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A REVIEW ON PHARMACOLOGICAL PROPERTIES OF SIDDHA FORMULATION *VISHNUKRANTHI KUDINEER* FOR THE MANAGEMENT OF FEVER IN PEDIATRICS

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ABSTRACT

Vishnukranthi kudineer is a polyherbal preparation which is indicated for 64 types of fever in children mentioned in Siddha pediatric textbook of *Kuzhanthai maruthuvam*. Fever in children is a common presenting problem of pediatric practice. Though it is a physiological phenomenon with enhanced immune function and possible benefits, the risk-benefit balance swings back as fever can cause fatigue, arthralgia, myalgia, anorexia, delirium, tachycardia, tachypnoea added to the risk of febrile convulsions especially in children. Pathologically fever occurs mainly through inflammation, infection and immune mediated response. In this review, the traditional Siddha formulation of *Vishnukranthi kudineer Vishnukranthi* [Evolvulus alsinoides.L] *Sukku* [*Zingiber officinale*] *kadukkai thol* [*Terminalia chebula*] *Inndu*[*Acacia caesia*], *Vaaluzhuvai* [*Celastrus paniculatus*] have been evaluated in the light of both traditional Siddha humoural concept and its scientific evidences on its pharmacological action against fever. Through this study the scientific exploration of traditional Siddha formulation has been extensively explored for further preclinical and clinical studies on the general management of fever in Pediatric age groups.

KEYWORDS: Pediatrics, Kuzhanthai maruthuvam, fever, antipyretic, anti-inflammatory, antimicrobial.

INTRODUCTION

Fever is an objective sign of an abnormal increase in body temperature of ≥ 37.5 °C caused by elevation of the hypothalamic set-point.[1] It is a normal physiological response to illness that facilitates and accelerates recovery.[2] Fever is produced by the action of pyrogens on the thermoregulatory centre of the hypothalamus. Except in extremely young children, it is rare to see a significant systemic infection in the absence of fever.[3] The infectious agents, microbial products, cytokines, inflammatory processes inducing macrophages, endothelial cells and the reticuloendothelial system synthesize and release pyrogenic cytokines such as interleukins(IL-1, IL-6), tumor necrosis factor (TNF) and interferon(IFN).[4] These cytokines cause the synthesis of prostaglandin E2 (PGE2), which binds to prostaglandin receptors in the hypothalamus to raise the thermostatic set point to febrile levels.Currently, the treatment of fever includes physical cooling and antipyretic medications such as NSAIDs and Paracetamol. Although fever and pain are both nonspecific symptoms, a patient's discomfort mostly relies on pain. Hence antipyretics are also used as analgesics.[5][6]

Traditional herbs have been the original source for most of the drugs throughout the world since centuries. Medicinal plants contain many chemical compounds which are the major source of therapeutic agents to cure human diseases. Recent discovery and advancement in medicinal and aromatic plants have led to the enhancement of health care of mankind. Various medicinal plants like Neem, Arjuna, Aswagandha, Tulsi, etc. traditionally used for treating fever.[7] The in-vitro screening methods also contribute to the demand on vital primary inquisition which is crucial to retrieve desired plant extract with promising and effective attributes for upcoming chemical and pharmacological research.[8][9] The present review on the Siddha herbal formulation *Vishnukiranthi kudineer* indicated in the Siddha Text *Balavagadam* (Pediatric text) for the management of 64 types of fever as classified based on Siddha humoural concept. The literature review involves exploration of Siddha concept of Suram (fever) and the role of ingredients of *Vishnukiranthi Kudineer* towards its management. Scientific evidences on the antipyretic, anti-inflammatory, antimicrobial and antioxidant properties that are significant in the management of fever have also been analyzed through this review.

Siddha Humoural concept of fever

Kuppusamy muthaliyar in his book Siddha Maruthuvam mentioned that *"Kudalil Seethem allathu Suram varathu, Ageerana minri Suramvarathu"* (Indigestion as the cause of *Suram*).

Suram is considered as one of the separate disease in Siddha system of Medicine. The functional units of the human body namely *Vatha, Pitha* and *Kapha* are said to be in ratios 1:1/2:1/4 respectively. The ratio of these functional units can change by the consumption of unhealthy food pattern and habits by which the body gets diseased. Wandering in mist, too much of chills, wetting in rain, too much of bathing increases *Kapha* which fluctuates *Kledaka kapha* and results in *Ama* and fever. This shows that *Suram* is caused by increased *Kapha dosha*.[10] *Evolvulus alsinoides* also known as *Vishnukranthi*, *vishnukrantha* or *vishnugandhi* is used as home remedy to treat high fever due to various infections. It is used to enhance digestion to get relief from gastric irritation and also relieves post viral fever symptoms like that of dengue and chikungunya.[11]

Pathology of Suram (fever) in Siddha system

Formation of *Amam* is the main reason for increasing body temperature. *Ama* means indigestible particle that are formed in the intestine. This *Amam* is absorbed by the vessels and distributes all over the body and obstructs the excretion of sweat. *Prasaka Pitham* (type of *Pitham*), *Kledaka Kabam* (type of *Kabam*) and *Praana*, Samaana and Viyanavayu (types of Vatham) are involved in the gastro- intestinal digestion. The digestive effect of Prasaka Pitham and the emulsifying, soothing effects of Kledaka Kabam are antagonistic to one another. Hence the balance or harmony of the effects of *Vatham, Pitham and Kabam* concerned with the gastro-intestinal digestion, is of paramount importance and imbalance between these interrelated functional factors results in '*Amam*'. Generally, the properties and effects in *Amam* resembles those of vitiated *Kabam* which is markedly increased (*Prakobam*). *Amam* could produce poisonous and toxic effects.[10]

Taste based concept on Ingredients of *Vishnukranthi Kudineer*.[12]

S.No	Ingredients	Botanical Name	Suvai	Veeryam
1.	*Vishnukranthi*	Evolvulus alsinoides.Linn	Bitter, Mild pungent	Veppam
2.	*Sukku*	Zingiber officinale.R	Pungent	Veppam
3.	*Kadukkai Thol*	Terminalia chebula.R	Pungent	Veppam
4.	*Indu*	Acacia caesia(L.)Willd	Pungent	Veppam
5.	*Vaaluzhuvai*	Celastrus paniculatus.Willd	Bitter	Veppam

Suvai Based Humoural Concept

The five elemental link between Thirithodam and Taste shows that Pungent, bitter, astringent are the pacifying tastes of Kapha.[13] The bitter and pungent taste of the ingredients helps to

pacify the Kapha and reduce the Ama which is the root cause of *Suram*. This shows the Anti-pyretic action of Vishnukranthi Kudineer based on the concept of suvai in Siddha treatment.

STUDY DRUG PREPARATION

Table 1: Ingredients of Vishnukiranthi Kudineer.

S.No	Ingredients	Botanical Name	Quantity
1.	*Vishnukranthi*	Evolvulus alsinoides.Linn	10Grams
2.	*Sukku*	Zingiber officinale.R	10Grams
3.	*Kadukkai Thol*	Terminalia chebula.R	10Grams
4.	*Indu*	Acacia caesia(L.)Willd	10Grams
5.	*Vaaluzhuvai*	Celastrus paniculatus.Willd	10Grams

Procedure: These raw drugs are added in equal proportion 10gm each and crushed coarsely. Then four parts of water is added to this mixture and allowed to boil until it is reduced to one fourth. Then the decoction is filtered and is ready for consumption.[14]

Scientific evidence on pharmacological properties of the ingredients of VKK

1. Evolvulus alsinoides. Linn

It is a herbaceous plant, belongs to the family Convolvulaceae and the whole part of this herb is used in the polyherbal preparation. Evolvulus alsinoides (Linn.) Linn. is a supine perennial herb consisting small branched rootstock of wood. They are enclosed with plentiful branches that are annual and beyond 30 cm long. The branches include long hairs and frequently prostrate. Evolvulus alsinoides (Linn.) Linn. incorporates small leaves which are elliptic in shape. They are acute, susceptive and are densely hairy.[15] Evolvulus alsinoides (Linn.) Linn. was interpreted to find the phytochemicals like alkaloids, carbohydrates, steroidal glucosides, saponin, tannins, pseudo tannins, chlorogenic acids, flavones, flavonoids, coumarin, anthocyanin, phenol, terpenoides, resins, volatile oil, anthraquinones, phytosterol and triterpenoids. The analysis portrayed the potentiality of components that are known to illustrate medicinal constituents as well as physiological activities.[16] In research oriented view, the plant was made into a powder and subjected to extraction process and the extract is used in wistar albino rats to study the anti-pyretic and anti-inflammatory actions. Within 2 hours of administration of the plant extract, it was as effective as paracetamol in reducing hyperthermia.[17] The organisms used for the antimicrobial activity of E.alsinoides (L.) L. aqueous extract are Escherichia coli, Pseudomonas aeruginosa, Candida albicans and Staphylococcus aureus. The inhibition values (mm) for the concentration 10 mg/ml, for E.coli was 14 and for Pseudomonas aeruginosa is 11. Metals like Lead and Mercury were not

detected in the extract.t. The plant extract produced a reduction in hyper pyrexia induced by yeast injection in rats, with activity being pronounced within 90 min after administration of the extract. Also, within 2 h of administration of the extract, the plant extract was as effective as paracetamol in reducing hyperthermia ($P < 0.05$).[17]

Zingiber officinale.R

Ginger (Zingiber officinale Rosc.) belongs to the family Zingiberaceae.[18] The rich phytochemistry of ginger includes components that scavenge free radicals produced in biological systems. For the purpose of energy production, some free radicals which generated during the process of oxidation are essential.[19] Gingerol, shogaol, and other structurally-related substances in ginger inhibit prostaglandin and leukotriene biosynthesis through suppression of 5-lipoxygenase or prostaglandin synthetase. Additionally, they can also inhibit synthesis of pro-inflammatory cytokines such as IL-1, TNF-α, and IL-8.[20] [21] In another investigation, Pan *et al*. showed that in macrophages, shogaol can down-regulate inflammatory iNOS and COX-2 gene expression.[22] 6-Shogaol has exhibited the most potent antioxidant and anti-inflammatory properties in ginger, which can be attributed to the presence of alpha, beta-unsaturated ketone moiety.[23]

Ginger suppresses prostaglandin synthesis through inhibition of cyclo oxygenase -1 and cyclo oxygenase -2.The characterization of the pharmacological properties of ginger entered a new phase with the discovery that a ginger extract inhibits the induction of several genes involved in the inflammatory response. A phytochemical in ginger named 6-gingerol acts as an anti-inflammatory compound that may be useful to treat inflammation without interfering with antigen presenting function of macrophages. An another study showed that ginger has potent antimicrobial activity against Salmonella spp., Escherichia coli., Staphylococcus aureus.[24]

Terminalia chebula.R

Terminalia chebula (Gaertn.) Roxb. (Family Combretaceae), popularly known as '*Belleric myrobalan*', is a large deciduous tree widely occurring throughout the Indian subcontinent, Nepal, Sri Lanka, and south-east Asia.[25] *T. chebula* fruit is one of the main components or integral part of the traditional laxative formulation, '*Triphala*' which is used in a variety of ailments such as leucorrhoea, common cold, constipation, headache, pharyngitis, liver diseases, gastrointestinal complaints and hair fall[26] A study concludes that the ethanolic extract of Terminalia chebula fruits possesses analgesic and anti inflammatory activities in mice and rats at the dose of 250 mg/kg and 500mg/kg respectively.[27] Ellagic acid possesses

significant protective potential against oxidative stress and liver injury resulting from long term intake of diclofenac as compared to *T. chebula* fruit aqueous and ethyl acetate extracts. Antioxidant evaluation of *T. chebula* fruit extracts showed significant radical scavenging activities during *in vitro* ABTS radical scavenging and FRAP assays.[28]

Acacia caesia(L.)Willd.

Acacia caesia Linnaeus is a leguminous perennial climbing shrub of the family Mimosaceae, native to south-east Asia. The extract from the stem bark is a frequently used remedy among the Miza tribes of north-east India for gastrointestinal infections.[29] An antimicrobial study on Acacia caesia revealed that all extracts showed varied degree of antimicrobial activity against the tested pathogens. However, the ethyl acetate extracts exhibited higher inhibition zone (15.73 mm) against the bacterium, *Bacillus subtilis*, whereas the ethyl acetate extract showed high degree of inhibition zone against the fungus, *Mucor rouxii* (20.67 mm). These results support the therapeutic importance of *Acacia caesia* in curing infectious diseases and encourage the extensive use of it in health care practices.[30] Another assays Confirms the activity of the stem extract to be comparable to that of Ciprofloxacin, which suggest the drug like potential of the extract compounds. The disc diffusion studies also shows a comparatively higher activity of the stem extract against gram negative bacteria (E.coli and P.aeruginosa) as compared to gram positive bacteria (S.aureus) which could prove therapeutically significant due to the inability of antibiotics to penetrate gram negative bacteria.[31] The widely publicized antimicrobial properties of the plant stem could be attributed to the interplay of the known antimicrobial compounds such as isoeugenol, methoxyeugenol, 4-((1e)-3- hydroxy-1-propenyl)-2-methoxyphenol, dibutyl phthalate, phytol and also other compounds present in the stem.[32] Research study shows that the extract of this plant are effective in inhibiting protein denaturation, and exhibited significant in vivo anti-inflammatory activity and it also contain strong anti-oxidant power which supports the traditional medicinal utilization of the plant.[33] The results a study clearly indicate that the methanolic leaf extract of the study species is effective in scavenging free radicals and has the potential to be powerful antioxidant.IC50 values observed for DPPH, hydroxyl radical scavenging and metal chelating assays were 109, 177 and 295 µg/ml respectively.[30]

Celastrus paniculatus

Celastrus paniculatus Willd (*CP*) belonging to the family Celastraceae is a well-known plant in Indian traditional medicine with different medicinal uses and negligible side effects. It is

generally known as *Malkangani, Valuluvai* or black oil plant. It is climbing in nature with long slender like branches which are brown in colour. The traditional uses of this plant and seeds include arthritis, asthma, antipyretic, thermo genic, intellect orders, anti-paralysis, sedative, tranquilizer, in paralysis, rheumatism, leprosy, bacterial infection and as wound healing agents.[34] Literature review showed that most of the reported activities like anti-arthritic, antioxidant, hypo lipidemic, nootropic and cognitive enhancement activity are by different extracts of *CP* seeds which may be due to celapanin, celapagine, celapanigine, β-amyrin, β-sitosterol, stigmaserol, malkanguinol, malkangunin and paniculatadiol.[35] Chemical examination of fixed oil from the CP seed showed presence of fatty acids, viz., oleic, linoleic, linolenic, palmitic, stearic, crude lignoceric acid, benzoic and acetic acid as volatile acids. The aqueous extract of *CP* seed contained traces of tannins, reducing sugars but no starch.[36] *CP* extract exhibit antioxidant properties by scavenging superoxide anion and hydroxyl radical to reduce the hydrogen peroxide-induced cytotoxicity and DNA damage in human fibroblast cells. The activity of cellular acetylcholinesterase (AChE) not being affected suggest that *CP* provided neuro-protection in part by virtue of their antioxidant properties, and their ability to induce antioxidant enzymes.[37] *CP* fruit seed oil showed good antioxidant activity when performed by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging method inhibiting activity of authentic proxy nitrite and total reactive oxygen species. Mean increase in the paw volume and percentage inhibition of inflammation in carrageenan paw edema method revealed that *CP* seeds possess good anti-inflammatory activity due to inhibition of prostaglandin synthesis and IL-1β.[35]

CONCLUSION

The wide range of chemical structures provided by natural sources is presently under investigation for their chemical as well as pharmacological screening. Evaluation of Indian traditional medicine with light of modern tools & technique is possible through the proper exploitation of wide biodiversity and great ancient treatise. This article reviewed the pharmacological actions of raw drugs used in Siddha polyherbal preparation *Vishnukranthi kudineer* against 64 types of fever in children for its antipyretic, antiinflammatory, antimicrobial and antioxidant properties that are significant in the management of fever in children. Further there is an emergent need to explore *Vishnukranthi kudineer* with preclinical and clinical studies to substantiate the literature evidences of this review.

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