International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
DOI: 10.22192/ijarbs Coden: IJARQG(USA) Volume 5, Issue 1 - 2018

Review Article

DOI: http://dx.doi.org/10.22192/ijarbs.2018.05.01.023

Toxicity profile and chemical constituents of the ingredients of a siddha drug - *Parangipattai Rasayanam*

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Abstract

Siddha system of medicine, which is practised prevalently in the southern part of India, especially in Tamil Nadu, is familiar among Tamil-speaking people and outside of the landscape too. The name Siddha medicine owes its origin to medicinal ideas and practices rendered by sages called Siddhar's/"Holy immortals". Siddha system of medicine is established mainly by18 Siddhas and the most renowned are Agathiyar, Thiru moolar and Bhogar. *Parangipattai Rasayanam* is a poly herbal formulation mentioned in classic Siddha text. It is used in treating skin diseases, various ulcers, venereal diseases, peptic ulcer 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 anti-psoriatic, antimicrobial, antifungal and antioxidant properties. This poly herbal formulation mentioned in Siddha literature is thus validated.

Keywords: *Parangipattai Rasayanam*, Skin diseases, Phytochemistry, Poly herbal formulation.

Introduction

Siddha is one of traditional medical science which describes the lifestyle methods for living a healthy life. According to Siddha, Management and treatment of disease included both mental and Physical which gives effectively relieves from Diseases. The medicines in Siddha are prepared from herbs, metals/minerals and animal products [1] .*Parangipattai Rasayanam* is a classic Siddha drug chosen from the text *Pulippani vaithiyam-500.* It is indicated for all kind of skin diseases, various ulcers, venereal diseases, peptic ulcer etc.[2]. This review article is aimed to document the chemical constituents, and toxicity profile of each ingredient of *Parangipattai Rasayanam*. This is to validate the traditional claim in treating the skin diseases, various ulcers, venereal diseases, peptic ulcer etc. 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 *Parangipattai Rasayanam*were done. The drug has undergone all preliminary analytical studies, toxicity study and open clinical trial for treating Psoriasis. (results yet to be published). The results of the preliminary phytochemistry of *Parangipattai Rasayanam*revealed the presence of many secondary metabolites attributing to its

therapeutic activity. The toxicity profile and phytocostituents are discussed in this review. Drug name:*Parangipattai Rasayanam*.Dose : 8grams. Twice daily.Source :*Pulippani vaithiyam-500.*

Ingredients of *parangipattai rasayanam*:

The drug consists of 21 herbs .The herbs are *Withania somnifera, Smilax china, Zingiber officinale, Piper nigrum, Piper longum, Plumbago zeylanicum, Azima tetracantha, Clerodendrum inerme Linn, Curculigo orchioides, Gmelina orborea, Gmelina asiatica, Tribulus terrestris, Thespesia populnea, Capparis sepiaria, Carum copticum, Cinnamomum verum, Costus speciosus, Mesua nagassarium, Alpinia galangal, Syzygium aromaticum.*

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 observed[3]. 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 LD_{50} 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 phosphatise level in blood was also increased compared to normal control[4].Mishra etal has stated that *amukkara* possess various therapeutic effects with little/ no toxicity[5].

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 [6,7] .

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 rats[8].

Piper nigrum

Chunlaratthanaphorn 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 rats[9].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 route[10].

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 observed[11].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 toxicity[12].

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 application[13]. Another research article has concluded that the dermotoxicity of *Plumbago zeylanica* might be limited to effects like moderate irritation[14].

Gmelina arborea

Kulkarni et al, et al studied the toxicity of *G. arborea* alcoholic extract and its analgesic activity in female Swiss albino mice. Alcoholic extract and its fractions did not produce mortality, changes in behavior or any other physiological activities in mice[15]. Kulkarni et al also reported the administration of ME from the *G. arborea* bark at 300-5000 mg/kg did not produce mortality or significant changes in the clinical signs and it was found to be safe in acute and repeated dose toxicity studies when tested in mice and rats[16].

Gmelina asiatica

Acute oral toxicity of chloroform extracts of *G. asiatica* was carried out as per OECD-423 guidelines. The chloroform extract of *Gmelina asiatica* (GA) was administered orally at the dose of 5 mg kg-1 body weight. The animals were then observed for 14 days and maintained with normal food. A mortality rate of 2 or 3 at 14 days was recorded as a toxic dose. But when mortality was observed in one animal, then the

same dose was repeated again for confirmation. However, if mortality was not observed, the procedure was repeated for further higher doses such as 50, 300 and 2,000 mg kg-1 body weight. The extract was found to be safe up to 2000 mg/kg of body weight[17].

Costus speciosus

Costus speciosus extract was subjected to toxicity studies. For the LD50 dose determination, CSRE was administered at the dose level of 2000 and 5000 mg/kg. This dose did not produce any abnormal symptoms and mortality when compared to the control group[18]. The acute toxicity of leaf extracts of *Costus speciosus* was determined by using albino mice. No mortality was observed upto dose 2000mg/kg From the LD50 dose, 100 mg/kg and 200 mg/kg doses were selected and considered as low and high doses respectively. Both the petroleum ether and methanol extracts did not produced any sign of toxicity[19].

Tribulus terrestris

Nerunjil kudineer, a siddha drug with *Tribulus terrestris*as a major ingredient was tested for toxicity in rats.*Nerunjil kudineer* at the dose of 2000mg/kg/po did not exhibit any mortality in rats. *Nerunjil kudineer* at the dose 500 mg/kg/po when administered for 28 days in rats orally did not show toxicity.*Nerunjil kudineer* is safe and is considered to be used widely at the clinical application[20].

Curculigo Orchioides

C. orchioides extract did not showed any toxicity at a dose of 2000 mg/kg as evidenced by observations. No signs of abnormal behavior or mortality were observed during the study period[21]. Acute toxicity evaluation *of C. orchioides* extract, there were no mortality and toxicity signs observed at 2000 mg/kg. Acute oral toxicity study There was no treatment related death or signs of toxicity developed in the control, MECO treated rats through the study. A 28-day repeated oral toxicity study was performed following OECD test guideline 407 in both male and female Wistar Albino rats. This reveals that it does not adversely affect the basic metabolic processes of the experimental rats. In biochemical evaluation the extracts treated groups showed reduction in serum glucose levels[22].

Azima tetracantha

Acute oral toxicity study was conducted as per OECD-423 guidelines. The rats were fasted overnight and given orally 5, 50, 300 and 2000 mg/kg of ATR extract. No mortality or toxicity was observed up to the dose of 2000 mg/kg. Hence, the drug was found to be safe[23].

Clerodendrum inerme

In acute toxicity study, all four extracts of three plants were found to be well tolerated up to the dose of 2000 mg/kg. These produced neither mortality nor any change in the behavior in mice. In sub-acute toxicity study, all four extracts of three plants at the LD50 dose level did not produce any significant alteration in hematological and biochemical parameters in rats.

Each extract was evaluated for its sub-acute toxicity at its MTD and was found to be non toxic[24].

Acute oral toxicity was performed in rats. Before study the rats were fasted overnight with free access to water. They were received ethanolic and chloroform extract with a single oral dose (2000mg/kg body weight). Both the extracts of *C. inerme* were found to be safe up to 2000 mg/kg body weight[25].

Thespesia populnea

Acute oral toxicity study was performed as per OECD-423 guidelines (acute toxic class method). Then the bark extracts of*Thespesia populnea*were administered orally at the dose of 2000 mg/kg by intragastric tube and observed for 2 days for the gross behavioral changes and mortality[26].

Capparis sepiaria

Acute, Sub-acute and Chronic Toxicity Studies The LD50 was carried out by adopting the method outlined OECD guidelines. On the toxicity evaluation acute, sub-acute and chronic toxicities were showed that the LD50value of 300-5000mg/ kg body weight in mice i.p. signifies the extract to be non-toxic to the experimental model[27].

Cinnamomum verum

The acute toxicity test result showed that the LD50 of the aqueous bark extract of *Cinnamomum verum* was greater than 5000mg/kg body weight. The fact that the experimental rats survived the acute toxicity testing up to a dose of 5000mg/kg showed that the aqueous bark extract of *Cinnamomumverum* is practically non-toxic[28]. This is in accordance with a study by Shah *et al*. [29] who demonstrated that the ethanolic extract of *Cinnamomumzeynalicum bark* was non-toxic after acute toxicity tests. Rabiatu *et al*.[30] also reported that *Cinnamomumverum* possess low moderate toxicity, evidenced by high LD50 values with no lethality, thus the low toxicity of *Cinnamomum verum* offers a wide margin of safety for beneficial doses.

Mesua nagassarium

In-vivo acute oral toxicity study for safety assessment of n-hexane extract of *M. ferrea* was carried out as per OECD guidelines test no. 420. Study was performed on Swiss Albino female mice. The extract was found safe in mice in acute oral toxicity studies.The n-hexane extract of *M. ferrea* stamens was found completely safe in mice at a dose level of 2000 mg/kg body weight of an animal[31].

Alpinia galangal

Acute toxicity study of ethanolic extract of *Alpiniagalanga* substance is classified in the hazard category 2000mg/kg < LD50 < 5000mg/kg according to globally harmonized classification system[32].

Chemical constituents of ingredients of *Parangipattai 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 years [33].Ashwagandha belongs to Solanaceae family. It is a perennial, xerophytic plant. *Withania somnifera* has been given the name Indian ginseng [34].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 sides[35]. 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, glycosides[36]*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 properties[37]. 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- gloyloxy tropane, choline, cuscohygrine, isopelletierine, anaferine andanahydrine sitoindoside VII & sitoindoside VIII are the two acyl steryl glycoside isolated from the root of *Withania somnifera* . Withanolides are steroidal lactones present in leaf[38].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, Somniferiene,Tropanol,Withanine, Withaninie And Withanolides [39,40] .

Smilax china

Smilax china commonly called as Chopchini, Madhunchi belongs to the family Liliaceae. It grows in temperate zones, tropics and sub tropics [41]. It is imported from China and Japan[42] . 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 kaemperol 7-o-beta-D glucopyranoside, engeletin, isoengeletin, kaempferol, dihydrokaempferol, dihydrokaempferol- 5-o-P-D-glucopyranoside, rutin, kaempferol-5-o-beta-Dglucopyranoside,3,5,4 trihydroxystibene, vanillic acid, 3,5-dimethyl 4-0- beta-D-gluccopyranosylcinnamic acid,beta sitosterol, and beta-daucosterol [43,44] .

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 etc. [45]. The major constituent of ginger is sequiterpenoids with Zingiberene as the main component. It also contains β-sesquiphellandrene bisabolene and farnesene [46, 47]. 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, ß-bisabolene, sesquiphellandrene, and others). It also contains aldehydes and alcohols [48, 49]. Dried ginger powder contains Shogaol which is a dehydrated product of gingerol[50, 51.]A novel product Amadaldehyde has been isolated from ginger extract[52]. 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 rhizome[53] . 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- gingerdione [54].

Piper nigrum

Piper nigrum, the black pepper belongs to the family piperaceae[55]. 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 piperine[56]. It grows in tropical and subtropical regions of India[57].The petroleum ether extract of *Piper nigrum* contains 2E,4E,8Z-Nisobutyleicosatrienamide, pellitorine, trachyone, pergumidiene and isopiperolein B1. Piperidine and pyrrolidine alkamides are present in *Piper nigrum*.The most important of these is piperine [58-61], Pergumidiene and trachyone are also present in *Piper nigrum*[62] .Black pepper contains piptrigine, wisamine[63],Dipiperamide D and dipiperamide E.[64]

Piper longum

Piper longum is commonly known as pipli, 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 forests [65]. Pipli is native of Indo- Malaya region [66].*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 absent [67] . The alkaloids piperine, piperlongumine, piperlonguminine and methyl3,4,5-trimehoxycinnamate are the major chemical constituents.The spikes of pipli plant contains piperine and piplatin. Alkaloid A, a new one closely related to pellitorine is isolated from pipli. It also contains 3 new alkaloids, namely, piperolactum A, piperolactum B and piporadione[68]. Neelam and Krishnaswamy (2000) has mentioned that the roots of long pepper contains the following alkaloids, piperine, piperlongumine, piperlonguminine. Piperlongumine on purification yielded Cepharadione B, Cepharadione A , Cepharanone B, aristolactum A II norcepharadione B and 2 hydroxy (methoxy 4H dibenzoquinoline – 4,5 (6H) dione), ligins (Pluriatilol, fargosin, sesamine, asarinine, guinensine pipercide) [69], Syvatine, dieudesmine are isolated from seeds [70] . The essential oils in the plant consist of long chain hydrocarbons, mono and sesquiterpenes, caryophyllene as the main product [71, 72].The pungency of the fruit is due to the alkaloid piperine. The fruit contains calcium, phosphorus and iron.

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, Karmataka, Maharashtra etc[73]. The root contains plumbagin. The alkaloid Plumbagin is a natural napthquinone (5-hydroxy-2-methyl-1,4- naphthoquinon). 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 plant [74] .Elliptinone, droserone are also present in chitraka [75,76] . Napthaquinones [77], 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, ß- sitosterol, ß-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 [78, 79, 80]. It also contains aspartic acid, tryptophan, tyrosine, threonine, alanine, histidine, glycine, methionine, hydroxyproline, were isolated from the aerial parts [81].

Gmelina arborea

Rao et al (1970)., were isolated apigenin, luteolin, quercetin, hentriacontanol and *β*-sitosterol from *Gmelina arborea*. They also identified the presence of flavones glycosides[82].

Nair et al, reported the Quercetagetin and other glycosides of kaempferol, apigenin, and luteolin were isolated from *G. arborea* and *G. asiatica* [83].Vidya D et al, a simple, fast and precise reverse phase high performance liquid chromatography method is developed for the quantitative determination of apigenin, a flavonoid from the dried root powder of *Gmelinaarborea*. Apigenin was extracted from root powder of *Gmelina arborea* by using warm methanol.[84].Niyati et al, reported a high-performance thin-layer chromatography (HPTLC) method for the quantitative analysis of roots using *β*-sitosterol as a chemical Marker. Validated HPTLC method developed can be used as a tool for standardization of roots in different formulations using *β*-sitosterol as a marker[85].

Gmelina asiatica

Qualitative phytochemical analysis of aqueous, petroleum ether, chloroform, ethanol and acetone extracts of *G. asiatica* leaf indicated the presence of alkaloids, carbohydrates, glycosides, coumarins, quinones, saponins, steroids, terpenoids, proteins, phytosterols, tannins and flavonoids. Among the tested extracts, the ethanolic extract showed the presence of maximum number of (9/12) compounds. This is because ethanol is much polar than chloroform and acetone, hence extracting many of the active ingredients from the plant parts[86]. Netala Silvia et al evaluate the phytochemical constituents and antioxidant activities of methanolic extract of *Gmelina asiatica* stem which is locally used for the treatment of various diseases[87].

Costus speciosus

J.E. Smith Sanjay Jagtap et al.evaluatedphytochemical and antioxidant activity of the rhizome extracts of *Costus speciosus* were evaluated. Phytochemical screening indicated that, rhizomes are rich in a variety of primary and secondary metabolites such as carbohydrates, alkaloids, vitamin C, vitamin E, flavonoids, phenols, glycosides, saponins and minerals like Zn, Cu, Mn, Se and Fe[88].The ethanol leaf extract of *Costus speciosus* indicate the presence of chemical constituents such as Alkaloids, Tannins, Saponins, Steroid, Terpenoids, Flavonoid and Total phenol[89]. The rhizome of *Costus speciosus* are a good source of saponin like diosgenin, sapogenin, tigogenin, steroids, diosgenin, 5α-stigmast-9(11)-en-3β-ol, sitosterol-β-D-glucoside, dioscin, prosapogenins A and B of dioscin, gracillin, quinines, α-tocopherol, tricontanoic acids, curcumin, tricontanol, α-amyrin stearate, β-amyrin and lupeol [90, 91].

Tribulus terrestris

The preliminary phytochemical study of TT revealed the presence of saponins, flavonoids, glycosides, alkaloids, and tannins[92]. According to literature data, the saponin composition and the saponin content of TT from different geographic regions is different[93]. Kostova *et al*. studied the chemistry and bioactivity of saponins in TT. They reported that furostanol and spirostanol saponins of tigogenin, neotigogenin, gitogenin, neogitogenin, hecogenin, neohecogenin, diosgenin, chlorogenin, ruscogenin, and sarsasapogenin types are frequently found in this plant. In addition, four sulfated saponins of tigogenin and diosgenin type were also isolated. Majorly present are furostanol glycosides including protodioscin and protogracillin, of which protodioscin is the most dominant saponin and spirostanol glycosides are present in small quantities.[94, 95]. Wu *et al*. found that the quantity of main flavonoids is about 1.5 times that of main saponins. This indicated that the flavonoid contents in TT should be studied, developed, and further used[96].

Curculigo Orchioides :

The qualitative investigation test performed in four extracts (Pet. ether, Chloroform, Ethyl acetate & methanol) revealed the presence of alkaloids, glycosides, steroids, saponin & flavonoids etc. Methanol Extract of the drug shows the presence of carbohydrate & glycosides, saponins in high concentration followed by alkaloids, protein & amino acid, phytosteroids and gums & mucilage in extracts where as the phenolic compounds are present in lower concentration with more percentage yield. Phytochemical screening of extract demonstrated presence of flavonoids, polyphenolics, and alkaloids.

The total amount of phenolic content present in extract was found to be 752.23 ± 5.78 mg pyrocatechol equivalent (PE)/100 g. By using the standard curve of quercetin (R^2 = 0.9998), the total flavonoid content of extract was found to be 203.52 ± 4.56 mg quercetin equivalent (QE)/100 g[97, 98].

Azima tetracantha

The preliminary phytochemical screening carried out on various extracts of *A. tetracantha* revealed the presence of phytoconstituents such as alkaloids, flavonoids, glycosides, steroids, carbohydrates, tannins, proteins and aminoacids. Other compounds such as friedelin, lupeol, glutinol and β- sitosterol have also been reported in *A. tetracantha*[99].

Clerodendrum inerme

Clerodendrum inerme contained cardiac glycosides, anthraquinones, proteins, phenolics, flavonoids, saponins, tannins, iridoids, diterpenes, triterpenes, sterols, steroids, carbohydrates, fixed oils, volatile oils and lignin[100-103]. A new triterpenic glucoside, lup-1,5,20(29)-trien-3-O-β-D-glucopyranoside, n-octacosane, friedelin and β-amyrin, has been isolated from the leaves of *Clerodendrum inerme* (L.) Gaertn. (Verbenaceae)[104].B-friedoolean-5-ene-3-β-ol, β-sitosterol, stigmasta-5,22,25-trien-3-β-ol, betulinic acid, and 5-hydroxy-6,7,4′-trimethoxyflavone were isolated from the aerial parts of *Clerodendrum inerme*[105]. Volatile constituents such as 5-Oethylcleroindicin D, linalool, benzyl acetate and benzyl benzoate, have been isolated from C. inerme[106].

Thespesia populnea

The phytochemical studies indicated the presence of carbohydrate, protein, tannins, phenol, flavonoids, terpenes, saponins and gums in the ethanolic and aqueous extract of the bark. Ethanolic extract has increased the volume of urine significantly at 400 mg/kg. The results of the present study are in conformity with the reports that the plant possesses flavonoids like β sistosterol, etc[107].A new sesquiterpenequinone Thespesenone and Dehydrooxoperezinone-6-methyl Ether were isolated from *Thespesia populnea* [108]. Stem bark contains alkaloids, carbohydrates, protein, tannins, phenols, flavonoids, gums and mucilage, saponins and terpenes [109] of *Thespesia populnea* are reported to containβ-sitosterol-3-O- β-D-glucopyranoside-6'-O-stearate, β-sitosterol, daucosterol, kaempferol, 1-hentriacontanol, stearic acid, betulin [110]. Leaves of *T. populnea* contain lupeol, β-sitosterol as the major constituents it also contain presence of lupenone, alkanes[111].

A rare flavanoid, quercetin-7-O-rhamnoglucoside, was isolated from this plant and confirmed by spectral studies which shows significant antihepatotoxic activity[112].

Capparis sepiaria

The phytochemicals are flavonoids, reducing sugars, saponins, starch, gums, mucilages presented in the aqueous extract of *C. sepiaria*. The phytochemicals are alkaloids, flavonoids, glycosides, proteins, reducing sugars, saponins, starch, steroids tannins, mucilages, gums presented in the ethanolic extract of *C. sepiaria*[113].

Cinnamomum verum

FTIR analysis results proved the presence of alcohols, phenols, alkynes, alkanes, aromatic amines, alkyl halides, aliphatic amines and major functional groups observed were cinnamaldehyde and eugenol[114]. Cinnamic aldehyde and cinnamic acid, isolated from C. cassia and C.*verum* against myocardial ischemia[115], demonstrating that cinnamon additionally has thepossibility to be utilized to treat cardiovascular diseases.

Mesua nagassarium

Qualitative phytochemical tests for the potent antibacterial n-hexane extract of *M. ferrea* stamens revealed presence of classes of phytoconstituents such as terpenoids, steroids and volatile oil components[116]. Mesua genus is rich in secondary metabolites such as Phenylcoumarins, xanthones and triterpenoides.[117-119]. A oil which is commonly called nahor can be extracted from the seed of the plant.[120, 121]. It was also reported that form the seeds of M.ferrae 4-Phenylcoumarins such as mesuol, mesuagin, mammeisin and mesuone were isolated. Stamens can given α and β- sitosterol, biflavonoids mesuaferrones A & B euxanthone 7-methyl ether and other essential constituents. It is reported that two extremely new yellow pigments i.e. meauxanthone A & meauxanthone B have been identified. In the heart wood extracts of plant M.ferrae. Stamens consists the drug namely Nagakeshara is composed of mesuferrone A & B, mesuaferrol, mesuanic acid, α & β amyrin.[122]

It is also evaluated that the alcoholic extracts as well as H2O extracts of M.ferrae were highly rich. In reducing sugars, tannins and saponins.[123].

Alpinia galangal

Alpinia galanga belongs to the family *Zingiberaceae*. The ethanolic extract of Alpinia galanga had an extractive yield of 2.24% with total ash value of 6.17 %, water soluble ash 2.26 % and acid insoluble ash of 3.78% .Qualitative phytochemical analysis revealed the presence of various constituents such as alkaloids, carbohydrates, saponins, tannins, protein, glycosides, flavonoids, steroids and terpinoids[124].Quantitative Phyto chemical analysis of ethanolic extract of *Alpinia galanga* is reported to have maximum total phenol and flavonol content[125].

Carum copticum

The constituents of the seed of *C. copticum* included carbohydrates (38.6%), fat (18.1%), protein (15.4%), fiber (11.9%), tannins, glycosides, moisture (8.9%), saponins, flavone, and mineral matter (7.1%) containing calcium, phosphorous, iron, cobalt, copper, iodine, manganese, thiamine, riboflavin, and nicotinic acid[126]. *C. copticum* grows in different areas of the world containing different compounds. Main components of the oil of Iranian and African C. copticum oil are carvacrol, γ-terpinene, and p-cymene while thymol (97.9%) is the main component of south Indian plant oil. It was also reported that thymol (45.9%), γ-terpinene (20.6%), and o-cymene (19%) are the major components of the oil of *C. copticum* but ethylene methacrylate (6.9%), β-pinene (1.9%), and hexadecane (1.1%) were the other constituents of the plant[127]. Thymol (72.3%), terpinolene (13.12%), and o-cymene (11.97%) were also identified as constituents of *C. copticum*[128]. Chemical composition of *C. copticum* in two areas in Iran was assessed and results showed that the plant in Kamfiruz contains γ-terpinene (48.07%), p-cymene (33.73%), and thymol (17.41%) compared to the composition of plant in Eghlid area which included γ-terpinene (50.22%), p-cymene (31.90%), and nerolidol (4.26%) as main components [129].Srivastava et al., the main constituents of fruit oil of C. copticum were p-cymene (41.98%), carvacrol (45.20%), and thymol (0.48%)[130].

Syzygium aromaticum

Syzygium aromaticum oil against the test organisms in this research is due to the presence of several constituents such as eugenol, betacaryophyllene, limonene, alpha terpinolene (Chaieb et al., 2007), acetyl eugenol, methyl salicylate, iso-eugenol, methyl-eugenol, phenylacetic acid, salicyclic acid, protocatechuic acid, p-hydroxybenzoic acid, eugenin, eugenitin (Yang et al., 2003), phenolic compounds (kaempferol, rhamnetin, isorhamnetin, myricetin, quercetin, gallic acid, caffeic acid and syringic acid) respectively (Cai and Wu, 1996)[131]. The phytochemical studies indicated the presence of saponins, tannins, phenols, cardiac glycoside, flavonoids, alkaloids and anthracene were detected in extract of Clove flower (S. aromaticum)[132].

Discussion

Most of the herbal ingredients of *Parangipattai Rasayanam* have been reported to possess alkaloids, tannins, flavanoids, glycosides, sterols saponins etc. Plumbagin contains amino acids. Cinnamon possess essential oil, volatile oils etc. Ashwagandha is rich in steroidal lactones and alkaloids. Clerodendrum inerme contains cardiac glycosides, anthraquinones, proteins, phenolics, flavonoids, saponins, tannins, iridoids, diterpenes, triterpenes, sterols, steroids, carbohydrates, fixed oils, volatile oils. 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.[133]. Phytochemical studies have shown that plants with antimicrobial activity contain bioactive constituents such as tannins, flavonoids, alkaloids and saponins, alkaloid & flavinoids have been used as antiviral, antibacterial, antiamoebial & anticancer agents.Phenolic and polyphenolic are the other group of secondary metabolites flavanoids,sterols, phenols possess antibacterial and antifungal activity in general[134,135].The toxicity studies on the ingredients show that the herbs are safe for consumption. Rabiatu *et al*. also reported that *Cinnamomumverum* possess low moderate toxicity.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 *Parangipattai Rasayanam*is a potent drug for skin diseases, various ulcers,venereal diseases, peptic ulcer etc. There was no toxicity reported with the individual herbs except for *Cinnamomumverum* possess low moderate toxicity. Hence, the poly herbal Siddha formulation can be taken as a safe and effective drug as mentioned in the classical text books.

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Quick Response Code

DOI:10.22192/ijarbs.2018.05.01.023

How to cite this article:

Mahalakshmi .V, Ramaswamy. R .S, Banumathi.V. (2018). T the ingredients of a siddha drug - *Parangipattai Rasayanam*. Int.

DOI: http://dx.doi.org/10.22192/ijarbs.2018.05.01.023