



TOXICITY PROFILE AND CHEMICAL CONSTITUENTS OF THE INGREDIENTS OF A SIDDHA DRUG - KANDHAGA RASAYANAM

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ABSTRACT

Siddha system of medicine is a traditional system practised among Tamil speaking people of India. Siddhars, the ancient scientists are the founders of this system. Herbs, minerals/metals and animal products are used in medicine preparation. Kandhaga Rasayanam is a herbo mineral drug mentioned in classic Siddha text. It is used in treating skin diseases, urinary infections, venereal diseases, arthritis etc. The present review is aimed to collect information about toxicity studies and phytoconstituents substantiating the traditional claim of safety and efficacy. Most of the herbal drugs were found to be nontoxic and rich in secondary metabolites responsible for antimicrobial, antifungal and antioxidant properties. This compound drug mentioned in Siddha literature is thus validated.

KEYWORDS: Siddha system, Siddhars, Herbo mineral drug, Kandhaga Rasayanam, skin diseases.



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INTRODUCTION

Siddha system of medicine is one of the ancient system of medicine. The Siddha system has its origin in Lemurian continent. It was followed by Dravidians. Siddha system is associated with religion, culture and philosophy. This system has a holistic approach to treatment. It not only treats the body, but also the mind and the soul. The medicines in Siddha are prepared from herbs, metals/minerals and animal products.¹ Kandhaga Rasayanam is a Siddha drug chosen from the classical Siddha text Siddha Vaidhya Thirattu. It is indicated for skin diseases, urinary tract infections, venereal diseases, arthritis etc.². This review article is aimed to document the chemical constituents, and toxicity profile of each ingredient of Kandhaga Rasayanam. This is to validate the traditional claim in treating the skin diseases, vatha diseases and venereal diseases. The drug acts by the concept of synergism. The drug is in practice since many decades and so far no toxicity was reported. A review of literature through books, articles in journals, publications and through a systematic search through major computerized databases pertaining to toxicity, chemical constituents of each ingredient of Kandhaga Rasayanam were done. The drug has undergone all preliminary analytical studies, toxicity study and has entered into an open clinical trial for treating Tinea infections. (results yet to be published). The results of the preliminary phytochemistry of Kandhaga Rasayanam revealed the presence of many secondary metabolites attributing to its therapeutic activity³. The toxicity profile and phytocostituents are discussed in this review. Drug name:Kandhaga Rasayanam.Dose : 2grams . Twice daily. Source : Siddha Vaidhya Thirattu.

INGREDIENTS OF KANDHAGA RASAYANAM:⁴

The drug consists of 15 herbs and one mineral.The herbs are *Withania somnifera*, *Smilax china*, *Phyllanthus emblica*, *Terminalia chebula*, *Terminalia bellerica*, *Zingiber officinale*, *Piper nigrum*, *Piper longum*, *Embelia*

ribes, *Elletaria cardamomum*, *Santalum album*, *Cinnamomum zeylanicum*, *Cicer arietinum*, *Semecarpus anacardium*, *Plumbago zeylanicum*.The mineral is sulphur. Other names of sulphur are : kaarilayin naadham, parai veeriyam, atheedha prakasam, peejam, selvivindhu, sakthi, sakthi peesam, sendhoorathadhi, dhanam, deviyuram, nadham, natram, parai nadham, ponvarni, rasa suronitham..Actions:Cholagogue, laxative, tonic⁵.

TOXICITY PROFILE OF INDIVIDUAL RAW DRUG

Withania somnifera

No toxic signs/ mortality was observed with 2000mg/kg of hydroalcoholic extract of *Withania somnifera* root extracts in rats.. Also, no histopathological lesions were observed⁶. Alcohol extracts of *Withania somnifera* were also found to be safe in mice and rats. No toxic signs were reported in acute and subacute toxicity. The LD₅₀ was determined as 1260 mg/kg body weight. The author has reported significant reduction in weight of spleen, adrenal and thymus in male rats alone. Acid phosphatase level in blood was also increased compared to normal control.⁷ Mishra et al has stated that amukkara possess various therapeutic effects with little/ no toxicity⁸.

Smilax china

Parangipattai rasayanam , a siddha drug with *Smilax china* as a major ingredient was tested for toxicity in rats. The drug at its maximum dose 1800 mg/kg did not exhibit any toxicity in acute and 28 days toxicity^{9,10}.

Terminalia chebula

Single oral dose of etanolic extract of *Terminalia chebula* (2000mg/kgb.w) did not produce any mortality. In 14 days repeated oral toxicity also there were no adverse effects observed in rats¹¹.There was no toxicity observed with the water extract of *Terminalia chebula* at a single oral dose of 5000mg/kgb.w. In chronic toxicity (270 days), the test substance at the dose of 300, 600 and 1200

mg/kg b.w. did not show any toxic signs in rats¹². In acute toxicity study, 50% alcoholic extract of *Terminalia chebula* showed no toxic changes¹³. Acute and subchronic toxicity of aqueous extract of *Terminalia chebula* dried fruits exhibited no toxic changes^{14,15}.

Phyllanthus emblica

Single oral dose of water extract of *Phyllanthus emblic* (5000mg/kg b.w) with 20% gallic acid showed no toxicity in Sprague Dawley rats. In chronic toxicity dose range of 300, 600 and 1200 mg/kg b.w resulted in slight differences in body weight and organ weight when compared with control animals. There were also changes in haematological and biochemical parameters, but within normal limits¹⁶. A study has reported that 49.6% hydroalcoholic extract of amla was found to be safe in rats. Acute and chronic study did not cause any untoward effect. LD₅₀ was above 1000mg/kg¹⁷.

Terminalia bellerica

The aqueous extracts of dried fruits of *Terminalia bellerica* were assessed for acute and chronic toxicity in Spargue – dawley rats. In acute toxicity the aqueous extract at a single oral dose of 5000mg/kg b.w did not show any toxicity. The *T.bellerica* was found to be nontoxic at the dose of 300, 600 and 1200 mg/kg b.w for 270 days⁸. Another study has reported that in acute toxicity study, the ethanol, chloroform, hexane and water extract of *Terminalia bellerica* was found to be nontoxic. The LD₅₀ was determined as 2000mg/kgb.w¹⁹.

Zingiber officinale

The crude ehanolic extract of *Zingiber officinale* Roscoe at the dose of 5000mg/kg body weight did not exhibit any toxicity in acute and subacute toxicity studies in rats²⁰.

Piper nigrum

Chunlarathanaphorn S, et al in his study has reported that water extracts of the dried fruits of *Piper nigrum* exhibit no toxicity in both acute and sub- acute toxicity in male and female rats²¹. Prashant B. Shamkuwar et al has studied the toxicity of aqueous extract of *Piper nigrum* and piperene as per OECD guidelines 423. There

was no toxicity observed upto the dose of 2000mg/kg in albino rats by oral route²²

Piper longum

According to the acute and subchronic toxicity study of *Piper longum* fruits conducted by Megha Pathak et al there was no serious toxic effects observed²³. Etanolic extract of *Piper longum* on mice showed a significant increase in weight of lungs and spleen in treatment group animals when compared with control group animals. The doses given in aute toxicity were 0.5, 1 and 3 gram / kgb.w. 100 mg/kg b.w of the test drug was given daily for 90 days in chronic toxicity²⁴.

Embelia ribes

Embelin present in *Embelia ribes* at the dose of 120 mg/ kg body weight for 6 weeks in female rats has shown increase weight of adrenal and several pathological changes²⁵. 1.25 g /kg body weight of *Embelia ribes* when administered to Chicks have shown degradation of ganglion cells of retina of chick. But at 0.25 g / kg no visual deficit or retino toxicity was detected²⁶. With the ethanolic extract of *Embelia ribes* no toxicity was observed at the dose of 2000 mg / kg b.w. in acute toxicity study conducted as per OECD guidelines²⁷.

Elettaria cardamomum

Jaila El Malti et al has reported in a study that *Elettaria cardamomum* produces toxicity at 0.3 mg/ g b.w. of mouse. It also affects the energy metabolism and oxidative stress²⁸. Shveta Sharma et al 2011 in her review has said that some of the components of cardamom possess mutagenicity and carcinogenicity. 1- heptanol, 1- hexanol, Decanal, Nerolidol in *Elettaria cardamomum* were found to be non-mutagenic and non- carcinogenic²⁹.

Semecarpis anacardium

An acute toxicity study of methanol, petroleum ether and chloroform extract of *Semecarpus anacardium* has been conducted and LD₅₀ was determined. LD₅₀ of petroleum ether and chloroform extract was 700 mg/kg. LD₅₀ of methanol extract was found to be 500 mg/ kgb.w. The researcher has concluded that

1/10th of the doses would be safe dose for administration³⁰. Sheajer have reported that *Semecarpus anacardium* nut oil extracts exhibit nephro toxicity (50% W/V) in groundnut oil^{31,32}. *Semecarpium anacardium* toxins lead to acute renal failure due to hemodynamic effects³³.

Plumbago zeylanica

Acute dermal irritation test was conducted for pate of *Plumbago zeylanica* and *Holoptela integrifolia*. The result showed that there was no major dermal irritation on single application³⁴. Another research article has concluded that the dermatotoxicity of *Plumbago zeylanica* might be limited to effects like moderate irritation³⁵.

Cicer arietinum

In acute toxicity study, methanolic and ethanolic extracts of *Cicer arietinum* seeds at the dose of 2g/kg did not reveal any toxicity in rats³⁶. Both acute and subacute toxicity study was conducted with the petroleum ether extract of *Cicer arietinum*. It was safe upto the dose of 5000mg/kg b.w.³⁷.

Santalum album

In Acute toxicity of hydroalcoholic extract of *Santalum album* leaves , there were no toxic signs up to the dose of 2000mg/kg b.w.³⁸. Sandalwood oil has low acute oral and dermal toxicity. Only limited information on toxicity of Sandal oil is present. Burdock GA has stated that it has a long history of oral administration without any repeated adverse effects³⁹. The hydro alcoholic extract of *Santalum album* stem revealed to be safe upto 5000mg/kg.⁴⁰

Cinnamomum zeylanicum

Acute and chronic toxicity studies on ethanolic extracts of *Cinnamomum zeylanicum* bark in mice was carried out by Shaw AM et al. In chronic toxicity 100 mg/ kg b.w dose / day caused a reduction in liver weight. There is increase in reproductive organ weight. In haematological report there was a crease in hb level.⁴¹ Experiments on the petroleum ether and chloroform extracts of *Cinnamomum*

zeylanicum were carried out by Chulasiri et al .It showed cytotoxic effects on human mouth carcinoma cell line and mouse lymphoid leukemia cell line⁴².

Sulphur

Sulphur has low toxicity. The risk to animal and human health is very low^{43,44}. Short term studies show that Sulfur has very low acute oral toxicity and it does not irritate the skin. (it has been placed in EPA Toxicity Category IV, the least toxic category, for these effects). The rat oral LD₅₀ of Sulphur was greater than 5000mg/kg and greater than 8437 mg/ kg^{45,46,47,48}. The dermal LD₅₀ for rats was greater than 5,000 mg/kg⁴⁹. Long term use of sulphur is not associated with risk of oncogenic, teratogenic or reproductive effects. It is non mutagenic in microorganisms⁵⁰.

DISTRIBUTION AND CHEMICAL CONSTITUENTS OF INGREDIENTS OF KANDHAGA RASAYANAM

Withania somnifera

Withania somnifera (L) Dunal is commonly called as Ashwagandha. Ashwagandha has been in use in Indian traditional medicine for more than 3000 years⁵¹. Ashwagandha belongs to Solanaceae family. It is a perennial, xerophytic plant. *Withania somnifera* has been given the name Indian ginseng⁵². This plant is found in the drier parts of India, Srilanka, Afghanistan, Baluchistan and Sind. In India it grows everywhere particularly on waste lands and on road sides⁵³. There are more than 35 chemical constituents present in the roots of *Withania somnifera*. It contains alkaloid, steroids, amino acids, volatile oil, starch, reducing sugar, glycosides⁵⁴ *Withania somnifera* root contains abundant iron. The active chemical constituents are alkaloids(isopellertierine, anferine), steroidal lactones (Withanolides, Withaferins) , saponins containing an additional acyl group (Sitoindoside VII & VIII), and Withanoloides with a glucose at Carbon 27 (Sitonidoside XI & X). The roots of *Withania somnifera* consist of Withanolides. Withanolides have extraordinary medicinal properties⁵⁵. Most of the pharmacological activities of Ashwagandha are

mainly due to the presence of 2 main withanolides, withaferin A & withanolide D. Alkaloids and steroidal lactones are believed to be the main constituent of Ashwagandha. Alkaloids : Main constituent : withanine, other alkaloids : somniferine, somnine, somniferinine, withananine, pseudo- withanine, tropine, pseudo- tropine, 3- a- glyoxy tropine, choline, cuscohygrine, isopelletierine, anaferine and anahydrine sitoindoside VII & sitoindoside VIII are the two acyl steryl glycoside isolated from the root of *Withania somnifera*. Withanolides are steroidal lactones present in leaf⁵⁶. Recent research says that the following chemical compounds are also present in Ashwagandha. They are Anaferin, Anahygrine, Cysteine, Chlorogenic Acid, Cuscohygrine, Iron, Pseudotropine, Scopoletin, Somniferine, Somniferine, Tropanol, Withanine, Withanine And Withanolides^{57,58}.

Smilax china

Smilax china commonly called as Chopchini, Madhunchi belongs to the family Liliaceae. It grows in temperate zones, tropics and sub tropics⁵⁹. It is imported from China and Japan⁶⁰. The major chemical constituents of *Smilax china* are fat, saponin, glucosides, gum, starch, flavanoids, tannins, terpenes and alkaloids. Nearly 13 compounds were identified from roots. They are kaempferol 7-o-beta-D glucopyranoside, engeletin, isoengeletin, kaempferol, dihydrokaempferol, dihydrokaempferol- 5-o-P-D- glucopyranoside, rutin, kaempferol-5-o-beta-D- glucopyranoside, 3,5,4 trihydroxystibene, vanillic acid, 3,5-dimethyl 4-O- beta-D-glucopyranosylcinnamic acid, beta sitosterol, and beta-daucosterol^{61,62}.

Terminalia chebula

Terminalia chebula called as Haritaki grows widely in India, Myanmar, Bangladesh, Iran, Egypt, Turkey, China etc. It is a moderate sized tree⁶³. In India, it is chiefly seen in deciduous forest and areas where there is light rainfall⁶⁴. It grows in subhimalayan tracks, eastern, western and southern parts of India⁶⁵. *Terminalia chebula* is rich in phenols, especially hydrolysable tannins. Tannins of

Terminalia chebula are pyrogallol type. There are nearly 14 hydrolysable tannins⁶⁶. It contains anthraquinones, flavanoids, sterols, aminoacids, carbohydrates, glucose and sorbitol, resins, fixed oils etc.⁶⁷. Chebulic acid⁶⁸, Chebulinic acid⁶⁹, Ellagic acid, gallic acid⁷⁰, Chebulagic acid⁷¹. It also contains punicalagin, terflavin A, terchebulin^{72,73}. The hydrolysable tannins in fruits were castalagin, ellagic acid, flavogallonic acid, punilagin, terchebulin⁷⁴. The kernels of the *Terminalia chebula* fruits contain fatty oil (49 %) which is quite similar to that of the composition of conventional oils⁷⁵.

Phyllanthus emblica

Phyllanthus emblica (Linn) or *Emblica officinalis* (Gaertn) is commonly known as amla . It belongs to the family Euphorbiaceae⁷⁶. It is a small to medium sized deciduous tree. This is cultivated in the dry forests of Chittagong, Chittagong Hill Tracts, Cox's Bazar, Sylhet, Dhaka – Tangail (Sal forest) and Dinajpur⁷⁷. It grows in tropical and subtropical regions of China, India, Indonesia and the Malay Peninsula. The fruit of Amla is very rich in vit C. It contains tannin, colloidal substances, lipids, quercitin, gallic acid, phyllambic acid, ellagic acid, trigalloylglucose, terchebin, corilagin and emblicol. The fruit pulp of amla contains Phyllembin and mucic acid. Bark, fruits and leaves all the three are rich in tannin. Fixed oil, phosphatides, tannins and essential oil are found in seeds. Bark, fruits and leaves contain lupeol, β -sitosterol and ellagic acid. Leucodelphinidin is present in the bark of *Phyllanthus emblica*. Linoleic acid is found in the oil from seeds^{78,79,80}. Yokozawa et al., 2007 has reported that cucuminoides, rutin and emblicol are found in amla⁸¹. More than 80% of chemical composition of the fruit is water. The ash of the fruit contains chromium zinc and copper⁸². The seed oil contains the following fatty acids. They are linolenic, linoleic, oleic, stearic, palmitic and myristic acid⁸³. The hydrolysable tannins are Emblicanin A, Emblicanin B, punigluconin, pedunculagin⁸⁴. Rahman 2007 has reported the presence of kaempferol 3 O alpha L (6'' methyl) rhamnopyranoside, kaempferol 3 O alpha (6 ''ethylamropyranoside) are the

flavanoids present in the seed oil. Khanna et al, 1975 has reported the presence of phyllantidine and phyllantine alkaloids.

Terminalia bellerica

Terminalia bellerica Roxb. belongs to the family Combretaceae. It is a large deciduous tree. In India it is known as Bahera⁸⁵. Bahera grows throughout India, Srilanka and South East Asia^{86,87}. Fruits of *Terminalia bellerica* contains fixed oil with a phenolic ester known as , hexahydroxydiphenic acid esters^{88,89}. The fruits contain tannins) such as gallic acid, ethyl gallate and ellagic acid. Belleric acid, chebulagic acid, glucose, glucosides etc are found in fruits^{90,91}. Arjungenin, bellericagenin A & B are the triterpenoids present in bahera⁹². Bellericanin, a glycoside^{93,94}, Gallo-tannic acid , resins & a greenish yellow oil are present in bahera⁹⁵. Ellargic acid, gallic acid, lignane namely termilignane and thanni lignin, 7-hydroxy 3'4' (methylene dioxy) flavone and anolignan B10 are found in *Terminala bellerica*. It also contains tannins, ellargic acid, ethyl gallate, galloyl glucose, chebulaginic acid, phenyllembin, β -sitosterol, mannitol, glucose, fructose and rhamnose^{96,97,98}.

Zingiber officinale

Zingiber officinale ,Roscoe. belongs to the family zingiberaceae. The cultivation has its origin in China, which later spread to India, South East Asia, West Africa And Caribbean. Ginger is native to topical Asia. It is cultivated commonly in India, China, South East Asia, West Indies, Mexico etc⁹⁹. The major constituent of ginger is sesquiterpenoids with Zingiberene as the main component. It also contains β -sesquiphellandrene bisabolene and farnesene^{100,101}. Gingerol, a constituent of ginger imparts the pungent odour to the plant. The ginger oil contains monoterpenes (phellandrene, camphene, cineole, citral, and borneol) and sesquiterpenes (zingiberene, zingiberol, zingiberenol, β -bisabolene, sesquiphellandrene, and others). It also contains aldehydes and alcohols^{102,103}. Dried ginger powder contains Shogaol which is a dehydrated product of gingerol^{104,105}. A novel product Amadaldehyde has been isolated from ginger extract¹⁰⁶. Some pungent principles of

Zingiber officinale rhizome are paradols, gingerdiols, gingerdiacetates, gingerdiones, 6-gingersulfonic acid, gingerenones etc. Diterpenes and gingerglycolipids A, B and C are also present in the rhizome¹⁰⁷. Phenylalkylketones or vanillyl ketones present in ginger are 6-gingerol 8- gingerol and 10-gingerol, 6-shogaol, 8- shogaol, 10-shogaol and zingerone. It also includes 6-paradol, 6- and 10- dehydrogingerdione and 6- and 10-gingerdione¹⁰⁸.

Piper nigrum

Piper nigrum, the black pepper belongs to the family piperaceae¹⁰⁹. Black pepper is native to South India and Srilanka. They are cultivated in tropical region. The black pepper is considered as king of spices due to its pungent principle piperine¹¹⁰. It grows in tropical and subtropical regions of India¹¹¹. The petroleum ether extract of *Piper nigrum* contains 2E,4E,8Z-N-isobutyleicosatrienamides, pellitorine, trachyone, pergumidiene and isopiperolein B¹. Piperidine and pyrrolidine alkaloids are present in *Piper nigrum*. The most important of these is piperine^{113- 116}, Pergumidiene and trachyone are also present in *Piper nigrum*¹¹⁷. Black pepper contains piptrigine, wisamine¹¹⁸, Dipiperamide D and dipiperamide E.¹¹⁹.

Piper longum

Piper longum is commonly known as pipili, Indian long pepper. It has wide distribution in India especially in North – East India and Western Ghats. It usually grows in tropical semi evergreen type of forests¹²⁰. Pipili is native of Indo- Malaya region¹²¹. *Piper longum* belongs to the family Pperaceae. The fruits of *Piper longum* shows the presence of volatile oil, starch, protein, alkaloids, saponins, carbohydrate and amygdalin. Tannins are absent¹²². The alkaloids piperine, piperlongumine, piperlonguminine and methyl-3,4,5-trimehoxycinnamate are the major chemical constituents. The spikes of pipili plant contains piperine and piplatin. Alkaloid A, a new one closely related to pellitorine is isolated from pipili. It also contains 3 new alkaloids, namely, piperolactum A, piperolactum B and piporadione¹²³. Neelam and Krishnaswamy

(2000) has mentioned that the roots of long pepper contains the following alkaloids, piperine, piperlongumine, piperlonguminine. Piperlongumine on purification yielded Cephadione B, Cephadione A, Cepharonone B, aristolactum A II norcephadione B and 2 hydroxy (methoxy 4H dibenzoquinoline – 4,5 (6H) dione), lignins (Pluriatilol, fargosin, sesamine, asarinine, guinensine pipericide)¹²⁴, Syvatine, dieudesmine are isolated from seeds¹²⁵. The essential oils in the plant consist of long chain hydrocarbons, mono and sesquiterpenes, caryophyllene as the main product^{126,127}. The pungency of the fruit is due to the alkaloid piperine. The fruit contains calcium, phosphorus and iron.

Elettaria cardamomum

Elettaria cardamomum. Manton is commonly known as Cardamom. It is locally known as "elachi"¹²⁸. It belongs to the family Zingiberaceae. Elam is historically known as "queen of spices". It is commercially cultivated in India, Srilanka, Guatemala and Tanzania^{129,130}. Elachi is a perennial herb which is indigenous to India, Pakistan, Myanmar and Srilanka¹³¹. *Elettaria cardamomum* contains α -terpineol, myrcene, heptane, subinene, limonene, cineol, menthone, α -pinene, β -pinene, (Shabnam et al 1987.) linalol, nerolidol, (Okugawa et al 1998) β -sitostenone, phytol, eugenyl acetate, (132bisabolene, borneol, citronellol, geraniol, geranyl acetate, stigmaterol and terpinene¹³³.

Embelia ribes

Embelia ribes Burm. belongs to the family Myrsinaceae. It is found in semi evergreen to evergreen forests of India, Srilanka. It is a climbing shrub¹³⁴. The berries of *Embelia ribes* contains embelic acid, volatile oil, fixed oil, resin, tannin, christembine (alkaloid)¹³⁵, phenolic acids like caffeic acid, vanillic acid, chlorogenic acid, cinnamic acid, o-cumaric acid¹³⁶. Embelin is isolated from *Embelia ribes*¹³⁷. It also contains potassium embelate¹³⁸. 2, 5-dihydroxy, 3-undecyl-1,4-benzoquinone, embelin, quercitol, fatty ingredients, vilangin¹³⁹. The seeds show the

presence of Cr, K, Ca, Cu, Zn and Mn along with increased carbohydrates¹⁴⁰. The active compound of the ripe fruit of *Embelia ribes* is embelin¹⁴¹. Newer compounds isolated from the seeds of *Embelia ribes* are 3 – (4"-hydroxyoctadecanyloxy)-p-quinonyl-5-methylene-8-(10-pentanyloxy)-p-quinone (embelinol), n-pentacosanyl-n-nonadeca-71-en-91- α -ol-11-oate (embeliaribyl ester), 1,2,4,5-tetrahydroxy 3-undecanyl benzene (embeliol) and embelin¹⁴².

Santalum album

Santalum album L. Known as sandalwood is one of the precious trees in the world¹⁴³. It belongs to Santalaceae family. The trees are widely distributed in India particularly in Southern region, namely Karnataka, Tamil Nadu and Kerala¹⁴⁴. The bark and sapwood of *Santalum album* tree are odourless. The essential oil is present in the roots and heartwood. Santylacetate and santalene are present in sandalwood¹⁴⁵. Santalol (90% or more) is the chief constituent of the volatile oil extracted from the roots and heartwood. It is a mixture of two primary sesquiterpene alcohols, C₁₅H₂₄O viz, α -santalol (bp-166- 1670C) and β -santalol (b.p-177-1780C). More than hundred constituents are reported in sandalwood oil. Tannins, terpenes, resins and waxes have been reported. Hydrocarbons- santene (C₉H₁₄), nor- tricyclo-ekasantalene (C₁₁H₁₈), α - and β - santalenes (C₁₅H₂₄), alcohols- santenol (C₉H₁₆O), teresantalol (C₁₀H₁₆O), aldehydes- nor-tricyclo-kasantal (C₁₁H₁₆O) 3,7,8 and the acids α -and β -santallic acids (C₁₅H₂₂O₂) and teresantallic acids (C₁₀H₁₄O₂) are present in sandalwood oil¹⁴⁶. A new acid – ketosantallic (as methyl ester) & gamma – L – glutamyl-S-(trans-1-propenyl)-L-cysteine sulfoxide, have been isolated from sandal. Tricyclosantalol, α -santalene, trans- β - bergamotene, β -santalene (S & E), α -curcumine, α -santalol, beta-santalol (S&E), nuciferol, α -santalol and β -santalol are also present in *Santalum album*^{147,148}. The presence of antioxidants is also proved in Sandalwood¹⁴⁹.

Cicer arietinum

Cicer arietinum is commonly called as chick pea or Bengal gram. It belongs to the family Fabaceae. Chick pea is cultivated in Sind, Bombay Presidency and as a pulse crop throughout India¹⁵⁰. Chick pea secretes highly acidic exudates. Rambold in 1981 has reported the pH of the exudates as 1. The most abundant organic acid in the nodules and roots is malonic acid. Malic acid is the major organic acid in the leaves and stem^{151,152}. The major group of flavanoid present in chick pea is isoflavanoid. Bose and Siddique in 1945 first reported the presence of isoflavanoids in chick pea. Chu et al isolated glucanase, a chitinase, an antifungal cyclophyllin-like protein, and three antifungal peptides - cicerin, arietin, and cicearin from Chick pea. Stilbene compounds are isolated from the roots of chick pea. Ye et al has reported the isolation of 2 antifungal peptides having N- terminal sequence¹⁵³. Chick pea contains saponin formononetin-7-O-glucoside-6''-malonate, biochanin A-7-O-glucoside-6''-malonate and biochanin A-7-O-glucoside^{154,155}.

Semecarpus anacardium

Semecarpus anacardium Linn. is commonly called as bibba, bhallataki. It belongs to the family Anacardaceae. Its trade name is Marking nut/ Dhobi nut. The tree is widely distributed throughout the hotter parts of India. It is frequently found in dry deciduous forests of Central India. It is distributed in tropical and central parts of India. It is abundantly found in Assam, Bihar, Bengal and Orissa, Chittagong, Central India¹⁵⁶. Phenolic compounds are the most significant component of *Semecarpus anacardium* oil. Bhilvanol A (mono-pentadecyl catechol I) and bhilvanol B (dien-pentadecyl catechol II) are the two main phenolic compounds^{157,158}. The glucoside present is anacardoside. The important biflavonoids isolated from *Semecarpus anacardium* are semecarpuflavone^{159,160}, Jeediflavone^{161,162}, galluflavone^{163,164}, nallaf flavanone, semecarpetin and anacarduflavanone¹⁶⁵. The nut contains anacardic acid, sterols, glycosides, vitamins, aminoacids¹⁶⁶. The preliminary chemistry analysis of nuts shows the presence of

alkaloid, tannins, saponin, flavanoid, anthraquinones, ascorbic acid^{167,168}. Nut shell of *S.anacardium* contains biflavones A, C, A1, A2, tetrahydrorobustaflavone, B (tetrahydromentoflavone)¹⁶⁹.

Plumbago zeylanica

Plumbago zeylanica belongs to the family Plumbaginaceae. It is commonly called as Ceylon leadwort, Chitraka. It is distributed as a weed in tropical and sub-tropical countries. Large scale of cultivation is common in west Bengal and southern India. It grows in Andhra Pradesh, Karnataka, Maharashtra etc¹⁷⁰. The root contains plumbagin. The alkaloid Plumbagin is a natural naphthoquinone (5-hydroxy-2-methyl-1,4-naphthoquinone). Only 1% plumbagin is present in whole plant and its concentration is increased in roots. The other constituents of the root are chitranone, zeylanone, dihydrosterone, 2-methyl naphthaquin, plumbazeylanone and terpenoids, lupeol and teraxesterol. Alkaloids, glycosides, tannin, saponin and steroids are also present in the plant¹⁷¹. Elliptinone, droserone are also present in chitraka^{172,173}. Naphthaquinones¹⁷⁴, 3-plumbagin, chloroplumbagin, chitranone, elliptone, coumarins, seselin, 5-methoxyseselin, xanthyletin and suberosin are present in the root of *Plumbago zeylanica*. The other compounds present are 2,2-dimethyl-5-hydroxy-6-acetylchromene, plumbagin acid, β -sitosterol, β -sitosteryl-glucoside, bakuchiol, 12-hydroxyisobakuchiol, saponaretin, isoorientin, isoaffinetin, psorealen. Enzyme protease, invertase are present in the leaves and stem. Plumbagin is present very little or absent in leaves and stem. The aerial part of the plant contains naphthoquinones, sitosterol, lupeol, lupenylacetate, hentriacontane, and amino acids^{175,176,177}. It also contains aspartic acid, tryptophan, tyrosine, threonine, alanine, histidine, glycine, methionine, hydroxyproline, were isolated from the aerial parts¹⁷⁸.

Cinnamomum zeylanicum

Cinnamomum zeylanicum is indigenous to Srilanka and Southern part of India. It belongs to the family Lauraceae¹⁷⁹. The genus cinnamomum is distributed in tropical and sub-

tropical region of North America, Central America, South America, Asia and Australia¹⁸⁰. Cinnamaldehyde is the primary constituent in the bark, eugenol in leaf and camphor in root¹⁸¹. Trans-cinnamaldehyde, eugenol and linalool are the main constituents of the essential oil obtained from *Cinnamomum zeylanicum* bark.

Sulphur

The element sulphur is a ubiquitous compound of the environment. It is registered by Environmental Pollution Agency as insecticide, fungicide and rodenticide. Sulphur has low toxicity and possesses very little risk, if any to human health. It is a non-systemic contact and protectant fungicide with secondary acaricidal activity¹⁸².

DISCUSSION

Most of the herbal ingredients of Kandhaga Rasayanam have been reported to possess alkaloids, tannins, flavanoids, glycosides, sterols saponins etc. Plumbagin contains amino acids. Marking nut possess alkaloid, tannins, saponin, flavanoid, anthraquinones, ascorbic acid. Sandal wood, cinnamon, cardamomum contains essential oil, volatile oils etc. Haritaki is found to contain anthraquinones, flavanoids, sterols, aminoacids, carbohydrates, glucose and sorbitol, resins, fixed oils etc. Ashwagandha is rich in steroidal lactones and alkaloids. In this, each ingredient has many chemical constituents which support its therapeutic usage. It is evident from previous research that the secondary metabolites, including

antibiotics show activity against bacteria, fungi amoeba etc.¹⁸³. Phytochemical studies have shown that plants with antimicrobial activity contain bioactive constituents such as tannins, flavonoids, alkaloids and saponins, alkaloids & flavinoids have been used as antiviral, antibacterial, anti-amoebic & anticancer agents. Phenolic and polyphenolic are the other group of secondary metabolites flavanoids, sterols, phenols possess antibacterial and antifungal activity in general^{184,185}. The GC-MS analysis of the compound drug, Kandhaga Rasayanam showed the presence of Imidazole, Pyrazole compounds, Hexadecanoic acid, octadecanoic acid etc, which have antifungal property (unpublished). The toxicity studies on the ingredients show that the herbs are safe for consumption. At high doses, *Semecarpus anacardium* showed toxicity. *Elettaria cardamomum* produces toxicity at 0.3 mg/g b.w. of mouse. This is evident from the review that drug at prescribed dose is safe for oral administration.

CONCLUSION

From the above review, it is clear that the drug Kandhaga Rasayanam is a potent drug for skin infections, urinary diseases, venereal diseases and vata diseases. There was no toxicity reported with the individual herbs except for marking nut, *Elettaria cardamomum* at high dose. Hence, the herbo-mineral Siddha formulation can be taken as a safe and effective drug as mentioned in the classical text books.

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