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Ravinder Singh
Department of Chemistry,
Punjab Agricultural University,
Ludhiana, Punjab, India

KK Chahal
Department of Chemistry,
Punjab Agricultural University,
Ludhiana, Punjab, India

Nancy Singla
Department of Chemistry,
Punjab Agricultural University,
Ludhiana, Punjab, India

Chemical composition and pharmacological activities of *Saussurea lappa*: A review

Ravinder Singh, KK Chahal and Nancy Singla

Abstract

Saussurea lappa C.B. Clarke is a well-known and important medicinal plant widely used in several medicinal systems for the treatment of various diseases, viz. inflammatory diseases, ulcer, asthma and stomach problems. Sesquiterpenoid lactones were reported as the major phytoconstituents of this species. Various pharmacological experimental studies using *in vitro* and *in vivo* models demonstrated the ability of *S. lappa* to exhibit anti-inflammatory, anti-ulcer, anticancer and hepatoprotective activities, lending support to the several of its traditional uses. Dehydrocostus lactone, Costunolide and Cynaropicrin, isolated from this plant, were identified as the bioactive molecules. Due to the remarkable biological activity of *S. lappa* and its constituents it will be worthwhile to develop them as a medicine. The present review is an inclusive analysis of chemistry and pharmacological uses of *S. lappa*.

Keywords: *Saussurea lappa*, Sesquiterpene lactones, Pharmacological activities, Dehydrocostus lactone, Costunolide.

1. Introduction

Secondary metabolites of plants, due to their various biological and therapeutic applications, are gaining importance these days. These natural products continue to be a source for innovation in drug discovery by playing a significant role in the discovery and understanding of cellular pathways that are essential steps in the drug-discovery process. The Asteraceae family of plants comprises about 1000 genera, mainly distributed in Asia and Europe. *Saussurea* DC., as the largest subgenus of this family, comprises more than 300 known species in the world, of which 61 species occur in India. *Saussurea* species contain sesquiterpene lactones (Hajra 1995) [17], flavonoids, lignans, triterpenes, steroids, glycosides, and some possess interesting properties such as anti-inflammation, anticancer, immunomodulation, free radical scavenging, and anti-fatigue activities. *Saussurea lappa* C.B. Clarke, belonging to the family Asteraceae, is one of the best-known species within this genus and used as 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 (Pandey *et al.* 2007) [44]. Sesquiterpene lactones were reported as the major phytoconstituents of this species. Costunolide, Dehydrocostus lactone and Cynaropicrin, isolated from this plant, have been known to possess potential as bioactive molecules. *S. lappa* is commonly known as costus in English by different vernacular names in India like Kuth (Hindi), Kut (Gujrati), Kur (Bengali), Postkhai (Kashmiri), Sepuddy (Malayalam), Kot (Punjabi), Kushta (Sanskrit), Kostum (Tamil), Kustam (Telgu), Kushta (Marathi) and Koshta (Kannada) (Kirtikar and Basu 2001) [29]. *S. lappa* (root oil and roots) is an important drug in the international market. Increasing in-depth studies on the chemical ingredients, pharmacological activity, and clinical applications of *S. lappa* led to development of *S. lappa* for treating cardiovascular disease, as well as its anti-inflammatory, anticancer, anti-ulcer, and antimicrobial properties. The present review is an up-to-date and comprehensive analysis of the chemistry and pharmacological activities of *S. lappa*.

2. Chemical Composition

Phytochemical analysis of *S. lappa* roots showed the presence of monoterpenes, sesquiterpenoids, flavonoids, lignans, triterpenes, steroids, glycosides etc. *S. lappa* roots are rich source of sesquiterpenoids specially sesquiterpene lactones. Essential oil of *S. lappa* roots obtained by hydrodistillation showed higher content of sesquiterpenoids (79.80%) than monoterpenoids (13.25%) (Liu *et al.* 2012) [34]. The principal compounds in *S. lappa* essential oil were Dehydrocostus lactone and Costunolide. Extraction of essential oil from *S. lappa* roots was carried out by hydro-distillation of dried and crushed *S. lappa* roots. Various chemical constituents isolated from *S. lappa* are as follows:

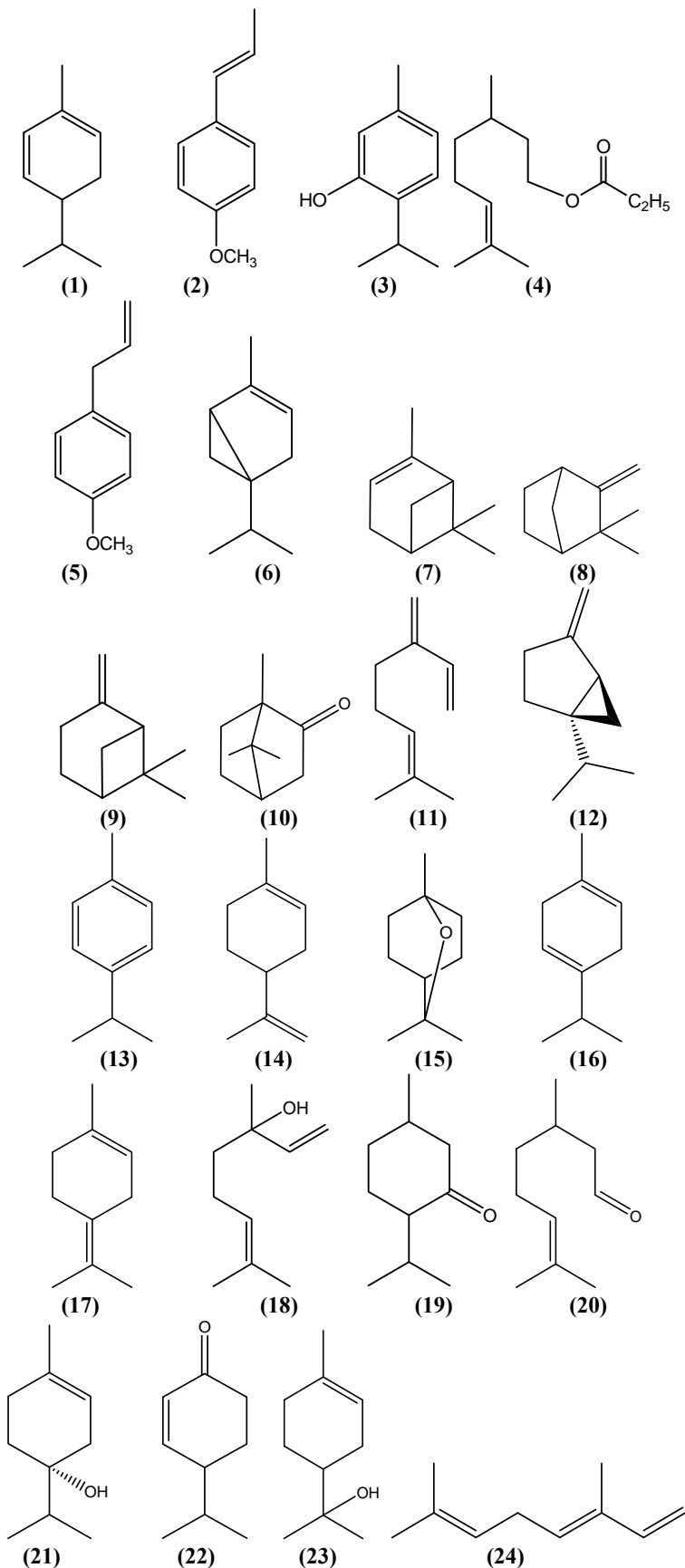
Correspondence

KK Chahal
Department of Chemistry,
Punjab Agricultural University,
Ludhiana, Punjab, India

2.1 Terpenes

Monoterpenes like Phellandrene (1), Anethole (2), Thymol (3), Citronellyl propionate (4), Estragole (5), α -Thujene (6), α -Pinene (7), Camphene (8), β -Pinene (9), Camphor (10), Myrcene (11), Sabinene (12), p-Cymene (13), Limonene (14),

1,8 Cineol (15), γ -Terpinene (16), α -Terpinolene (17), Linalool (18), Menthone (19), Citronellal (20), Terpinen-4-ol (21), Cryptone (22), α -Terpineol (23), Ocimene (24) etc. were reported from *S. lappa* root. (Chang and Kim 2008, Gwari *et al.* 2013)^[6, 16].

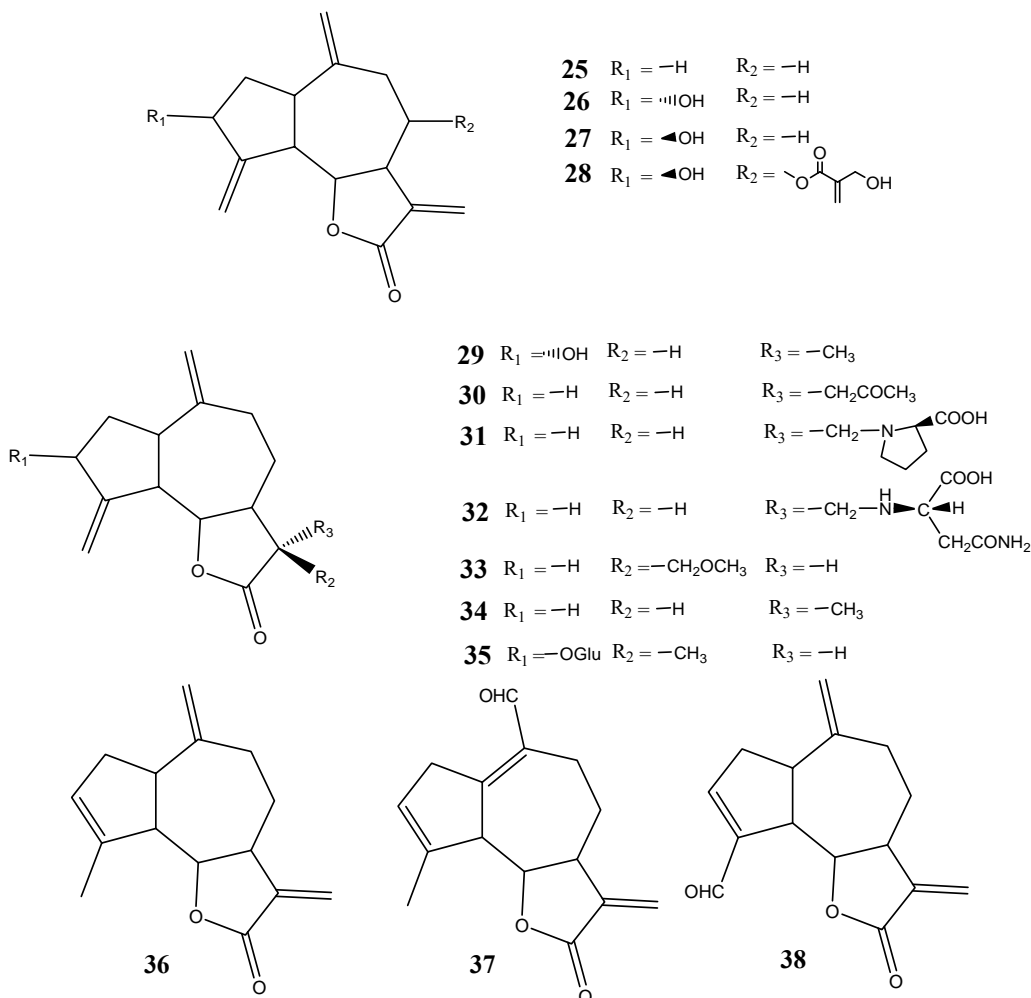


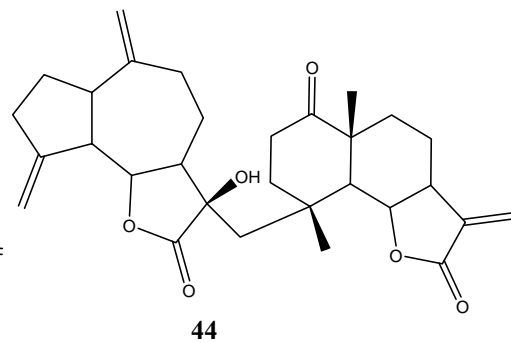
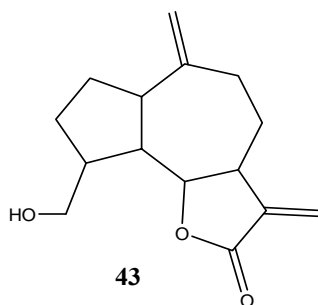
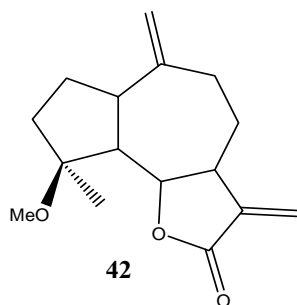
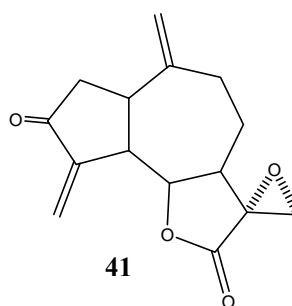
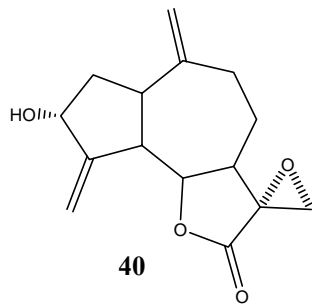
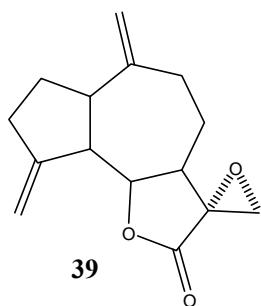
2.2 Sesquiterpenes

S. lappa are very rich source of sesquiterpenes. With respect to the carbocyclic skeleton, these sesquiterpenes roughly belong to three groups: Guaiane, eudesmane, and germacrane types. They were sequentially biosynthesized, and due to the instability of germacrane, half of the sesquiterpenes turn up as guaianes and 40% as eudesmanes and remaining germacrane. Guaianes type sesquiterpene lactones reported from *S. lappa* are Dehydrocostus lactone (25) (Govindan and Bhattacharaya 1977) [14], Isozaluzanin (26), Zaluzanin C (27), 11 β , 13-Dihydro-3-epizaluzanin C (28), (Chhabra *et al.* 1998, Kalsi *et al.* 1983) [7, 27], Cynaropicrin (29) (Cho *et al.* 1998) [10], Lappalone (30) (Sun *et al.* 2003) [48], Saussureamine B (31), Saussureamine C (32) (Yoshikawa *et al.* 1993) [59], 12-Methoxy-dihydrodehydrocostus lactone (33) (Dhillon *et al.* 1987) [13], Mokko lactone (34), 11,13-Dihydroglucoaluzanin C (35), Isodehydrocostus lactone (36) (Kalsi *et al.* 1983) [27], Saussurealdehyde (37), Isodehydrocostuslactone-15-aldehyde (38) (Kumar *et al.* 1995) [31], 11,13-Epoxydehydrocostus lactone(39), 11,13-Epoxyisozaluzanin C (40), (Chhabra *et al.* 1997) [8], 11, 13-Epoxy-3-ketodehydrocostus lactone (41) (Chhabra *et al.* 1998) [7], 4 β -Methoxy-dehydrocostus lactone (42), 15-Hydroxydehydrocostus lactone (43), Lappadilactone

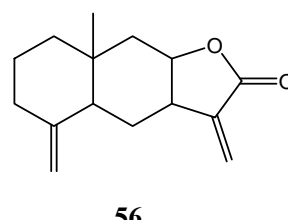
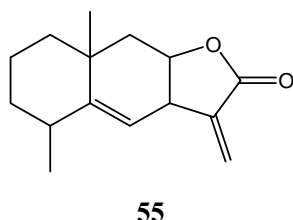
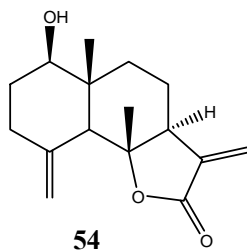
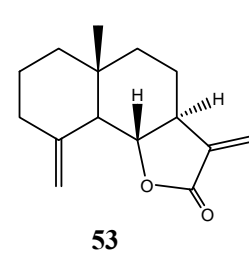
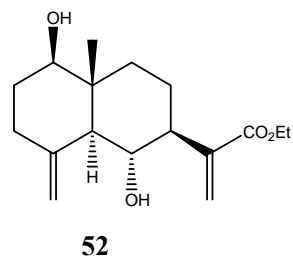
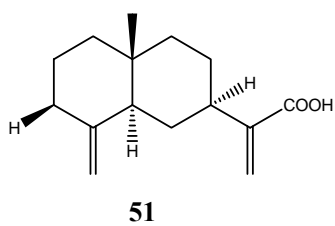
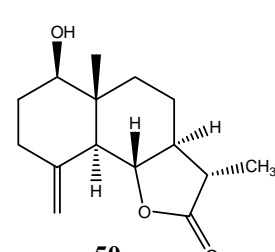
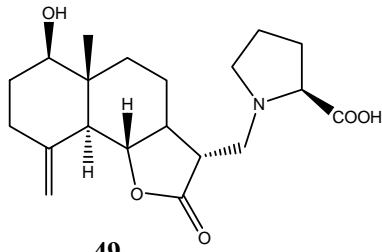
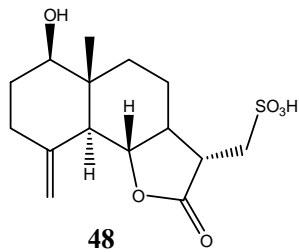
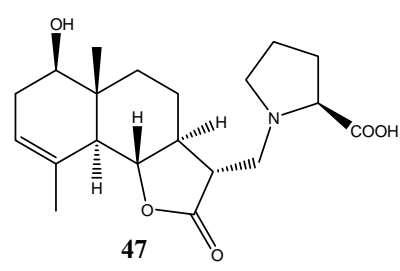
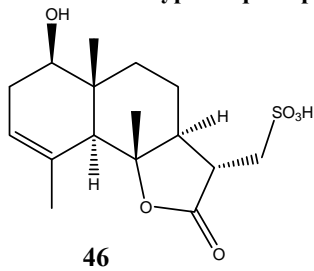
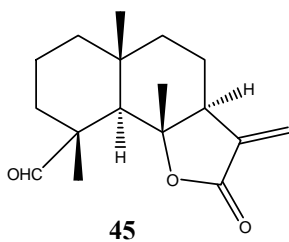
(44) etc. whereas Eudesmanes type sesquiterpenoids reported are Saussureal (45), 13-Sulfodihydrosantamarine (46) (Yin *et al.* 2005) [58], Saussureamine D (47) (Yoshikawa *et al.* 1993) [59], 13- Sulfodihydroreyosin (48) (Yin *et al.* 2005) [58], Saussureamine E (49) (Yoshikawa *et al.* 1993) [59], 11 β , 13-Dihydroreyosin (50), Reynosin (51) (Cho *et al.* 1998) [10], β -Costic acid (52) (Govindan and Bhattacharaya 1977) [14], 1 β , 6 α - Dihydroxycostic acid ethyl ester(53) (Sun *et al.* 2003) [48], α -Cyclocostunolide (54), Alantolactone (55), Isoalantolactone(56), β -Cyclocostunolide(57), (Govindan and Bhattacharaya 1977) [14], Magnolialide (58), 4 β -Hydroxyendesin- 11(13)-en-12-al (59), 4 α -Hydroxy-4 β -Methyldihydrocostol (60), α -Costol (61), Isocostic acid (62), Santamarine (63) (Cho *et al.* 1998) [10], Arbusculin A (64), Colartin (65) etc. and some Germacrane type sesquiterpene lactones i.e. Dihydrocostunolide (66), Costunolide (67), (Kang *et al.* 1999) [28], Saussureamine A (68) (Yoshikawa *et al.* 1993) [59], 12-Methoxy dihydrocostunolide (69), Costunolide 15-o- β -d-glucopyranoside(70) etc. were also reported.

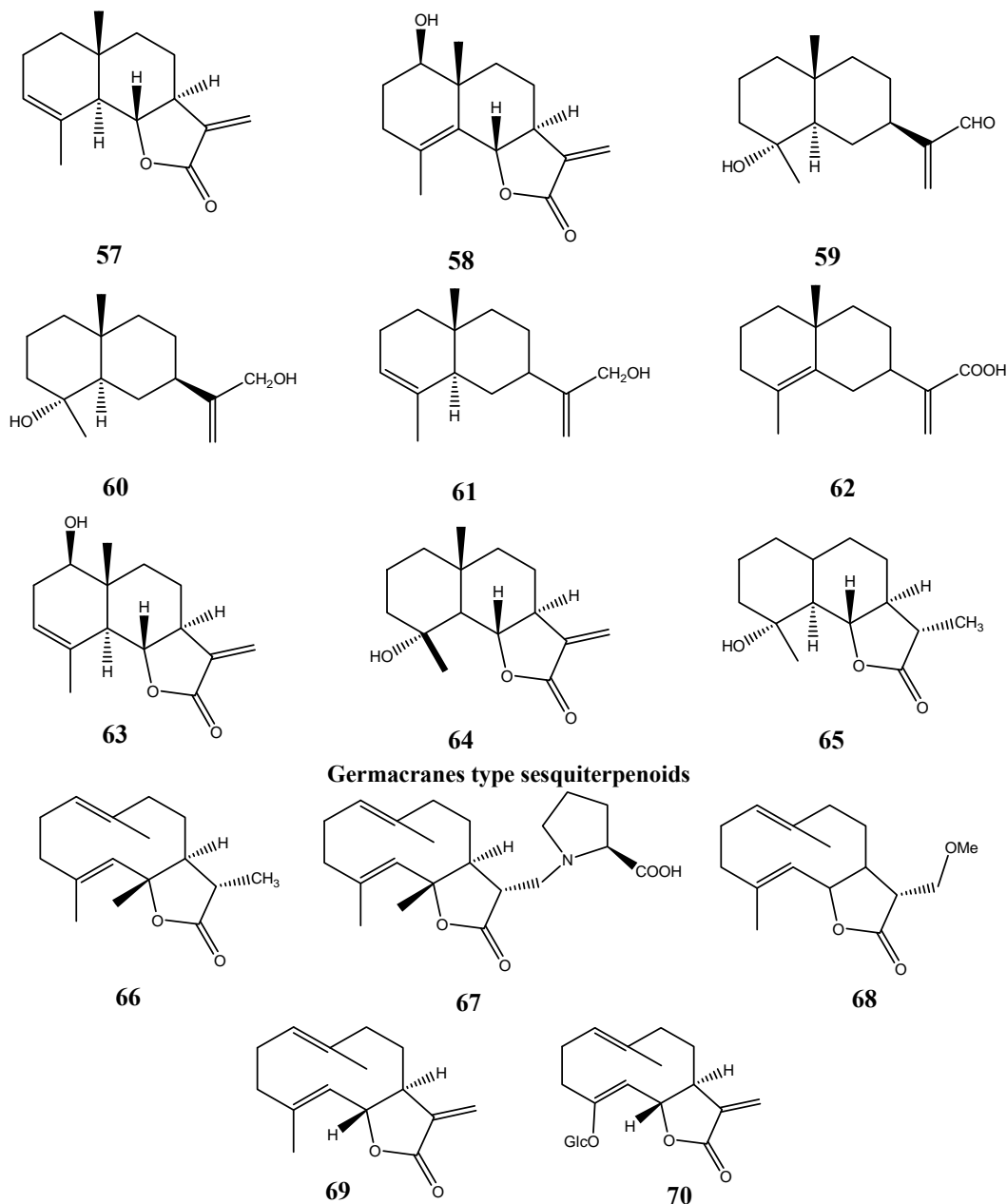
Guaianes type sesquiterpenoids





Eudesmanes type sesquiterpenoids

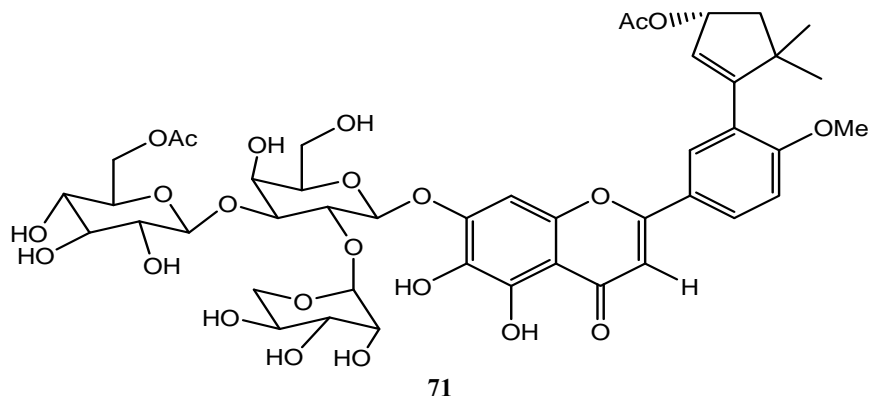




2.3 Flavonoids

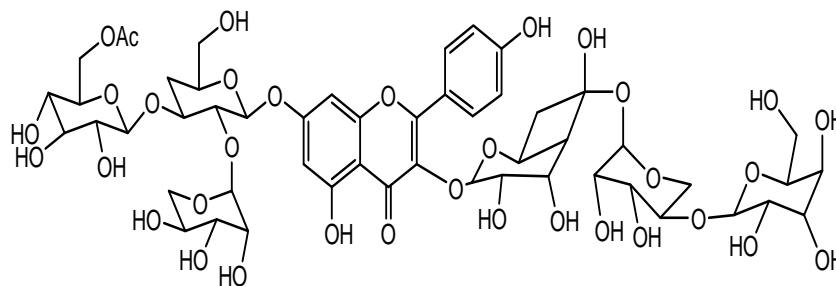
Flavonoids isolated from the roots of *S. lappa* with one glucoside substituent were Luteolin-7-O- β -D-glucoside, Rutin and Apigenin-7-O- β -D-glucoside (Alaagib and Ayoub 2015) [1] whereas flavonoids with large substituents, such as with three glucosides at C (3), were rare. Rao *et al.* (2007) [45]

reported following acylated flavonoids from *S. lappa* roots: 3'-[(3R)-3-Acetoxy-5,5-dimethylcyclopent-1-en-1-yl]-4'-O-methylscutellarein 7-O-(β -O-6'''-O-acetylglucopyranosyl-(1 \rightarrow 3)-[α -L-rhamnopyranosyl-(1 \rightarrow 2)]- β -D-glucopyranoside (71),



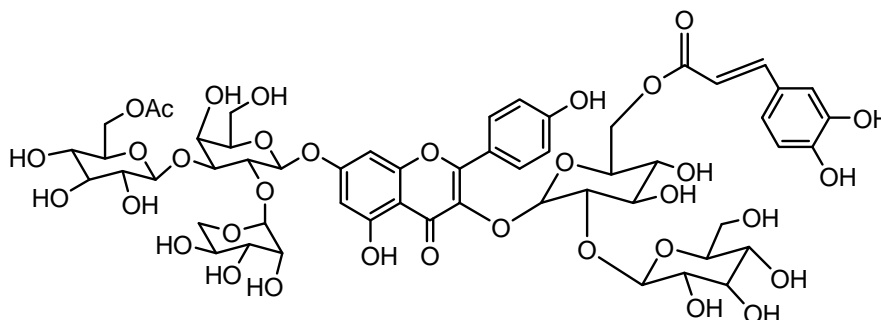
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Kaempferol 3- O- β -D-glucopyranosyl-(1 \rightarrow 4)- α -L-rhamnopyranosyl- (1 \rightarrow 6)- β -D-galactopyranoside 7- O- (6'''-O- acetyl- β -D-glucopyranosyl- (1 \rightarrow 3)- [α - L- rhamnopyranosyl-(1 \rightarrow 2)]- β -D-glucopyranoside (72),



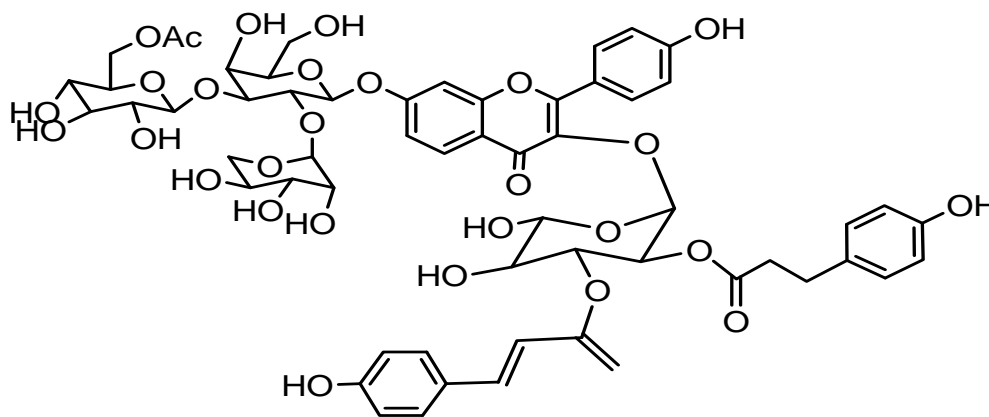
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Kaempferol 3- O- β -D-glucopyranosyl-(1 \rightarrow 2)- β -D- (6 α' -O-caffeoyl) galactopyranoside 7- O- (β -D-6'''-O- acetyl- β -D-glucopyranosyl- (1 \rightarrow 3)- [β - L- rhamnopyranosyl-(1 \rightarrow 2)]- β -D-glucopyranoside. (73)



73

Kaempferol 3- O- α -L-(2 α' , 3 α' - (E)-di-p-coumaroyl) rhamnoside 7- O- (6'''-O- acetyl- β -D glucopyranosyl- (1 \rightarrow 3)- [α - L- rhamnopyranosyl-(1 \rightarrow 2)]- β -D-glucopyranoside. (74)



74

2.4 Other constituents

Phytosterols like Lappasterol, 3-Epilappasterol, β - Sitosterol, Daucosterol, Pregnenolone, Lappalanasterol were also reported from *S. lappa* roots. *S. lappa* has three anthraquinone compounds, namely, Aloeemodin- 8-O- β -d-glucopyranoside, Rhein-8-O- β -d-glucopyranoside and Chrysophanol, which inhibited the activity of protein tyrosine phosphatase (PTP-1B). (Li *et al.* 2006) [32] 3- β -Acetoxy-9(11)-baccharene, α -Amyrin (Yang *et al.* 1997a,b) [55, 56] and α -Amyrin eicosanoate were triterpenes reported from the roots of *S. lappa*. (Robinson *et al.* 2010) [46]. Saussurine relieves smooth muscle spasms of the bronchi and gastrointestinal tract. Shikokiols possessed antitumor activity (Jung *et al.* 1998) [24], whereas chlorogenic acid prevented oxidation and removed free radicals. (Jeong *et al.* 2007) [23].

3. Pharmacological activities

3.1 Antiulcerogenic activity

Ethyl acetate extract of *S. lappa* roots was found to be effective in different model of gastric and duodenal ulceration in rats. The extract was induced at two doses 200 and 400 mg/kg body weight, 30 min prior to ulcer induction. Gastric ulceration was caused by oral administration of ethanol and aspirin whereas pyloric and duodenal ulcer was induced by cysteamine hydrochloride. Ranitide at dose of 50 mg/kg a standard drug and the results revealed that at the *S. lappa* showed maximum inhibitory effect on the gastric acid, free acid and total acid by 53.53, 52.55 and 30.30%, respectively at the dose of 400 mg (Niranjan *et al.* 2011) [41].

Herbal formulation, UL-409 consisting *S. Lappa*, one of the major ingredients was tested for its antiulcer activity in Wistar

rats of either sex and in male guinea pigs. 600 mg/kg dose of the drug was given orally and showed significant effect in cold-resistant induced ulcerations, gastric ulceration induced by alcohol and aspirin, cysteamine and histamine induced duodenal ulcer models (Mitra *et al.* 1996)^[35].

3.2 Anti-cancer activity

The major components of *S. lappa* i.e. Alantolactone, Caryophyllene, Costic acid, Costunolide, and Dehydrocostuslactone were tested against HaCaT human keratinocyte cell line. HaCaT cells were stimulated with tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ), and treated with *S. lappa* or each of five marker compounds. Chemokine production and expression were analyzed by enzyme-linked immunosorbent assay and reverse transcription-polymerase chain reaction, respectively. Phosphorylation of signal transducer and activator of transcription (STAT) 1 was determined by immunoblotting. Stimulation with TNF- α and IFN- γ significantly increased the production of the following chemokines: Thymus-regulated and activation-regulated chemokine (TARC), regulated on activation normal T-cell expressed and secreted (RANTES), macrophage-derived chemokine (MDC) and interleukin-8 (IL-8). By contrast, *S. lappa* and the five marker compounds significantly reduced the production of these chemokines by TNF- α and IFN- γ -treated cells. *S. lappa* and alantolactone suppressed the TNF- α and IFN- γ -stimulated increase in the phosphorylation of STAT1 (Lim *et al.* 2015)^[33].

Cytotoxicity studies of the chloroformic extract of *S. lappa* were carried out on three cancer cell lines - HT-29 (Colon cancer), A549 (Lung cancer) and MDA-MB (Breast Cancer). Cytotoxic activity on breast cancer cell lines (MDA-MB) was nearly comparable to that of the standard compound, doxorubicin. However, it was not significant on the other two cell lines (HT-29 and A549) studied. (Sunkara *et al.* 2010)^[49]. Youn *et al.* (2013)^[60] demonstrated that Costunolide extracted from *S. lappa* suppressed tumour growth and metastases of MDA-MB-231 highly metastatic human breast cancer cells via inhibiting TNF α -induced NF- κ B activation. Costunolide inhibited MDA-MB-231 tumor growth and metastases without affecting body weights in the *in vivo* mouse orthotopic tumor growth assays. In addition, Costunolide inhibited *in vitro* TNF α -induced invasion and migration of MDA-MB-231 cells thus it is concluded that *S. lappa* and its derivative Costunolide suppressed breast cancer growth and metastases by inhibiting TNF α -induced NF- κ B activation, which suggested that Costunolide as well as *S. lappa* Clarke may be promising anticancer drugs, especially for metastatic breast cancer.

Azhar *et al.* (2012)^[5] showed that the antitumor capacity of Costunolide was due to inhibition of proliferation, invasion and metastasis, as well as induction of apoptosis, which indicated that Costunolide possessed potential to become an effective and systemic antitumor remedy. Treatment with *S. lappa* extract onto KB cells reduced cell viability significantly with an IC₅₀ value of 300 μ g/mL. Thus it can be concluded that *S. lappa* extract inhibited cell proliferation through the apoptosis pathway in KB human oral cancer cells (Moon *et al.* 2013)^[38].

A study revealed that treatment with *S. lappa* dramatically reduced cell viabilities in dose and time dependent manner as compared to *Taraxacum mongolicum* flow cytometry analysis and Annexin V staining assay showed that *Saussurea lappa* induced apoptotic cell death of human gastric cell line and expression analyses via reverse transcription polymerase

chain reaction (RT-PCR) and Western blots revealed that *S. lappa* increased expression of the p53 and its downstream effector p21 Waf1, and that the both increased expression of apoptosis related Bax and cleavage of active caspase-3 protein. (Seung *et al.* 2004)^[47]

Hubal (2005)^[22] reported that *S. lappa* showed strong anticancer activity against malignant, leukaemia and lymphoma. It was may be due to main chemical constituents Costunolide, Dehydrocostus lactone and Cynaropicrin. However Umadevi *et al.* (2013)^[53] also reported that water extract of *S. lappa* inhibited the growth and spread of intestinal cancer may be due to the presence of Costunolide. Mokokolactone and an alkaloid isolated from *S. lappa* induced apoptosis in leukaemic cells. Shikokiols isolated from *S. lappa* revealed anticancer activity due to inhibited growth and spread of cancer by arresting cancer cell division in G2 phase of cell cycle and induced apoptosis against various cancers of the ovary, lung, colon and central nervous system (Ko *et al.* 2005)^[30].

3.3 Anti-inflammatory activity

In vitro anti-inflammatory activity was evaluated by monitoring the TNF- α levels and Nitric Oxide (NO) levels in mouse macrophage cells. RAW-264.2 mouse macrophage cells were cultured in T25 flasks in Dulbeccos Modified Eagles Medium (DMEM) without phenol red and 10% heat inactivated serum at 37 °C temperature and 5% CO₂ with 90% relative humidity. After 85% confluence, cells were trypsinized with trypsin and ethylene diamine tetra acetic acid (EDTA) solution and plated in 12 well plate at a density of 1 x 10⁵ cells to each well and incubated at 37 °C for 24hrs and results indicated that the test compound exhibited significant effect on TNF- α levels. The percent inhibition of TNF- α by the test compound was 33.76% (Sunkara *et al.* 2010)^[49].

Damre *et al.* (2003)^[12] reported that the sesquiterpene lactone fraction of *S. lappa* roots were evaluated for their effect on the transudative, exudative and proliferative phases of inflammation using the cotton pellet granuloma assay in rats, revealed that fraction (25–100 mg/kg, p.o.) showed significant dose-dependent inhibition of the increase in wet weight of the cotton pellet at 3hrs (transudative phase). Thus anti-inflammatory activity of the sesquiterpene lactone fraction of *S. lappa* may be due to stabilization of lysosomal membranes and an antiproliferative effect.

3.5 Antibacterial activity

The aqueous and methanol extracts of 12 plants including *S. lappa* each belonging to different families were evaluated for antibacterial activity against medically important bacteria viz. *Bacillus cereus* (ATCC11778), *Staphylococcus epidermidis* (ATCC12228), *Enterobacter aerogenes* (ATCC13048), *Proteus vulgaris* (NCTC 8313), *Salmonella typhimurium* (ATCC 23564). The *in vitro* antibacterial activity was performed by agar disc diffusion and agar well diffusion method. The result revealed that aqueous extracts were inactive but methanol extracts showed some degree of antibacterial activity against the tested bacterial strains (Parekh and Chanda 2007)^[42].

Dose dependent antibacterial activity of the ethanolic extract of *S. lappa* root against human bacteria isolates through the agar diffusion method (zone of inhibition in mm) was reported. The extracts showed significant inhibitory activity against clinical isolates of methicillin resistant: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumonia* and extended

spectrum beta-lactemase: *Acinetobacter baumannii*. The minimum inhibitory concentration values obtained using the agar dilution test ranged from 2.0 - 12.0 µg/µL. However, the water extract showed no activity at all against tested bacteria. (Hasson *et al.* 2013)^[20].

The *in vitro* antimycobacterial activity of *S. lappa* was investigated where oil, its fractions and pure active compounds were determined by fluorometric Alamar Blue microassay (FMABA) and the result revealed that Costunolide and Dehydrocostuslactone were mainly responsible for antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv with MICs of 6.25 and 12.5 mg/L, respectively. Antimycobacterial activity was found to be better for the mixture than pure compounds thus both lactones presented synergistic activity, i.e. analysis of relative fluorescence units presented an X/Y value <0.5 at a concentration of 1/8 MIC of each compound in the combination. (Herrera *et al.* 2007).^[21]

The petroleum ether, chloroform, methanol and water extracts of *S. lappa* were assessed by the cup plate diffusion method against two standard Gram positive: *K. pneumoniae* and three standard Gram negative bacteria: *Bacillus subtilis*; *S. aureus*; *E. coli* and *P. aeruginosa*. The chloroform extract showed the highest activity (Alaagib and Ayoub, 2015).^[1]

3.6 Hepatoprotective activity

The aqueous-methanolic extract of *S. lappa* Clarke roots was investigated against D-Galactosamine (D-GalN) and lipopolysaccharide (LPS)-induced hepatitis in mice. Co-administration of D-GalN (700 mg/kg) and LPS (1 microg/kg) significantly raised the plasma transaminase levels (ALT/AST) as compared to the control group ($p < 0.05$). Pretreatment of mice with different doses of Sl.Cr (150, 300 and 600 mg/kg) significantly prevented the D-GalN and LPS-induced rise in plasma levels of ALT and AST in a dose-dependent manner ($p < 0.05$). Post-treatment with *S. lappa* (600 mg/kg) significantly restricted the progression of hepatic damage induced by D-GalN and LPS ($p < 0.05$). The improvement in plasma enzyme levels was further verified by histopathology of the liver, which showed improved architecture, absence of parenchyma congestion, decreased cellular swelling and apoptotic cells in treatment groups as compared to the toxin group of animals. These data indicated that the *S. lappa* exhibited hepatoprotective effect in mice and study rationalized the traditional use of this plant in liver disorders (Yaesh *et al.* 2010)^[54].

Alnahdi *et al.* (2016)^[2] investigated the hepatoprotective effect of *S. lappa* versus liver toxicity induced by deltamethrin exposure. Experimental design: Sixty adult male albino rats *Rattus norvegicus* (150-180 gm) were divided into 6 groups treated for 28 days as ; G1 control group, G2 (CT = costus 300 mg/ kg), G3 (DH = high dose deltamethrin 1/15 LD₅₀; 4 m/kg), G4 (CTDH), G5 (DL = low dose deltamethrin 1/30 LD₅₀; 2 mg/kg), G6 (CTDL). Results showed remarkable elevation in plasma liver biomarkers; alanine aminotransferase (ALT), aspartate aminotransferase (AST) alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) in both deltamethrin treated groups, as well as slight elevation total plasma proteins. These results were in consequence to the recorded significant reduction in the defence system biomarkers (SH-protein) and antioxidant enzymes; superoxide dismutase (SOD), catalase and detoxifying enzyme glutathione s-transferase (GST). Degeneration in hepatocytes with congestion in the central veins was recorded in liver tissues. However supplementation

with 300 mg/kg aqueous extract of costus *S. lappa* induced partial counteract in the above tested parameters especially in CTDL group. Thus aqueous extract of *S. lappa* induced early improvement in injured liver that promised better results on longer repeated use.

3.8 Immunomodulatory activity

The immunomodulatory effect of hydroalcoholic *S. lappa* root extract was observed at the dose of 100 and 200 mg/kg and found that at 250mg/kg showed no significant effect on humoral immunity and number of antibody producing cells of spleen, reflecting *S. lappa* showed no effect on such responses on short term treatment. Higher dose of *S. lappa* extract showed potentiation of immunomodulatory activity in both humoral as well as cellular arms of the immune system (Pandey 2012)^[43].

A study conducted on Costunolide and Dehydrocostus lactone which were isolated from an extract of *S. lappa* reported that Constunolide inhibited the killing activity of CTL through preventing the increase in tyrosine phosphorylation in response to the crosslinking of T cell receptors (Taniguchi *et al.* 1995, Pandey *et al.* 2007)^[50, 44].

3.9 Cardiovascular diseases

The investigation of cardioprotective effect of aqueous extract of root of *S. lappa* against administration of isoproterenol at (85 mg/kg) induced myocardial injury revealed that myocardial injury in rat. The rats were pretreated with the aqueous extract of *S. lappa* in three different doses (100, 200 and 300 mg/kg) through the oral route. It was observed that AESL at 200 mg/kg only significantly reduced the oxidative stress and lower (100 mg) or higher (300 mg) doses offered no significant protection against oxidative stress. The mechanism of such protection by the chronic oral administration of AESL may be due to myocardial adaptation, oxidative stress is mediated through reduction in the TBARS level (Mohamed *et al.* 2013)^[36].

The cardiac activity of *S. lappa* roots was evaluated in isolated perfused rabbit heart by the Langendorff's technique. Heart rate, contractility and coronary flow were determined in the presence of different concentrations of methanolic extract of *S. lappa*, digoxin and diltiazem. It results revealed that methanolic extract of *S. lappa* showed the cardiotonic effects of methanolic extract of *S. lappa*, which might be due to the presence of flavonoids, sesquiterpene lactones, calcium channel blocker and cholinergic constituents (Muhammad *et al.* 2013)^[39].

3.10 Anticonvulsant

Anticonvulsant activity of petroleum ether, alcoholic and water extract of *S. lappa* was evaluated against pentylenetetrazole and picrotoxin-induced convulsions, and maximal electroshock (MES) test in mice. It was found that petroleum ether extract of *S. lappa* roots showed potent anticonvulsant activity against pentylenetetrazole and picrotoxin-induced convulsions in mice, by elevating the seizure threshold through GABAergic the mechanism (Ambavade *et al.* 2009)^[3].

3.11 Larvicidal activity

Dehydrocostus lactone and Costunolide exhibited strong larvicidal activity against *A. albopictus* with LC₅₀ values of 2.34 and 3.26 µg/mL, respectively, while the essential oil possessed LC₅₀ value of 12.41µg/mL. The result indicated that the essential oil of *S. lappa* and the two isolated constituents

possessed potential for use in control of *A. albopictus* larvae and could be useful in search of newer, safer and more effective natural compounds as larvicides (Liu *et al.* 2012)^[34].

3.12 Angiogenesis activity

An experiment reported that Costunolide, a sesquiterpene lactone constituent isolated from *S. lappa* exhibited an antiangiogenic effect by inhibiting the endothelial cell proliferation which was induced by vascular endothelial growth factor (VEGF). During *in-vitro* method of chemotaxis induced by VEGF of human umbilical vein endothelial cells (HUVECs) was significantly inhibited at IC₅₀ of 3.4 μM. The same compound was tested for angiogenesis for *in-vivo* method by mouse corneal micro pocket assay the neo vascularisation of mouse corneal induced by VEGF significantly inhibited at 100 mg/kg/day, which demonstrated its angiogenesis effect (Thara and Zuhra 2012, Mohammad *et al.* 2013)^[52, 37].

3.13 Antidiarrheal activity

Negi *et al.* (2013)^[40], reported antidiarrheal activity of *S. lappa* oil and major constituents. Five groups of Wistar rats (210 to 230 g), each group consisting of five animals were taken for the study. Group I was kept as control, providing only saline while group II, III and IV were considered as test group, and the plant extracts (100, 300 and 500 mg/kg body weight) were administered orally. The fifth group received the standard drug loperamide (5 mg/kg body weight). It was observed that three different doses of 100, 300 and 500 mg/kg inhibited diarrhoea by 26.33, 32.28 and 66.77%, respectively. Thus methanolic extract of *Saussurea lappa* significantly protected the rats against diarrhoea evoked by castor oil in dose dependent manner. β-Costol and δ-Elemene were found as major components in the extracted essential oil.

3.14 Anti-epileptic activity

The alcoholic extract of root of *S. lappa* exhibited significant anti-epileptic activity maximal electroshock seizure (MES) induced convulsions and Pentylentetrazole-induced seizures PTZ-induced convulsions at the doses of 50, 100 and 200 mg/kg p (Gupta *et al.* 2009, Harish *et al.* 2010)^[15, 19].

3.15 Antihyperlipidemic activity

The ethanolic extract of *S. lappa* reduced the triglycerides level and significantly increased the HDL-C level in both serum and as well as in tissue (Anbu *et al.* 2011)^[4].

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