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A REVIEW ON SIDDHA POLYHERBAL FORMULATION *SARVASURA KUDINEER* FOR THE MANAGEMENT OF PYREXIA (FEVER)

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ABSTRACT

The *Siddha* system of medicine emphasize on safety with remarkable clinical outcome. This medical system contains an enormous source of drugs obtained from the three sources i.e. botanical, animal and minerals. *Sarvasura kudineer* is a polyherbal combination which is indicated in the Siddha literature *Noigalukku Siddha parigaram* for the treatment of pyrexia. Since there is no scientific data available for the antipyretic action of *Sarvasura kudineer*, this review article was attempted to focus on the pharmacological actions from previous research works on each of its herbal ingredients *Evolvulus alsinoides(Vishnu kiranthi), Phyllanthus niruri(Keezhanelli), Justicia Adathoda(Adathodai), Zingiber officinalis(Chukku), Piper nigrum(Milagu), Piper longum(Thippili), Piper longum root(Thippili Moolam), Alpinia galanga (Arathai), Taxus baccatum(Thalisapathiri), Costus speciosus(Koshtam), Glycirrhiza glabra(Athimathuram), Anacyclus pyrethrum(Akkirakaram), Smilax chinensis(Parangi chakkai), Cyperus rotundus(Korai kizhangu), Mollugo cerviana(Parpadagam), Tinospora cordifolia(Seenthil), Andrographis paniculata(Nilavembu), Trichosanthes cucumerina(Peipudal), Vitis vinifera(Thiratchai).* Upon analysing the phytoconstituents and pharmacological action, *Sarvasura Kudineer* can be concluded to have antipyretic, anti inflammatory, antioxidant, immunomodulatory and antimicrobial action hence substantiating the traditional claims of *Sarvasura kudineer* for the management of all kinds of fevers.

KEYWORDS: Antipyretic action, *Sarvasura kudineer*, Fever, Siddha medicine, Natural medicine, Herbal medicine.

INTRODUCTION

'Nature' is an immense wealth of biologically active phytoconstituents which has been used since time immemorial as a cure for millions of diseases. Herbs have always proved to be the predominant source of origin and root cause of medicinal field, pharmacy and pharmacology and still being used as a source of bioactive compounds.[1] Fever (also known as pyrexia) is when a human's body temperature goes above the normal range of 36.5 ^{o}C -37.5^{o}C (98 ^{o}F - 100^{o}F). A fever is usually accompanied by sick behaviour, consisting of lethargy, depression, anorexia, drowsiness, hyperalgesia, and the inability to concentrate.[2-3] Pyrexia is a natural and complex mechanism of our own immune system to combat the severity of illness to prevent and reduce the multiplication of viruses and bacteria. This innate observable fact in the immune system has been for centuries even before medicine was invented. Pyrexia may also occur secondary due to infection caused by parasites, viruses, bacteria, inflammation, malignancy, auto immunereactionsor other diseased status. The formation of cytokines, interleukins and Tumour necrosing factors (TNF) enhance the synthesis of PGE2 in many tissues near to the pre-optic hypothalamic area via increase in cyclic AMP and triggers the hypothalamus to elevate the normal body temperature resulting in pyrexia.[4-6]

Medical science embodies a vast base of thoughts and concepts preserved in ancient heritage and profusedly enriched by cultural, religious and social traditions of early times from evolutionary phase to developmental process. The antiquity of medicine can be exploited through the authentic and documented sources of literary and logical evidences.[7] According to WHO about 80% of the world population rely mainly on plant-based drugs and the investigation of the efficacy of traditional medicine have been paid great attention because they are cheap and have little side effects.[8] The motto of this work is to screen the herbal ingredients of siddha drug *Sarvasura kudineer* to evaluate its effectiveness towards the management of fevers.

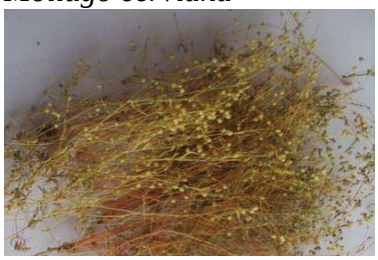
Preparation of *Sarvasura kudineer*

The 19 herbal ingredients of sarvasura kudineer as shown in the table-1 below are to be taken in equal quantity and ground into coarse powder. It is prepared as herbal decoction by boiling in water and reducing it in the ratio of 4:1 and should be consumed twice a day. As the name indicates, *Sarvasura Kudineer* means that it is indicated for "All kinds of fevers".

Phytochemical evaluation of Sarvasura kudineer

S.No	Botanical Name	Tamil Name	Phytoconstituents
1.	Evolvulus alsinoides 	Vishnu kiranthi	Evolvine , β-sitosterol, two alkaloids betaine and shankpushpin, erythritol, kaempferol.[10]
2.	*Phyllanthus niruri* 	Keezhanelli	MethylSalicylate,CarbohydrateAlkaloids,Glycosides,Saponins,Flavanoids,Tannins,PhenolicCompounds,Proteins, Amino acids, Mucilage, Terpenoids[11,12]
3.	*Justicia Adathoda* 	Adathodai	Vasicinone, Vasicinol, Adhatodine, Adhatonine, Adhvasinone, Anisotine and Hydroxypeganine[13,14]
4	*Zingiber officinalis* 	Chukku	Acetylsalicyclic Acid[15]
5	*Piper nigrum* 	Milagu	Ascorbic acid, Benzoic-acid, Beta-sitosterol[16]

6	*Piper longum* 	Thippili	Piperine[17]
7	*Piper longum root* 	Thippili Moolam	Piperine[17]
8	*Alpinia galanga* 	Arathai	Ascorbic acid, Borneol, Eugenol[17]
9	*Taxus baccatum* 	Thalisapathiri	Presence of 29 phytochemical compounds and more quantities of benzene propanol,2-butanone, furan carboxaldehyde, pentadecadien, and nhexadecanoic acid.[18]
10	*Costus speciosus* 	Koshtam	Beta-sitosterol, diosgenin[19]

11	*Glycirrhiza glabra* 	Athimathuram	Ascorbic acid , Benzoic acid , beta-sitosterol , eugenol [17]
12	*Anacyclus pyrethrum* 	Akkirakaram	N-isobutyldienediynamide and polysaccharides[20]
13	*Smilax chinensis* 	Parangichakkai	Steroidal sapogenins, spirostane, isospirostane, furostane, pregnane, and cholestane .[21]
14	*Cyperus rotundus* 	Koraikizhangu	β-sitosterol, the presence of alkaloids, flavonoids, tannins, starch, glycosides and furochromones, and many novel sesquiterpenoids[22-24]
15	*Mollugo cerviana* 	Parpadagam	Flavonoids,vitexin, glucosides, orientin[25]
16	*Tinospora cordifolia* 	Seenthil	β -sitosterol, δ-sitosterol, 20 β-Hydroxy ecdysone.Ecdysterone , Makisterone A,Giloinsterol.[26]

17	*Andrographis paniculata* 	Nilavembu	Andrographolide, neoandrographolide and 14-deoxyandrographolide, flavonoids, quinic acids, and xanthones [27]
18	*Trichosanthes cucumerina* 	Peipudal	β –sitosterol, Luteolin-7-glucoside Cucurbitacin B, Cucurbitacin E; IsocucurbitacinB;23,24dihydroisocucurbitacin B; 23,24-dihydrocucurbitacin E; β -sitosterol and stigmasterol.[28]
19	*Vitis vinifera* 	Thiratchai	Quinicacid, umbelliferone, Hydroxybenzic acid,Esculetin , Caftaric acid, Coumaroyltartaric acid, Ferulic acid pentosyl, Stilbenes, Resveratrol, Eriodictyol-7-glucoside, Flavonols, QuercetinKaempferol [30]

Pharmacological profile of ingredients forAntipyretic activity

1. Evolvulus alsinoides

The antipyretic properties of Evolvulus alsinoides was studied in rats 18 h after yeast injection, and hyperthermia was recorded and continued throughout the test in comparison with paracetamol. The study results show that the plant extract produced a reduction in hyper pyrexia being pronounced within 90 min after administration of the plant extract. Also, it was found that the plant extract was as effective as paracetamol in reducing hyperthermia ($P < 0.05$) within 2 h of administration of the extract.[31]

2. Phyllanthus niruri

Akila Elias. et al. carried out the pharmacological study to evaluate the Analgesic and Anti-Pyretic potential of the plant *Phyllanthus niruri* in experimwental animals. In this study, water and ethanol extract of *Phyllanthus niruri* showed significant Analgesic and Anti-Pyretic activity.[32] Also in another study performed by Paithankar et al., *Phyllanthus niruri* has been reported to exhibit marked anti hepatitis B virus surface antigen activity in in-vivo and in-vitro studies.[33]

3. Justicia adhatoda

Chakraborty, A. and Brantner, A. H. 2010, conducted a study to evaluate the anti inflammatory activity of the methanol extract, of *Justicia Adhatoda* extract. In their study,the non-alkaloid fraction, containing the saponins and the alkaloids was evaluated by the modified hen's egg chorioallantoic membrane test. The alkaloid fraction showed potent activity at a dose of 50 µg/pellet equivalent to that of hydrocortisone while the MeOH extract and the other fractions showed less activity. In another study by Kathale, Antimicrobial effect ofethanol extract of *A.vasica* showed maximum activity against staphylococcus aureus, than Proteus vulgaris and Pseudomonas aeruginosa the least activity was shown against E. Coli[34,35].

4. Zingiber officinalis

The analgesic and antiinflammatory effect of ethanolic extract of *Zingiber officinalis*in doses of 100,200 and 300 mg/kgB.W,Ibuprofen20mg/kg was carried out by using Hot plate test, acetic acid – induced writhing and Carrageenan induced inflammation in male mice. The study results revealed that *Zingiber officinalis* extract had excellent analgesic and anti-inflammatory activity as it showed a significant inhibition of writhing response and increase in hot plate reaction time and also caused significant decrease $P<0.05$ in paw edema comparable with standard anti-inflammatory drug drug Ibuprofen.[36] Mosco et al., concluded that the antipyretic effect of the plant may correlate to some extent with inhibition of release of prostaglandins, as shown in his invitro study using rat peritoneal leucocytes.[37]

5. Piper nigrum

Pavani et al., studied the antipyretic activity of *Piper nigrum* in alcoholic extract in Wistar albino rats by inducing pyrexia by injecting 15% (w/v) Brewer's yeast suspension. In his study results it was found that the *P. nigrum* extracts at doses of 250 and 500 mg/kg significantly reduced the body temperature and was comparable with standard drug Paracetamol.[38] Piperine an important phytoconstituent of the Piper family is believed to have the alleged anti-inflammatory capability and several other pharmacological activities which can be responsible for the management of pyrexia.[39]Also the aqueous methanolic extract of *Piper nigrum* 10mg/ml showed significant antimicrobial activity against *S.aureus & E.coli* with a zone of inhibition, compared to the standard drug 100µg/ml.[40]

6. Piper longum(Fruit)

The anti-inflammatory effects of *Piper longum* fruit was evaluated in Carrageenan induced paw oedema in rat models. The study results revealed that *Piper longum* fruit showed marked anti-inflammatory activity .[41] Experimental Studies by GP Choudhary revealed the mast cell stabilizing activity of *Piper longum*.[42]Also in an antimicrobial study conducted by Trivedi et al.,the aqueous extract of Piper longum at 10mg/ml showed powerful zone of inhibition against *S.aureus, Bacillis subtilis, E.coli, Pseudomonas aeruginosa, & Aspergillus niger, Candida albicans* when compared to the standard drug griseofulvin.[43] In another study by Ali et al., the petroleum ether and ethyl acetate extracts of *P. longum* were found to exert antimicrobial effects against various microorganisms.[44]

7. ***Piper longum (Root)***

In a study conducted by Vedhanayaki et al.,the aqueous suspension of *P. longum* root powder (200, 400, and 800 mg/kg) was given orally to mice to assess amount of writhing to chemical stimulus and in rat to evaluate the delay in reaction time to thermal stimulus thereby to study its analgesic effects. The effects of the 400 and 800 mg/kg doses of *P. longum* were similar to that of nonsteroidal anti-inflammatory drugs (p<0.001). Both ibuprofen (40 mg/kg) and *P. longum* (800 mg/kg) demonstrated 50% protection against writhing. The study results revealed that the plant root produces a weak opioid-type but potent nonsteroidal anti-inflammatory drug-type of analgesia.[45]

8. Alpinia galanga

A Pharmacological study was carried out by Ghosh Asim, et al. to assess the acute and chronic anti-inflammatory activity of *Alpinia galanga* using albino rats of either sex. The acute and chronic anti-inflammatory effects of this extract were evaluated using carrageenan-, bradykinin-, and 5-HT-induced rat paw edema and formaldehyde-induced rat paw edema respectively and the efficacy was compared with the standard drug. The study results concluded that *A. galanga* has anti-inflammatory properties and probably acts by blocking histaminic and serotonin pathways. Therefore *Alpinia galanga* can be suggested as an alternative to NASAIDs and corticosteroid in inflammatory disorders.[46]

9. Abeis webbiana

Dinesh et al., studied the methanolic extract of *Abeis webbiana* for its antipyretic potential by yeast induced pyrexia in rats of dose 200 and 400 mg/kg body weight. The study results revealed that 200 mg/kg body weight of the plant extract caused significant dose dependent

lowering body temperature up to 3hr and 400 mg/kg dose lowering of body temperature up to 6 hours.[47] Also in another study performed by Nayak et al., evaluated the antitussive effect on a cough model induced by sulphur dioxide gas in mice.In this study, themethanol extract of *A. webbiana* Lindl extract (400 and 600 mg/kg) showed maximum inhibition of cough frequency by 71.69% and 78.67%, respectively and exhibited significant antitussive activity compared with the control codeine phosphate in a dose dependent manner.[48]

10. Costus speciosus

In acute and sub acute anti-inflammatory study conducted in Carrageenan induced paw edema and cotton pellet induced granuloma by Bhavani et al., it was found that the Costus *speciosus* extract produced a dose dependent and statistically significant($p \leq 0.05$) acute and sub acute anti-inflammatory effect at 800mg/kg dose and 400mg/kg & 800mg/kg respectively. There was a mild reduction in rectal temperature of rats treated with 800mg/kg Ethanolic extract. This study provides a scientific document for the traditional use of this plant against inflammation and fevers[49] Similar reports on anti-inflammatory effect was also noted by Binny et al in his study to evaluate the anti-inflammatory and antipyretic effect of the rhizome *Costus speciosus*.[50]

11. Glycyrrhiza glabra

In a study by Srivastava et al, Glycyrrhetic acid a phytoconstituent of *Glycirrhiza glabra* showed anti-pyretic activity similar to that of Na salicylate on rectal temperature of normal & pyretic rats. Further, it was noted that in a clinical trial for traumatic inflammation *Glycyrrhiza glabra* possess more potent antipyretic effect than oxyphenylbutazone.[51] *Glycirrhiza glabra* was also found to possess immunomodulatory activity in a study to determine the In vivo phagocytosis, of cellular immune response haemagglutination antibody titre & plaque forming cell assay using sheep RBCs immunomodulatory activity.[52] In a study by Mirmala et al., it was found that the extract showed a maximum of 46.86% inhibitory action anti-inflammatory activity in Carrageenan induced rat paw oedema at dose levels of 100,200,300 mg/Kg.[53]

12. Anacyclus pyrethrum

Antipyretic activity of *Anacyclus pyrethrum* was screened in yeast induced pyrexia in rats at a dose of 100mg/kg i.p. and was observed to possess significant anti-pyretic activity. The activity was very comparable to standard drug Paracetamol 150mg/kg i.p. The maximum non

lethal dose was found to be 2g/kg. Hence *Anacyclus pyrethrum* was shown to have an effective antipyretic and anti-inflammatory agent [54, 55].

13. Smilax chinensis

Jana et al., studied the antipyretic effect of methanol extract of the root of *Smilax chinensis*in yeast induced elevated rectal temperature. The experimental results exhibited that chloroform, ethyl acetate, and metha-nol fractions of methanol extract of the root of *Smilax chinensis L* possess a significant antipyretic effect in the maintaining of normal body temperature and reduce yeast induced elevated rectal temperature in rabbits and their effect are comparable to that of standard antipyretic drug, paracetamol. The result of the present study suggests that all the fractions of *Smilax chinensis L*. root extract significantly produced antipyretic effect [56].

14. Cyperus rotundus

The alcoholic extract of *C. rotundus* showed highly significant (P<0.001) antipyretic activity against pyrexia produced in albino rats by the subcutaneous injection of suspension of dried Brewer's yeast in gum acacia in normal saline. A specific fraction obtained by chromatographic method from the petroleum ether extract was found to possess a significant anti-pyretic effect similar to acetyl salicylic acid when used on the same animal model [57].

15. Mollugo cervicana

Phytochemical analysis of *Mollugo cervicana* done by Bonjar et al., reveals the presence of Phytochemical constituents such as alkaloids, flavonoids, and Vitamins C and E that serve a defence mechanism against many microorganisms, insects and other herbivores[58]. Flavanoids act as anti-inflammatory, antipyretic, analgesic, spasmolytic and antioxidant as it removes the free radicals that damage the body cells [59]. Vitamin C and Vitamin E also has antioxidant properties which protects the membrane fatty acids from peroxidation[60].

16. Tinospora cordifolia

Aqueous and methanolic extract of leaves of *Tinospora cordifolia* was assessed for its antioxidant and anti-inflammatory activity by in vitro methods. The phytochemical analysis revealed the presence of carbohydrates, amino acid, alkaloids, saponins, tannins, flavonoids, terpenoids, glycosides, xanthoproteins and phenols. In vitro albumin denaturation assay, lipooxygenase inhibition, and membrane stabilization assay and proteinase inhibitory activity at different concentrations were performed to assess anti-inflammatory activity of the plant

extract. *T. cordifolia* leaf extracts exhibited significant anti-proteinase activity at different tested concentrations. Maximum inhibition was found to be 55.2% at 400 µg/ml for *T.cordifolia* against that of 77.6% for Aspirin. The non steroidal drugs act either by inhibiting these lysosomal enzymes or by stabilizing the lysosomal membrane. Inhibition of 69.2% for *T. cordifolia* against that of 71.3% for Aspirin. Plant extracts were found to be effective against both Gram-positive (S. aureus) and Gram-negative bacteria (P. aeruginosa, K. pneumonia and E. coli). Therefore the study results show that *T.cordifolia* has anti-inflammatory and antimicrobial acitivty[61].

17. Andrographis paniculata

Several studies have experimentally demonstrated the antipyretic effect of *Andrographis paniculata*. The antipyretic effect has been analysed to be due to the presence of a major phytoconstituent andrographolide which lowered the fever produced by different fever-inducing agents such as bacterial endotoxins, Pneumococcus, haemolytic streptococcus,typhoid and paratyphoid[62]. Intragastric administration of an ethanol extract of the aerial parts (500mg/kg body weight) to rats decreased yeast-induced pyrexia.The extract was reported to be as effective as 200 mg/kg body weight of aspirin, and no toxicity was observed at doses up to 600 mg/kg body weight[63,64]. Also, the intragastric administration of an ethanol extract of the aerial parts (25mg/kg body weight) or purified andrographolides (1 mg/kg body weight) to mice stimulated antibody production and the delayed-type hypersensitivity response to sheep red blood cells. The study indicateds that either andrographolide or neoandrographolide may be involved in the immunostimulant response[65,66].

18. *Trichosanthes cucumerina*

Arawwawala et al., evaluated the anti-inflammatory activity of *Trichosanthes cucumerina* and its effect was assessed by determining its effects onmembrane stabilizing activity andnitric oxide inhibitory activity by use of the carrageenan-induced paw oedema model in Wistar rats. Apart from the lowest dose of the Hot water extract of *Trichosanthes cucumerina*, other tested doses (500, 750, 1000 mg/kg) produced a significant ($P \leq 0.05$) inhibition of the inflammation, mostly evident at 5h after the injection of carrageenan. The anti-inflammatory effect induced by 750 mg/kg, was comparable to that of the reference drug, indomethacin at 4 and 5h. The study results revealed that the tested plant extract possessed remarkable anti-inflammatory effect [67].

19. Vitis vinifera

The methanolic extract of *Vitis vinifera* leaves (100, 200 and 400 mg/kg) was studied for anti-pyretic and anti-inflammatory activity. The anti-pyretic were evaluated by using Brewer's yeast-induced pyrexia in rats. The extract was also investigated for anti-inflammatory activity by usingcarrageenin-induced hind paw oedema in rats and the paw volume was measured plethysmometrically at 0, 1and 3 h after carrageenan injection. The antipyretic effect was started at 1h and extended for at least4h after the drug administration. MEVV showed significant ($p<0.01$) and dose dependent anti-pyretic and anti-inflammatory activity in comparison to control group. No acute toxicity was observed in rats after oral administration of the MEVV at the dose of2000 mg/kg. These results suggest that the metholic exyract of *Vitis vinifera* leaves possess antipyretic and anti-inflammatory action[68].

CONCLUSION

Thus the herbal ingredients of *Sarvasura kudineer*, a traditional Siddha formulation has beenscientifically analysed and has been found to possess multimodal effects like anti-inflammatory, analgesic, antipyretic, antimicrobial, antioxidant and immunostimulant effects. More evidence is warranted on the preclinical and clinical efficacy of this polyherbal antipyretic formulation.

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