gopumadhavan S, Sundar R and Mithra SK (1998). Evaluation of possible mechanism of anti ulcerogenic activity of UL-409 an herbal preparation. *Journal of Ethanopharmacology*, 63: 187-192.

Wang BX (1997). Pharmacological Science of Modern Chinese Medicine. Tianjin: *Tianjin Science and Technology Press*.

Wang XY (2004). Influence of *Saussurea lappa* on acute damage of gastric mucosa of rats. *Zhong Yi Yan Jiu*, 17(2): 21-2.

Yaeesh S, Jamal Q, Shah AJ and Gilani AH (2010). Antihepatotoxic activity of *Saussurea lappa*extract on D-galactosamine and lipopolysaccharide-induced hepatitis in mice. *Phytotherapy Research*, 2: 229-S232.

Yamahara J, Kobayashi M, Miki K, Kozuka M, Sawada T and Fujimura H (1985). Cholagogic and antiulcer effect of *Saussurea radix* and its components. *Chemical and Pharmceutical Bulletin*, 33: 1285-1288.

Yang H, Xie JL and Sun HD (1998). Research progress on the medicinal plant-*Saussurea lappa*. *Natural Product Research Development*, 10(2): 90-98.

Yoshikawa M, Hatakeyama S, Inoue Y and Yamahara J (1993). Saussureamines A, B, C, D, and E, new antiulcer principles from Chinese *Saussureae Radix*. *Chemical Pharmaceutical Bulletin (Tokyo)*, 41(1): 214-216.

Youn K, Sung G, Sang-M, Yee J, Jeakyung J, Wooyoung K, Yong C and Seong G (2013). *Saussurea lappa* Clarke Costunolide prevents TNF-α. Induced breast cancer NF-Kb activity. *Evidence Based Complementary and Alternative Medicine*. Article ID 936257: 10.

Yu ZJ (1986). Observation of action of 21 types of Chinese traditional medicine on in vitro solution of fibrous protein. *Zhong Xi Yi Jie He Za Zhi*, 6(8): 484.

Yun YG, Oh H, Oh GS, Pae HO, Choi BM, Kwon JW, Kwon TO, Jang SI and Chung HT(2004). In vitro cytotoxicity of mokko lactone in human leukemia HL-60 cells: Induction of apoptotic cell death by mitochondrial membrane potential collapse. *Immunopharmacology and Immunotoxicology*, 26(3): 343-53.

Yuuya S, Hagiwara H, Suzuki T, Ando M, Yamada A, Suda K, Kataoka T and Nagai K (1999). Guaianolides as immunomodulators, synthesis and biological activities of dehydro costous lactone, mokolactone, eremanthin, and their derivatives. *Journal of Natural Product*, 62: 22-30.

Zahara K, Tabassum S, Sabir S, Arshad M, Qureshi R, Amjad MS and Chaudhari SK (2014). A review of therapeutic potential of *Saussurea lappa* - an endangered plant from Himalaya. *Asian Pacific Journal of Tropical Medicine*, S1: S60-S69.

Zhao F, Xu H, He EQ, Jiang YT and Liu K (2008). Inhibitory effects of sesquiterpenes from *Saussurea lappa* on the overproduction of nitric oxide and TNF-alpha release in LPS-activated macrophages. *Journal of Asian Natural Product Research*, 10(11-12): 1045-1053.