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Medicine

A COMPREHENSIVE REVIEW OF THE CRITICALLY ENDANGERED MEDICINAL PLANT *SASSURAE COSTUS*

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ABSTRACT *Saussurea costus* (Falc.) Lipschitz, syn Saussurea lappa is an important medicinal plant and widely used for several diseases including anti-inflammatory, hepatoprotective, anti-ulcer, anti-cancer, immunomodulatory from last three decades. A number of in vivo and invitro experiments reveal that Saussurea costus exhibit a good potential against various diseases lending support the use in traditional medicine. This plant has a great demand in the market and indiscriminate harvesting from the wild leads to the depletion of the population of Saussurea costus and become critically endangered. This review will provide detailed botany, chemistry, and pharmacology of Saussurea costus reported by researchers.

KEYWORDS : Saussurea costus, Phtochemistry, History, critically endangered.

INTRODUCTION

Plants have been used by human beings for treating various ailments since time immemorial and *Saussurea lappa* is one of them. It is a potential herb belonging to the family Asteraceae and is indigenous to India, Pakistan and China. It grows in the Himalaya region at 2500 - 3500 m altitude. It is a well-identified medicinal plant and has several medicinal in several indigenous systems of medicine all over the world. Chemical constituents like Costunolide, dehydrocostus lactone and cyano-picrin isolated from costus have been documented to have more ability to be developed as bioactive molecules. China is the biggest exporter of about 1024 tons from 1983 to 2009 and India is the second largest exporter of about 266 tons in the same period. It is used to cure various diseases and disorders in ethnobotany such as headache, stomach ache, epilepsy, leprosy, typhoid and chemicals extracted from the roots of the plant show several pharmacological activities like anti-cancerous, anti-inflammatory and antimicrobial etc. Saussurea genus has over 300 species, 61 of which are found in India[1,2]. Every life form is found in this family such as annual, biennial, perennial herbs, shrubs, undershrubs, climber, trees and some aquatic also. There are a number of plants of this family found very useful in the traditional health care system. *Saussurea costus* (Falc.) Lipschitz, syn *Saussurea lappa* C.B. Clarke, one of the best-known species within this genus, is commonly known as costus in English and has different vernacular names in India like, Kut (Gujrati), Kur (Bengali), Postkhai (Kashmiri), Sepuddy (Malayalam), Kot (Punjabi), Kushta (Sanskrit), Kostum (Tamil), Kustam (Telgu), Kushta (Marathi), Koshta (Kannada) and Kuth (Hindi) [3]. *Saussurea costus* (root oil and roots) has become an important drug in the international market.

Population Structure

Convention on International Trade in Endangered Species of Wild Fauna and Flora in 1985, *S. costus* was listed in Appendix I of CITES (the Convention on International Trade in Endangered Species of Wild Fauna and Flora) as a severely endangered species in its natural habitat because the mature plant is removed for its roots. It is an export-quality medicine that is sent to China, Japan, and other European nations. Commercial cultivation had begun in 1930–1940 in Jammu and Kashmir, Lahul-Spiti, and Garhwal as its natural habitat amid the degradation in its native habitat.

Botanical Description

S. costus grows to a height of 1-2 meters and is a perennial herb. The leaves are lobate and about a meter in length, on a single stalk. Clusters of flowers make up the arrangements. The flower clusters are roughly 3–5 cm in diameter, lack a stalk, are rigid and spherical, and range in color from dark blue to black. Between the months of July and August, you can enjoy its beautiful blossoms. Fruit is around 3 mm in length, curled, cupped, and compressed. The root is 60 centimeters in length and has a potent, distinctive perfume. A mild bitterness can be detected in the dried roots. Harvesting occurs in the fall months of September and October[4].

Ethnobotanical Description

From ancient times, the people who live in the Himalayan region have relied on the products of the forest. Different diseases can be treated using the inherited traditional knowledge. The Himalayan tribes employed the root of *S. costus* either alone or in conjunction with other medicines to treat ailments like asthma, cough, cholera, leprosy, rheumatism, stomachaches, toothaches, typhoid fever, hair wash, diarrhoea, dysentery, neurological disorders, irregular menstrual issues, etc. In some areas, it is also used as a deodorant, antibacterial, treatment for high blood pressure, and liver dysfunction. In addition to these, this plant was a primary component of medicines in various Indian medical systems, including Ayurveda, Siddha, and Unani, as well as Chinese systems. Ayurveda, Siddha, and Unani, three of the Indian medical systems, use Saussurea costus either alone or in conjunction with other medications. Its roots are primarily utilized as an antispasmodic in the treatment of asthma, cough, cholera, chronic skin conditions, and rheumatism [5,6].

Pharmacology:

In numerous invitro and invivo experimental scenarios, several researchers have discussed the varied biological activities of *Saussurea costus*. It has been discovered that various extracts from this plant have anti-inflammatory, hepatoprotective, anti-ulcer, anti-cancer, immunomodulatory, and pesticidal properties.

Anti-inflammatory:

The anti-inflammatory activity of *Saussurea costus* manifests primarily as an inhibitory effect on pro-inflammatory cytokines mediated by its active components. At doses between 50 and 200 mg/kg, ethanolic extract reduces acute and chronic inflammation in mice and rats[7]. It reduces the production of inflammatory chemokines and cytokines, such as thymus activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC), and prevents the accumulation of infected cells at doses of 50–200 mg/kg of body weight (MDC). It has been discovered that certain isolated substances, including costunolide, dehydrocostus lactone, cynaropicrin, saussureamine A, B, and santamarin, have anti-inflammatory properties. The synthesis of inflammatory mediators and the growth of lymphocytes both are inhibited by cynaropicrin [8]. Homoeopathic dilutions of Saussurea costus roots have been investigated as potential treatments for autoimmune and chronic inflammatory diseases. The maximal leukocyte phagocytic activity to clear the soluble immune complexes that cause chronic inflammatory damage to tissue has been demonstrated to occur at a concentration of 2 M. Through a cell-mediated cytokine pathway, Saussurea costus's suppression of lymphocyte proliferation and IFN-gamma may help to reduce immune-mediated inflammatory responses [9]. In traditional Korean medicine, Saussurea costus is regularly prescribed for inflammatory illnesses. At a final dose of 0.1 mg/ml, its complete methanol extract showed a more than 50% suppression of the induction of cytokine-induced neutrophil chemotactic factor (CINC) [10]

Hepatoprotective:

Costunolide and dehydrocostus lactone are two active components that showed a considerable suppressive effect on the production of the hepatitis B surface antigen (HBsAg) in human hepatoma Hep 3B cells, but they had very little effect on the viability of the cells. In a dose-dependent manner, both costunolide and dehydrocostus lactone were able to suppress the production of HbsAg by Hep 3B cells. The IC50 values for these two compounds were 1.0 and 2.0 M, respectively.

Northern blotting analysis demonstrated that the suppression of HBs Ag gene expression by both costunolide and dehydrocostus lactone was primarily at the mRNA level. The inhibitory impact of costunolide on the reproduction of human life cells was also seen in another human hepatoma cell line known as Hep G2, which was produced from Hep G2 cells through the process of transfecting a tandemly repeating hapatitits B virus DNA. These two drugs were able to inhibit the production of mRNA for HbsAg in Hep A2 cells, yielding the same result. These two medications had the potential to be developed into treatments that are effective against HBV[11]

Anti-ulcer And Cholagogic:

Both the acetone extract of *Saussurea costus* and its active component, costunolide, prevented stomach ulcers from forming in mice, demonstrating their cholagogic and inhibitory effects[12]. During the perfusion of *Saussurea costus* decoction into the stomachs of patients with chronic superficial gastritis, variations in gastric acidity output, serum gastrin, and plasma somatostatin concentration were seen. Decoction could hasten stomach emptying and boost endogenous motilin release[13]. *Saussurea costus* is a key element in the formulation UL-409, which has anti-ulcer action[14]

Immunomodulator:

An extract of *Saussurea costus* was used to isolate two compounds that suppress the killing activity of cytotoxic T lymphocytes. These compounds are costunolide and dehydrocostus lactone, respectively. By inhibiting the rise in tyrosine phosphorylation that occurs in response to the cross-linking of T cell receptors, costunolide was able to stop CTL from engaging in their killing activity[15]. On the basis of the structure-activity relationship as inhibitors of the killing function of CTL and the induction of intercellular adhesion molecule-1 [ICAM-1], mokko lactone, dehydro costus lactone from Saussurea costus, and other guaianolides were studied. It was found that the guaianolides with a methylene-lactone moiety significantly inhibited both the killing activity of CTL and the induction of ICAM-1[16]

Bronchitis:

Chronic bronchitis and asthma are combated by Saussurea costus extract. When induced by histamine, it demonstrated a clear spasmolytic action on the smooth and tracheal muscles of the guinea pig and an antispasmodic impact on the isolated, perfused guinea pig lungs. Petroleum ether extract from the Saussurea tincture has also been the subject of studies. Saussurea tincture made from defatted roots and extracts obtained through repeated extraction of saussurea costus roots. In guinea pigs, tincture saussurea and petroleum ether extract caused bronchoconstriction, but had no such effects in those animals, indicating that tincture saussurea without the petroleum ether soluble fraction would be an effective treatment for chronic bronchitis and asthma[17,18]

Hypolipidimic:

The hypolipidemic effect of an aqueous extract of Saussurea costus was seen when it was given orally to twenty-seven rabbits at a dose of two milligrams per kilogram of body weight. It was discovered that there was a considerable reduction in both serum cholesterol and serum triglycerides[19]

Hypoglycaemic:

When a comprehensive surgical and clinical study on potent hypoglycaemic plants from various regions in India was conducted to find antidiabetic plants that were used in Indian folklore and by different tribes, Saussurea costus was found to be the most effective for obese patients who also suffered from diabetes[20].

Antiparasitic:

The effectiveness of Saussurea costus as an antiparasitic agent was examined in relation to infections caused by clonorchis sinensis, Trypanosoma cruzi, and several nematode species. The impact of Saussurea costus as an antinematodal drug was evaluated based on percentage reductions in the number of faecal eggs per gram (EPG) counts in children who had spontaneously acquired infections with the relevant worms[21]. The methanolic extract of Saussurea lappa was evaluated in vitro with the epimastigote form of Trypanosoma cruzi, clone Bra C15 C2, at a temperature of 270 degrees Celsius in F-29 medium at a concentration of 100 micrograms per milliliter in axenic cultures[22]

CNS-Depressant

Dehydrocostus lactone and costunolide from *Saussurea costus* exhibited CNS depressive activity by lengthening the time that it took for hexobarbital to induce sleeping and lowering both the body temperature and the nociception and spontaneous locomotor activity of the subjects [23]. Women who were in labor found that reducing their intake of the essential oil of *Saussurea costus* helped reduce the symptoms associated to the pain that they experienced during the process of labor. The medication alleviated worry, apprehension, and related symptoms, caused only mild drowsiness, and had no negative impact on either the mother or the developing fetus[24].

Anticancer/Antitumor

Costunolide, an active chemical derived from Saussurea costus root, was studied for its effect on inducing apoptosis in HL-60 human leukemia cells. Costunolide is a powerful inducer of apoptosis and enhances its action via ROS production, causing mitochondrial permeability transition (MPT) and cytochrome C release to the cytosol. Nacetylcystein prevented ROS generation, mitochondrial modification, and apoptosis in costunolide-treated cells (NAC). Cyclosporine A inhibits permeability transition and apoptosis. Costunolide increases ROS-mediated mitochondrial permeability and cytochrome C release. First report on constunolide's anticancer mechanism[25]. An AGS stomach cancer cell line was used in a study to investigate the molecular mechanism underlying the anticancer activities of Saussurea costus. Dose- and time-dependently, Saussurea costus lowered cell viability. FACS and Annexin V staining assays demonstrated Saussurea lappa triggered AGS apoptosis. RT-PCR and Western blots showed that it boosted p53 and p21Waf1 expression, as well as apoptosis-related Bax and active caspase-3 protein cleavage. It confirmed Bax's mitochondrial translocation. These effects were linked with down- and up-regulation of growth regulating apoptotic and tumor suppressor genes, respectively[26].

Phytochemistry

Semmler and Feldstein published the initial phytochemical investigation of *Saussurea costus* in 1914, followed by their supplementary study[27]. Despite the fact that two lactones with the molecular formulas $C_{15}H_{22}O_2$ and $C_{15}H_{20}O_2$ were isolated from *Saussurea costus's* root oil, their chemical structure and identity could not be determined. Salooja et al. examined the phytochemical composition of *S.costus* root oil in 1950. Later, around 1951, research by Rao and Verma showed the isolation of two novel crystalline lactones from the *S.costus* plant ; costunolide and saussurea lactone $C_{15}H_{20}O_2$[28].The phytochemical examination of *S.costus* confirms the presence of a number of secondary metabolites, including sesquiterpenes, terpenes, tannins, flavanoids, and alkaloids[29] . The percentage of sesquiterpenoids (79.80%) in *Saussurea costus's* essential oil is higher than that of monoterpenoids (13.25%)[30].

Costic, palmitic, and linoleic acids, as well as costunolide, dehydrocostuslactone, Alantolactone, cyclocostunolide, isozaluzanin-C, isoalantolactone, cyclocostunolide, isodehydrocostus lactone, guiainolides,4-methoxydehydrocostuslactone, saussurealdehyde, 12 –methoxy dihydro dehydro dehydrodehydrolactone, and isodehydrocostus-lactone Sesquiterpene lactones, 15-aldehyde 11,13-epoxy-isozazulanin-C, 11,13-epoxy-dehydroisozaluzamine, and 11,13-epoxydehydrocostuslactone Cynaropicrin, Reynosin, 3-keto dehydrocostus-lactone, and Santamarine, 6,10-dimethyl9-methyleneunused Additionally isolated were -S-E-en-2-one, (+)-germacrene A, and germacra-1[28] .Various other components such as 22-Dihydrostigmasterol, β-sitosterol, Shikokiols, lappalone were also fractionated from the roots of the plant.

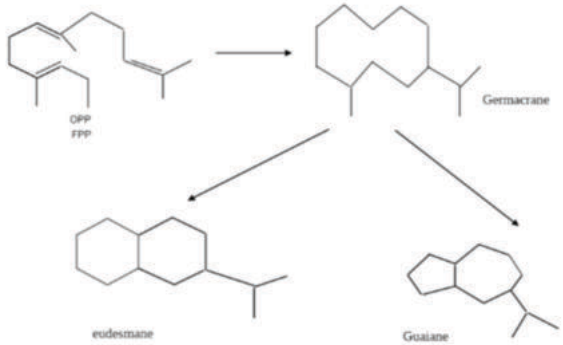


Fig.1 *Depicts The Biosynthesis Of Guaiane And Eudesmane From Farnesyl Pyrophosphate.*

According to their carbocyclic skeleton, the three types of sesquiterpnes found in Saussurea costus' sesquiterpene-rich species are Guaiane, Germacrane, and Eudesmane. Eudesmane and guaiane are produced by the acetate-mevalonate FPP route from the germacrane precursor[31].The oxidative sesquiterpene cyclase enzyme germacrane synthase is responsible for catalyzing the process. The site of enzyme-mediated epoxidation determines whether germacrane transforms into eudesmane or guaiane. Guaiane is produced by the germacrane C_4–C_5 epoxide, whereas eudesmane is produced by the germacrane C_1–C_{10} epoxide. Apart from germacrane synthase, an oxidizing enzyme, the biosynthesis of guaianolides and eudesmanolides involves two other enzymes that can cycle FPP into the skeleton of germacrane and another enzyme that can cycle germacrane into guaiane or eudesmane[32].

Sesquiterpenes

The presence of secondary metabolites including terpenoids, phenolics, flavonoids, and polyacetylenes, among others, is what gives plant extracts their most pervasive and physiologically active impact. FPP serves as the precursor for the colorless lipophilic sesquiterpenoids' biosynthesis in the endoplasmic reticulum. Sesquiterpenoids have 15 different carbon backbone configurations, the majority of which have cyclic topologies[33]. According to the research by Hahn et al., chromatographic methods were used to isolate 16 sesquiterpenoids from Saussurea costus plant root extracts. Along with established substances like costulide, 11β,13-dihydrozalanzamin, and 3β-[4-hydroxymethacryloyloxy-]8α-hydroxycostunolide, new substances like saussucostusoides A and B were also identified from the plant extract. Through NMR and HR-QTOF-MS investigations, it was possible to derive the chemical structure of these isolated molecules[34]

Eudesmane.

The eudesmanoids are biosynthesized from Farnesyl pyrophosphate, and over 1000 naturally occurring eudesmanoids from the Asteraceae family have been found. These eudesmanoids show a wide range of oxygenation and cleavage patterns[35]. The chemical structutre of Eudemane is indicated in Figure 2.

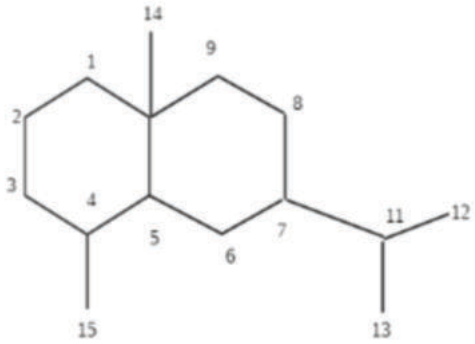
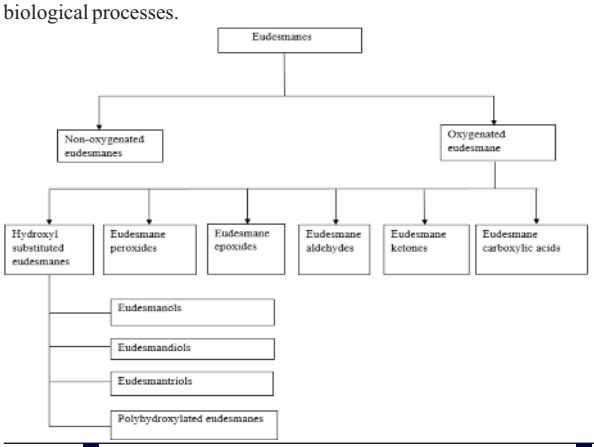


Fig.2 *Represents The Chemical Structure Of Eudemane.*

The eudesmanoids are divided into distinct groupings based on oxygenation and cleavage characteristics. In the flow chart provided below, the categorization heirarchy of eudesmanoids is displayed. The eudesmane type sesquiterpenoids help the Asteracea family's pharmacological and phytochemical functions, among other biological processes.



Non-Oxygenated Eudesmanes

The Asteracea family scarcely possesses non-oxygenated eudesmane, commonly known as eudesmene isolated from *Urisinia trifida.*

Oxygenated Eudesmanes

In Asteraceae species, oxygenated eudesmanes, which comprise alcohols, aldehydes, ketones, carboxyl acids, ethers, epoxides, peroxides, and lactones, make up the majority of the sesquiterpenoids. The numerous functional groups play a crucial role in determining the diverse sesquiterpenoids' unique biological actions. The oxygenated eudesmanes are further classified into Hydroxyl substituted eudesmanes, Eudesmane peroxides, Eudesmane epoxides, Eudesmane aldehydes, Eudesmane ketones and Eudesmane carboxylic acids according to the presence of functional groups. Among this, the Saussurea genus comprises eudemantriols belonging under the Hydroxyl substituted eudesmanes[35].

Hydroxyl substituted eudesmane class involves eudesmane compound bearing a hydroxyl group or an OH group. The eudesmane triols as the name suggests, are compounds with 3 hydroxyl groups attached to their chemical configuration. Below is a diagram of eudesmane, which denotes it's configuration as 1, 2-isopropyl-4a,8-dimethyldecahydronaphthalene in Figure 3.

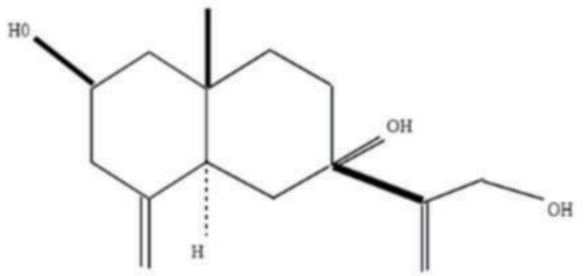


Fig.3 *Represents The Chemical Configuration Of Eudesmantriol.*

Guaiane

Guaiane is a bicyclic sesquiterpene found in about more than 70 plant genera. Sesquiterpenes of the guaiane-type have a variety of biological actions, including anticancer, anti-inflammatory, and antibacterial properties. According to their structural characteristics, guaiane-type sesquiterpenes can be categorized into five groups: guaianolides, tricycle guaiane-type sesquiterpenes, dimers or trimers containing guaiane-type sesquiterpenes mother nuclei, variant guaiane-type sesquiterpenes, and other guaiane-type sesquiterpenes[36].

Germacrane

Sesquiterpenes, or germacrenes, are a subclass of volatile organic hydrocarbons. Although they also serve as insect pheromones, germacrenes are typically generated by a variety of plant species for their antibacterial and insecticidal activities. Germacrene A and Germacrene D are two important compounds[37].

Flavanoids

Parts and products of plants such as the fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine all contain flavonoids, a class of organic compounds with varying phenolic structures. The health benefits of these natural compounds are well known, and efforts are being made to separate the so-called flavonoids from the other constituents. In a wide range of nutraceutical, pharmacological, therapeutic, and cosmetic applications, flavonoids are now seen as an essential component. This is demonstrated by their ability to influence important cellular enzyme function in addition to having anti-oxidative, anti-inflammatory effects[38].

Phytosterols

Phytosterols are triterpenes that resemble cholesterol both in terms of their structure ; a four-ring steroid nucleus, a 3bhydroxyl group, and frequently a 5,6-double bond, as well as their function in maintaining phospholipid bilayer stability in cell membranes. Vegetable oils and tall oil are the two main source materials used in the large-scale isolation of phytosterols. Regardless of the provenance, they have been applied to food, medicine, and health. Using phytosterols as raw materials to create therapeutic steroids is an entirely new function for them. In processes involving biotransformations and/or biotransformations, this is carried out. Apart from this, the ability of phytosterols to potentially replace cholesterol as a treatment solution

in patients with hypercholesterolemia is also explored[39].

Triterpenes

Triterpenoid saponins are a varied collection of naturally occurring substances found in plants that are thought to act as protective substances against herbivores and harmful microorganisms. Saponins are employed in a variety of ways besides medicine because of their many advantageous qualities for people[40].

Lignans

Lignans are classified as a type of secondary metabolites called phenylpropanoids (phenylpropane derivatives), which are substances with an aromatic nucleus and a tricarbon chain attached. Lignans are highly prevalent in plant creatures and have a wide range of effects on all organisms, including antioxidant, antibacterial, antiviral, fungicidal, insecticidal, estrogenic, antiestrogenic, anticarcinogenic, and anticardiovascullar properties. The shikimate biosynthesis pathway produces lignans. They come from derivatives of cinnamic acid, which are biochemically connected to the metabolism of phenylalanine[41]

Phenolics

The most prevalent secondary metabolites discovered in plants are phenolics. The primary groupings of phenolic compounds include flavonoids, phenolic acids, tannins, stilbenes, and lignans. Phenolic chemicals having an aromatic benzene ring and one or more hydroxyl groups primarily aid plants in coping with stress. Additionally, they assist in the creation of pigments and lignin, an intricate organic polymer that contains oxygen. Lignin, the second most important component of wood after cellulose.

Three distinct biosynthetic processes, including the shikimate/chorizmate/succinyl benzoate pathway, the acetate/mevalonate or polyketide pathway, and the acetate/mevalonate pathway, are involved in the production of phenolics in plants. Phenyl propanoid derivatives (C6-C3) are produced by the shikimate pathway, while certain quinones, big flavanoids, and phenyl propanoids (C6-C3-C6) are produced by the acetate/malonate pathway. The acetate/mevalonate pathway, generates monoterpenes and other volatile terpenoids. Phenolics have a wide range of bioactive qualities, and while not being nutrients, their consumption has wellbeing benefits. The figure below depicts the concentration of vivid phenolic compounds isolated from the extracts of *Saussurea costus* through the technique of HPLC. According to the studies by Daebes et.al, various components like Gallic acid, Chlorogenic acid,Catechin etc.. are found in the phenolic composition of *Saussurea costus*.

Phenolic compounds	Phenolic compounds Concentrations (µg/g)			
	Ethanol extract	Ethyl acetate	n-Hexane	n-Butanol
Gallic acid	24.8	0.00	75.2	3,830
Chlorogenic acid	27.4	18,269	14.5	10,436
Catechin	0.00	1,708	0.00	256
Methyl gallate	0.56	638.5	0.00	121
Coffeic acid	1.60	3,050	0.00	285
Syringic acid	9.79	1,109	13.6	92.3
Pyro catechol	0.00	1,776	0.00	0.00
Rutin	5.39	0.00	0.00	0.00
Ellagic acid	78.2	6710	43.8	572
Coumaric acid	0.00	0.00	0.00	0.00
Vanillin	17.0	802.31	22.6	73.1
Ferulic acid	19.9	8016.17	18.3	96.3
Naringenin	74.3	133,880	74.3	3,343
Taxifolin	60.9	3,514	53.2	209
Cinnamic acid	47.6	143	55.0	0.00
Kaempferol	16.8	316	14.9	0.00

Fig.4 *Depicts The HPLC Characterization And Identification Of Phenolic Compounds From Saussurea Costus*[42].

CONCLUSION:

The comprehensive review about its pharmacology and phytochemistry leads the escalated demand in the international market. Species is threatened due unregulated collection, over-exploitation, illegal trade and is placed by IUCN in critically endangered category. Need of sustainable collection and habitat management, agrotechnology development and development of invitro protocol required for stop further depletion of the population of species.

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Conflict Of Interest:

Authors have no conflict of interest in publishing the article.

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