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KUSTH (SAUSSUREA LAPPA): VALIDATION OF CLASSICAL PHARMACOLOGICAL PROPERTIES THROUGH REVERSE PHARMACOLOGY

[*1]Sharma Divya, [2]Mishra H. S. and [3]Yadav Arvind

[1]P. G. Scholar, [2]Lecturer Department of Dravyaguna, [3]Professor and Head, Department of Rasshastra and Bhaishajya Kalpana, Lalit Hari State P.G. Ayurvedic College and Hospital, Pilibhit, U.P.

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***Corresponding Author**
Dr. Sharma Divya
P. G. Scholar, Department of Rasshastra and Bhaishajya Kalpana, Lalit Hari State P.G. Ayurvedic College and Hospital, Pilibhit, U.P.

ABSTRACT

Indian Herbs are known for their miraculous action potential, *Kustha* is one of them. *Saussurea lappa* C.B.Clark (*Kusth)* is one of the ten herbs of *Lekhaniya Mahakashaya* of *Charak Samhita* and also well described in *Sushrut Samhita, Ashtang Hridayam, Chikitsa grantha* and *nighantus*. It is the member of family Asteraceae, growing wildly in Jammu and Kashmir in the Kishanganga valley and the higher elevation of Chenab valley. The plant is perennial herb about 1 to 2 m in height, distributed in Himalaya, Kashmir eastward at an altitude between 2500 and 3000 m and also cultivated in Himanchal Pradesh, Uttranchal and Sikkim. It is most commonly used plant in Ayurveda for the management of a large number of ailments from the time of *vedas*. In *Atharveda, Kustha* is known as *Takmnashan* and *Vishvabhesaj* because it is used to pacify various ailments of body. It is used for skin ailment most commonly for leprosy that's why plant got the name *Kustha.* It is traditionally used in the treatment of various ailment i.e., epilepsy, leprosy, rheumatoid arthritis, throat infection and many more. It shows antibiotic, antiulcer, anti-inflammatory, anticonvulsant, antidiarrheal, antihyperlipidemic, larvicidal, cardiovascular and immunomodulatory properties and other biological activities. Some of the major formulations of *Kustha* are *kusthadi churn, kusthadi kwath, kusthadi taila.* Present paper deals with a comprehensive review on classical drug *Kushtha* starting from *vedic* literature to current pharmacological studies.

KEYWORDS: *Kusth*, *Saussurea lappa*, Ayurveda, Pharmacological stydy.

INTRODUCTION

Saussurea lappa C.B.Clarke (Asteraceae) commonly known as *Kusth* because it cures disease[1] is a popular drug which has used globally in various systems of Medicine viz. Ayurveda, Homeopathy, Unani and Chinese from a very long time. In Ayurveda *Kusth* is mainly used in the treatment of *Aamvata, Medoroga, Visarpa, Kasa, Shwasa* as well as used to pacify headache, eye diseases, physical ailments and especially fever hence it is called *Takma-Nashana* (fever destroyer). Clinical and experimental studies shows that *S. lappa* has antibacterial, anti-inflammatory, anticancer, hepatoprotective, Antihyperlipidemic**,** immunomodulatory properties. Synonyms of *Kustha* mentioned in *Ayurvedic* classics are *Paribhavya* (reduces the impact of disease), *Utpal, Padmaka* (Flower resembles Lotus flower), *Vyapya, Paribhadrak* (grows near swamp and aquatic area) and *Pakal, Pakalam* (helps the wound to ripen). Other common name and synonyms are *Kot, Kur, Kust, Kut, Pachak in Hindi, Costus root* (English), *Kur, Pachak* (Bengali), *Kut, Upaleta* (Gujarati), *Sepuddy* (Malayalam), *Koshnaha, Kust, Kutshirin, Kuttalkh* (Persian), *Kot, Kust, Kut, Kutl* (Punjabi), *Goshtam, Kostam, Putchak* (Tamil), *Changala, Kustam* (Telgu), *Kut* (Urdu).[2]

Geographical Distribution

The plant S. lappa is native to India, Pakistan and China.[3] In India it is found in Himalayan range at an altitude of about 2500 to 3600 meters and in the valleys of the Kishanganga and Chenab rivers of Jammu and Kashmir about 2000 to 4000 meters altitude. According to certain reference of *Atharvaveda Kusth* grew along the *Soma*, especially in the mountains and on the high peaks of the Himalayas *(Himavant)* where the *Uskroshas* had their nests, and from where it was formerly brought to humans.[4] The divine tree *Kusth* is also cultivated in Garwal region of Kashmir, Himanchal Pradesh and Uttar Pradesh.[5]

Morphology[6]

It is a tall robust perennial herb growing to a height of 1-2 m, stem - Simple, stout, pubescent, erect 1-2meter height; leaves - Membranous, scaberulous above, glabrate beneath irregularly toothed. Basal leaves very large 0.6-1.2m long, triangular, with a long lobately winged stalk. Stem leaves smaller, stalked or stalkless, with 2 half stem clasping lobes at the base; Radical Very large, 16-25 cm long, lobately winged petiole. Flower Head stalkless, hard, rounded 2.5-3.8 cm. diameters, 2-5 forming axillary and terminal clusters, Bracts surrounding the heads, many, ovate- lanceolate, long pointed rigid, bent back, hairless. Flowering occurs from July to August. Corolla 2cm. long, tubular, dark blue purple of almost black. Stamens Free,

anther-tails finged. Pappus-hairs 1.7 cm. long, brown, all feathery. Fruits (Achene) Up to 8 mm. long, compressed, curved, tip narrowed, with 1 rib on each face, top contracted, cupped. Seed Inside the fruit is present a single seed surrounded by closely a depressed testa and pericarp. Root Fresh root is 60 cm. long, 30 cm. in girth and carrot like. The root is hot, bitter, sweetish, pungent odour. The dried roots have a strong and sweet aromatic odour and a somewhat bitter taste. They are greyish to dull brown, thick, light, stout, and fusiform to cylindrical 7-15 cm. long and 1-2 cm. thick.

Collection

Collect the root of three- to five-year-old plants in October. After drying it, cut 4-inch-long pieces and dry them again in the sun. thus, it is ready.[v] Seed are collected in the month of September. It can be propagated either by root cutting or by seed. The seed retained their viability for a year or more. In nature the *Kustha* seed lies under the snow in winter and begins to sprout during April to June, as snow melts.[7]

Chemical Composition[8] - The important chemical constituents of *Kustha* are as.

Table 1: Chemical composition of *Kustha* mentioned in classics.

S.No.	Chemical compound	Example
1.	Terpines[9,10]	Monoterpenes like Phellandrene, Anethole, Thymol, Citronellyl propionate, Estragole, a-Thujene. β-Pinene, Camphene, ß-Pinene, Myrcene, Sabinene (12), p-Cymene, Limonene, 1.8 Cincol, y-Terpinene, a-Terpinolene, Linool, Menthone, Citronellal, Terpinen-4-ol, Cryptone, a-Terpincol, Ocimen etc. were reported from S. lappa root.
2.	Sesquiterpenes[11,12,13]	Dehydrocostus lactone, Isomluranin, Zaluzanin C, 11β, 13 Dihydro-3-epzaluzanin C, Cynaropicrin Saussureamine A, B, C, D, and E.
3.	Flavonoids[14]	Luteolin-7-0-B-D-glucoside, Rutin and Apigenin-7-0-B-D-glucoside 3R)-3- Acetoxy- 5,5-dimethylcyclopent-1-en-1-yl)-4-0 methylscutellarein 7-0-(B-0-6-0- acetylglucopyranosyl-(1 3)- [a-L-rhamnopyranosyl- (1-2)]-B-D-glucopyranoside
4.	Phytosterols[15]	Phytosterols like Lappasterol, 3-Epilappasterol, B- Sitosterol, Daucosterol, Pregnenolone, Lappalanasterol
5.	Anthraquinone	Aloeemodin- 8-0-B-d-glucopyranoside. Rhein-8-O-B-dglucopyranoside and Chrysophanol, Kampeferol
6.	Others	Costunolide, ketone.

Classification of *Kusth* in classical texts

In Ayurveda, *Kusth* has been classified variously as on the basis of properties, morphological characters, therapeutic values, *doshkarma*, pharmacodynamics and many more. Classification of *kusth* cited in Table.1.

Table 2: Classification of *Kustha* in various classics.

S.N.	Classical text	*Maha-kashaya / Gana / Varga*	Reference
1.	*Charak Samhita*[16]	*Lekhaniya Mahakasya*	CS.Su.4/3
		Asthapanopaga Mahakasay	CS.Su.4/19
		Sukra Sodhan Mabakasaya	CS.Su.4/25
2.	*Sushruta Samhita*[17]	*Eladi gana*	SS. Su.38/25
		Mustadi gana	SS. Su.38/54
		Sansaman Dravya	SS. Su.39/7
3.	*Dhanwantari Nighantu*[18]	*Chandanadi Varga*	*Varga 3/47-48*
4.	*Sodhal Nighantu*[19]	*Anekartha Varga*	*Anekartha Varga Prathamobhaga-485*
5.	*Madanpal Nighantu*[20]	*Abhayadi Varga*	*Verse 98-99*
6.	*Kaiyadev Nighantu*[21]	*Aushadhi Varga*	*Aushadhi Varga-13-17*
7.	*Bhavaprakasha Nighantu*	*Haritakyadi Varga*	*Verse 173*
8.	*Raj Nighantu*[22]	*Chandanadi varga*	*Verse 115-116*
9.	*Priya Nighantu*[23]	*Shatpuspadi Varga*	*Verse 31-32*
10.	*Shaligram Nighantu*[24]	*Ark varga*	-

AYURVEDIC PHARMACODYNAMICS *(DRAVYA GUNA-KARMA)*

Acharya Charak states that some substances act in accordance with their *Rasa* (taste), some in accordance with their *Vipaka* (post digestive effects), some in accordance with their *Veerya* (potency), and yet others through *Prabhava* (specific action).[25] *Rasa* and *Vipaka* indicate the chemical structure of drugs while *Guna* and *Virya* indicate the pharmacological properties of the drugs.

Pharmacological Properties *(Rasa Panchaka)*

Rasa Panchaka of *Kustha* explained by our *Acharya* are as follows-

Table 2: *RasPanchak* of *Kustha* mentioned in different classics.

S.N.	*Granthas*	*Guna*	*Rasa*	*Vipaka*	*Veerya*
1.	*Sushruta Samhita*	-	-	*Katu*	-
2.	*Dhanwantari Nighantu*	-	*Katu, Tikta*	*Katu*	*Ushna*
3.	*Madanapala Nighantu*	*Madhur*	*Katu*	*Katu*	*Ushna*
4.	*Bhavaprakasha Nighantu*	*Laghu*	*Madhur tikta*	*Katu*	*Ushna*
5.	*Raj Nighantu*	-	*Katu, Tikta*	*Katu*	*Ushna*
6.	*Kaiyadev Nighantu*	*Laghu*	*Madhur,Katu, Tikta*	*Katu*	*Ushna*
7.	*Priya Nighantu*	-	*Katu, tikta*	*Katu*	*Ushna*

From above it is concluded that *Kusth* has *Laghu* (light), *Ruksha* (dry) and *Tikshna* (sharp) *guna* (physical property); *Tikta* (astringent), *katu* (bitter) and *madhur* (sweet) in *rasa* (taste); Hot (*ushna*) in potency (*veerya*) and becomes bitter (*katu*) after intestinal digestion and tissue metabolism (*vipaka*).

Pharmacological Action *(Karma)*- Action over different *doshas* reported in the *Nighantus* are listed in the Table 3.

Table 3: *Dosha-Karma* of *Kustha* according to *Nighantus.*

Karma	**D.Ni.**	**R.Ni.**	**BP.Ni.**	**MP.Ni**	**K.Ni.**	**Pr.Ni.**
Dosha Karma *Vaat dosh hara*	+	+	+	+	+	+
Pitta dosh hara	+	-	-	-	-	-
Kapha dosh hara	+	+	+	+	+	+
Dhatu Karma *Rakt dosha hara*	+	+	+	+	+	+
Mala Karma *Shrushtavinamutra*	-	-	-	-	-	-

Pharmacological uses (*Prayoga*)- Some of the important uses cited in classical texts are listed in the Table 4.

Table. 4: Uses of *S. lappa* in different ailments.

No.	**Diseases**	**D.Ni.**	**R.Ni.**	**BP.Ni.**	**M.Ni.**	**K.Ni.**	**Pr.Ni.**	**Sg.Ni.**
1.	*Vatrakta* (GoutyArthritis)	-	-	-	-	+	+	+
2.	*Dadru* (Ring Worm)	-	+	-	-	-	-	-
3.	*Gulma* (Abdominal lump)	+	-	-	-	-	-	-
4.	*Kandu* (Itching)	+	+	-	-	-	-	-
5.	*Kushtha* (Skin Diseases)	+	+	+	+	+	+	+
6.	*Visarpa* (Erysipelas)	-	+	-	-	+	+	-
7.	*Visha* (Poisoning)	+	+	-	-	+	-	-
8.	*Kasa* (Cough)	-	-	-	-	+	-	+

Traditional methods of application of S. lappa[26]

- A decoction made up of *kusth* root is used in the treatment of stomach-ache, root powder is taken with water also give good results.
- In backache and chest pain, root powder is administered with milk or massage the affected area with oil heated in S. lappa root. This oil is also applied in headache and stomach ache.
- Root powder of S. lappa is given with water in cough and cold.
- In throat infection *Kusth* root is chewed.
- Ghee roasted with *Kusth* root is useful application to rheumatoid arthritis, painful joints and skin rash of insect bite.
- A simple decoction of it, mixed with jaggery is given in scanty urination. Externally the paste of root is applied below umbilicus in it.

- Inhaled the smoke of its burning root in exhaustion.
- For lustre and hair growth, the decoction of root is used for hair wash. Mustard oil heated with root powder topically applied on hair.
- Externally fine powder of its root dusted over pustular wound.
- Root is rubbed in water and used as nasal drop in fainting. Root powder is also used for sneezing in it.
- Boiled milk with *Kusth* root is taken in weakness and fatigue.
- In epilepsy its root powder is administered with honey. Root powder is also administered in hiccups and leprosy.
- *Kusth* root is given along with Acorus calamus in haemorrhoid.
- Powder of *Kusth* root ingested with cow milk and ghee as *Rasayana*.
- Oil extracted from *S. lappa* root is applied in scalp scabies.

Modern Pharmacological Action

Modern scientists have done lot of work regarding pharmacological action and therapeutic uses of this drug. The details are as given below.

S.No.	Pharmacological Action	Part Used	Extract	References
1.	Antihyperlipidemic activity[27]	Root	Ethanol	Anbu J. et al. 2011
2.	Antiulcerogenic activity[28]	Root	Ethyl-acetate	Niranjan S.et al. 2011
3.	Antibacterial activity[29]	-	Aquous. Methanol	Parekh J. et al. 2007
4.	Hepatoprotective activity[30]	Root	Aquous. Methanol	Yaeesh S.et al.2010
5.	Immunomodulatory activity[31]	Root	Hydroalcoholic extract	Pandey R.et al 2012
6.	Cardiovascular activity[32]	Root	Aquous	Mahamed S. et al.2013
7.	Anticonvulsant activity[33]		Petrolium ether. Alcohol. Water	Ambavade S. et al 2009
8.	Larvicidal activity[34]	Essential oil		Liu ZL. et al. 2012
9.	Antidiarrheal activity[35]		Methanol	Negi S.et al 2013
10.	Antiepileptic activity[36]	Root	Alcohol	Gupta P. et al.2009

Anti-arthritic activity- *Kusth* root powder is administered with castor oil in rheumatoid arthritis by *Acharya Bhavmishra.* Hot water extract of *S. lappa* root has been used traditionally in inflammation and rheumatism.[37] Its anti-arthritic property has been validated in-vivo in animal model of male Wistar albino rats where it is treated with Chloroform, Petroleum ether and Alcohol extract of *S. lappa*.[38]

Antiulcerogenic activity- The plant *Kusth* has antiulcerogenic activity. In vivo antiulcerogenic activity of *Kusth* has been seen in cysteamine hydrochloride induced ulcerated rat model when treated with ethyl acetate extract of its root. In this study 30 min prior to ulcer induction, root extract was used in two doses 200 and 400 mg/kg body weight and it showed maximum inhibitory effect on the gastric acid, free acid and total acid at the dose of 400 mg/kg body weight.[39]

Anti-cancer activity- The major components of S. lappa i.e., Alantolactone, Caryophyllene, Costic acid, Costunelide, and Dehydrocosdialactone were tested against ItaCat human keratinocyte cell line. HaCaT cells were stimulated with tumour necrosis factor-alpha (TNF-a) and interferon gamma (IFN-y), and treated with S. lappa or each of five marker compounds, Chemokine production and expression were analysed by enzyme-linked immunosorbent assay and reverse transcription polymerase chain reaction, respectively. Phosphorylation of signal transducer and activator of transcription (STAT) I was determined by immunoblotting. Stimulation with TNF-4 and IFN-7 A 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- (IL- 3) By contrast, S. lappa and the five marker compounds significantly reduced the production of these chemokines by TNF-a and IFN-y-treated cells. S. lappa and alantolactone suppressed the TNF and IFN- y-stimulated increase in the phosphorylation of STAT1.[40]

Anti-inflammatory activity In vitro anti-inflammatory activity was evaluated by monitoring the TNF-a levels and Nitric Oxide (NO) levels in mouse macrophage cells RAW-2642 mouse macrophage cells were cultured in T25 flasks in Dulbeccos Modifiel Eagles Medium (DMEM) without phenol red and 10% heat inactivated senim at 37 C temperature and 5% CO, 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 I 105 cells to cach well and incubated at 37 °C for 24hrs and results indicated that the test compound exhibited significant effect on TNF-al levels. The percent inhibition of TNF-a by the test compound was 33,76%.[41]

Antibacterial activity-The aqueous and methanol extracts of 12 plants including S lappa cach belonging to different families were evaluated for antibacterial activity against medically important bacteria viz Bacillus cerest (ATCC11778), Staphylococcus epidermidis

(ATCC12228), Enterobacter aergenes (ATCC13048), Proteus vulgaris (NCTC 8313), Salmonella typhimurium (ATCC 23564). The in vivo 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.[42]

Hepatoprotective activity- This plant is used in liver disorders in traditional system of medicine. *S. lappa* shows hepatoprotective activity when its aqueous-methanolic extract was investigated against D-Galactosamine lipopolysaccharide (LPS)-induced hepatitis in mice. Co administration of D-GalN (700 mg/kg) and LPS significantly raised the plasma transaminase levels (ALT/AST) as compared to the control group ($p< 0.051$). Pre-treatment of mice with different doses of St.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 ($p< 0.05$). This significant improvement in plasma enzyme levels was further verified by histopathology of liver, which revealed improved architecture, absence of parenchyma congestion, decreased cellular swelling and apoptotic cells in treatment groups as compared to the taxin group of animals. These data indicated that the S. lappa exhibited hepatoprotective effect in mice.[43]

Immunomodulatory activity- The immunomodulatory effect was seen in hydroalcoholic extract of *S. lappa* root. It is used at the dose of 100 and 200 mg/kg. Higher dose of S. lappa extract showed potentiation of immunomodulatory activity in both humoral as well as cellular arms of the immune system.[44]

Cardiovascular diseases- The cardioprotective effect of aqueous extract of root of S. lappa was seen against isoproterenol (85 mg/kg) induced myocardial injury in rat. The rats were pre-treated 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, at 200 mg/kg dose showed significantly reduction in 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 aqueous extract of *S. lappa* may be due to myocardial adaptation, oxidative stress is mediated through reduction in the TBARS level.[45]

Anticonvulsant- Anticonvulsant activity of petroleum ether, alcoholic and water extract of S. lappa was validated against pentylenetetrazol and picrotoxin-induced convulsions, and maximal electroshock (MES) test in mice. It was found that petroleum ether extract of S. lappa roots exhibit potent anticonvulsant activity against pentylenetetrazol and picrotoxin-induced convulsions in mice, by elevating the seizure threshold through GABAergic the mechanism.[46]

Larvicidal activity- The essential oil of S. lappa and the two isolated constituents (Dehydrocostus lactone and Costunolide) possessed potential for use in control of A. albopictus larvae. The essential oil of S. lappa exhibited strung larvicidal activity against A. albopictus with LC value of 12.41pg/ml, while the Dehydrocostus lactone and Costunolide possessed LC values 2.34 and 3.26pg/ml, respectively.[47]

Angiogenesis activity -An in vitro study revealed 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 this study, chemotaxis induced by VEGF of human umbilical vein endothelial cells (HUVECS) was significantly inhibited at ICss of 3.4 M. Costunolide was also tested for angiogenesis via 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 showed its angiogenesis effect.[48]

Antidiarrheal activity- Antidiarrheal activity of S lappa oil and its major constitutes (B-Costol) was observed in a test involving five groups of Wistar rats, each group sting of five animals were taken for the study. Group I was a control group, providing only saline water while group II, III and IV were considered as test group, and the plant extracts (100, 300 and 500 mg/kg body weight) were administrated orally. The fifth group administered the standard drug loperamide (5 mg/kg body weight). It was showed 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. B-Costol and 8-Elemenet were found as major components in the extracted essential oil.[49]

Anti-epileptic activity- The alcoholic root extract of S. lappa exhibited significant anti-epileptic activity maximal electroshock seizure (MES) induced convulsions and

Pentylenetetrazol-induced seizures, PTZ-induced convulsions at the doses of 50, 100 and 200 mg/kg.[50]

Antihyperlipidemic activity- Anti hypercholesterolemic effect of the aq. extract of Indian costus root was examined in diet induced hypercholesterolemic mice. There is administration of single dose of 10 microlitre of aq. extract of Indian costus root everyday through oral route for 3 weeks. As a result, a significant decreased in the body weight compared to untreated hypercholesterolemic mice reported (Kaula Ahmed Saad et.al. 2018). Another study done on 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.[51]

Other Uses- Powder of S. lappa roots are used as insecticide for which it is sprinkled over crops and woollen fabrics. Dried leaves of Kusth are used as tobacco. Its upper part is also used as fuel and fodder.

Substitutes and Adulterants- In the *Ayurvedic* literature there are no references of adulteration starting from *Veda* to *Samhitas* due to the abundance of herbal drugs at that time. *Bhav Prakash Nighantu* has references of substitution for some precious drug which may not be available due to extinction. The credibility of *Ayurvedic* system of Medicine depends on availability of authentic raw material. Adulteration indicates either the admission of impurities or removal of all a part of valuable portion of drug and replacing it with low grade or spoiled drug. Adulteration is done with intension to defraud, or occurred during collection, improper preservation, and packaging. It may also occur due to wrong botanical identification and prevalence as same or similar common names for different plants and many names for a single plant. Substitution is generally done when original genuine material is not available or is not in sufficient quantity. Substitute indicates the replacing of one drug either in whole or in part by another drug. In case of *Kustha* it is substituted with *Pushkarmool* (*Inula racemosa*)[52] and *Arctium lappa* (a plant from same family).

Important Formulation - *Kottachukkadi (Kustha shunthyadi taila) taila., Kusthadi churn, Kusthadi taila.*

Dose –According to A.P.I 0.2-1.0g of the drug in powder form. According to Raj Nighantu- *Churn* (500mg - 3gm) and *Kwath* (50gm – 100gm).

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