



Review Article

AN EXPLORATORY REVIEW OF PHARMCOLOGICAL ACTIVITIES OF *NOTCHI KUDINEER*- A
SIDDHA HERBAL DECOCTION USED IN COVID-19

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ABSTRACT

COVID-19 Caused by the novel corona virus (SARS-CoV-2), which has already pushed the entire global community to change their priorities towards finding a suitable anti-viral medicine and a vaccine. While most of the countries have started to prescribe vaccines, which show varied levels of efficacy, finding an effective anti-viral medicine against the virus is still in the early stages despite full-fledged research activities at global level. Many countries particularly those having a rich traditional health science background like India and China started to recommend medicines belonging to local health traditions. The public utilization of those medicines also yielded good results in terms of prevention of the viral infection, reducing the severity of disease or/and reducing the number of days required to recover from the disease as perceived and reported by the patients and doctors.

In Tamil Nadu, there are more than 80 million populations. Siddha medicine is the most widely used system of traditional medicine. 'Suram' is the Tamil word equivalent to the term 'fever'. *Kabasuram* (Also known as *Aiya suram*) is one among the 64 types of fevers mentioned in Siddha symptoms of which are identical to those of COVID-19. "*Notchi kudineer*"- a Siddha herbal formulation is being used since many centuries for fever and respiratory disorders with remarkable success. This review article attempts to explore the pharmacological evidence in support of the therapeutic usage of "*Notchi kudineer*" hence justifying its usage in respiratory related illnesses having fever as a main symptom like the current pandemic of COVID-19.

KEYWORDS: *Notchi kudineer*, COVID-19, Anti-inflammatory, Anti-pyretic, Analgesic Activity, Anti-tussive Activity, Immunomodulatory activity.

INTRODUCTION

Emerging at the end of 2019, COVID-19 pandemic is still spreading quickly around the world. Mutations of the SARS-CoV-2 and the successive next waves have made it very tough to find a suitable solution in the form of vaccine or anti-viral medicine. Many countries have started vaccinating their people since the beginning of the year 2021. However there can be no second opinion in the important and urgent need of a suitable and proven anti-viral drug against SARS-CoV-2. In the absence of such an anti-viral drug, many countries started to prescribe their traditional medicines - by repurposing the existing medicines as a prophylactic and therapeutic measure against this disease.

Since Siddha system is the most widely practiced traditional system in Tamil Nadu, many Siddha medicines were prescribed after long consultations with the experts of Siddha system of medicine.

As per *Siddha* science of healthcare, diseases or derangements or disorders appear when there is vitiation of one or more of the three biohumors- *Vali*, *Azhal* and *Aiyam*. *Thottru Noigal* (communicable diseases or infectious diseases) are associated with changes in either *Aiyam* or *Azhal*. *Aiyam* (*Syn-Kabam*) which is responsible for structure and stability of the body gets affected. As per the Siddha text *Guru Naadi*, *Thottru Noigal* is caused by *Kirumi* (Pathogens). The severity of the outcome of the infection depends upon the *Noiyinan vanmai* (immunity of the individual) and if it is good, the individual will be less affected. Hence, the Siddha formulations are designed in such a way to neutralize the *Aiyakuttram* and to maintain the immunomodulatory mechanism during this period^[1]. Siddha system mentions 32 forms of internal medicines and another 32 forms of external drugs used for treatment. Among all the internal medicines, *Kudineer* (decoction) is one showing quick

therapeutic action and having the shortest shelf life of just three hours.

“Notchi kudineer” a Siddha formulation described in Siddha manuscript “Citta Vaittiya Tirattu” is prescribed in *Kulir curam* (fever with rigor) and vitiated conditions of *Aiyam*. In clinical practice, this formulation is found useful in relieving the symptoms of fever with rigor, throat pain, breathing difficulty, body pain, airway obstruction with phlegm etc., and reinstate respiratory health. Drugs used in this formulation majorly possess bitter taste or pungent taste. These drugs on post digestive

MATERIALS AND METHODS

Table 1: Ingredients of Notchi kudineer chooranam^[3]

S.No	Tamil Name	Botanical Name	Parts used	Quantity
1.	<i>Notchi</i>	<i>Vitex negundo</i>	Leaves	One handful
2.	<i>Milagu</i>	<i>Piper nigrum</i>	Seed	8 grams
3.	<i>Vellai poondu</i>	<i>Allium sativum</i>	Bulb	4 grams
4.	<i>Kammaaru vetrilai</i>	<i>Piper betel</i>	Leaves	Ten numbers

Preparation of Notchi kudineer (decoction for consumption)

Before preparing the decoction first raw drugs would be cleaned and gently pound into a course form. The decoction should be prepared by boiling 10gm of the drug mixture with 500ml of water till reduced to 125ml.

Dose: 30-60ml, twice daily

Therapeutic Usage: *Kulir curam, Aiyam*

Review of Individual Ingredients of Notchi Kudineer- Morphological and Chemical

Morphological description of *Vitex negundo*^[4]

A large shrub or sometimes a small slender tree; bark thin, grey; branchlets quadrangular, whitish with a fine tomentum. Leaves 3-5 foliate; leaflets lanceolate, acute, the terminal leaflet 5-10 by 1.6-3.2cm. with a petiole 1-1.3cm.

Long, the lateral leaflets smaller with a very short petiole, all nearly glabrous above, covered with a fine white tomentum beneath, base acute; common petioles 2.5-3.8cm long.

Chemical Constituents^[5]

Leaves- hydroxy-3,6,7,3',4'-pentamethoxyflavone; 6'-phydroxybenzoyl mussaenosidic acid; 2'-p-hydroxybenzoyl mussaenosidic acid; protocatechuic acid; oleanolic acid; flavonoids; 5, 3'-dihydroxy-7,8,4'-trimethoxyflavanone; 5, 3'- dihydroxy-6,7,4'-trimethoxy flavanone; viridiflorol; β caryophyllene; sabinene; 4-terpineol; gamma-terpinene; caryophyllene oxide; 1 -oceten-3-ol; globulol; angusid; casticin; vitamin-C; nishindine; gluconitol; phydroxybenzoic acid; sitosterol; betulinic acid [3 β hydroxylup-20-(29)-en-28-oic acid]; ursolic

transformation get converted to hot potency which increases and normalizes *Pitham* and expels out excessive *Kapham* (also means phlegm) out of airway, which is the rationale behind selecting these formulation.^[2]

As the herbs in *Notchi Kudineer* have found to possess anti-viral properties and the same has been published, this review is attempted to explore the same herbs in terms of other supportive pharmacological activities like anti-inflammatory, anti-pyretic, analgesic, anti-tussive and immunomodulatory activities.

acid [2 β - hydroxyurs-12-en-28-oic acid]; n-hentriacontanol; β sitosterol; p-hydroxybenzoic acid .

Morphological Description of *Allium sativum*^[6]

Garlic is arranged in a head, called a “bulb,” which averages about 2 inches in height and diameter and consists of numerous small separate cloves. With the exception of the single clove types, garlic bulbs are normally divided in to numerous fleshy sections called cloves.

Both the cloves and the entire bulb are encased in paper-like sheathes that can be white, off-white, or have a pink/purple hue. Although garlic cloves have a firm texture, they can be easily cut or crushed. The taste of garlic is like no other, it hits the palate with a hot pungency that is shadowed by very subtle background sweetness. While elephant garlic has larger cloves; it is more closely related to the leek and therefore does not offer the full health benefits of regular garlic. Each bulb is made up of 1 to 20 cloves, and each clove weighs about 1-3 grams.

Medium to large bulbs comprised of 1 to 12 symmetrical cloves around a hard central stalk. Large bulbs comprised of 12 to 20 cloves, with the largest ones on the outside of the bulbs. The bulb can be up to 2.8 inches in diameter and is made up of 1-15 cloves. The compound bulb is the part used for both spice and medicine.

Chemical Constituents^[6]

The composition of the bulb is approximately 84.09% water, 13.38% organic matter, and 1.53% inorganic matter, while the leaves are 87.14% water, 11.27% organic matter, and 1.59% inorganic matter.

Morphological Description of *Piper nigrum*^[7]

The black pepper's fruits are small (3 to 4mm in diameter) called a drupe and the dried unripe fruits of *Piper nigrum* are known as a peppercorn. The fully mature fruits are dark red in color and approximately 5mm in diameter. A fruit contains a single seed. The plants bear fruits from 4th or 5th year, and continue to bear fruits up to seven years. A single stem contains 20-30 spikes of fruits. The collected spikes are sun dried to separate the peppercorns from the spikes. The fresh harvested unripe green fruits may freeze-dry to make green pepper. The fresh harvested unripe green fruits may sun-dried to make black pepper. The red skin of the ripen fruits is removed and the stony seeds are sun-dried to make white pepper.

Chemical Constituents^[8]

Black pepper contains moisture -13.2%, protein -11.5%, carbohydrate- 49.2%, Mineral matter- 4.4%, fat- 6.8%, fiber- 14.9%, phosphorus-198mg/100g; calcium- 460mg/100g; phytin phosphorus-5mg/100g; Vitamin A value - 1800IU/100g, Iron- 16.8mg/100g. The presence of oxalic acid (0.4-3.4%) has been reported starch is the predominant constituents of black pepper it accounts 34.1% in it. The alkaloid piperine (C₁₇H₁₉O₃N₁) is

considered to be the major constituents responsible for the bitter taste of black pepper. Other pungent alkaloids, occurring in pepper in smaller quantity are chavicine, piperdines & Piperettine. Oil of the pepper is an important colorless to slightly greenish liquid with a characteristics odor of pepper and also of phellandrene.

Morphological Description *Piper betle*^[9]

Leaves are light green to bright green, glossy, deeply veined and hairless. They are heart-shaped with entire leaf margin. Leaf stalk is reddish like the stem.

Chemical Constituents^[10]

Betel leaves contain tannins, sugar and diastases and an essential oil. The essential oil is a light yellow liquid of aromatic odor and sharp burning in taste. It contains a phenol called chavicol which has powerful antiseptic properties. The alkaloid arakene in it has properties resembling cocaine in some respects. An analysis of the betel leaf shows it to consist of moisture 85.4 percent, protein 3.1percent, fat 0.8 percent, minerals 2.3 percent, fiber 2.3 percent and carbohydrates 6.1 percent per 100grams. Its minerals and vitamin contents are calcium, carotene, thiamine, riboflavin, niacin and vitamin C. Its calorific value is 44.

Siddha Concepts about Constituents of “*Nochi kudineer*”^[11]**Table 2: Siddha Pharmacological properties of the Ingredients of *Notchi kudineer***

S. No	Name of the drug	Taste	Pancha bootham	Thanmai	Pirivu	Parts used	Action
1	<i>Vitex negundo</i> (<i>Notchi</i>)	Bitter Astringent Pungent	Air+Space Earth+Air Air+Fire	<i>Veppam</i> (hot)	Pungent	Leaf Flower Root Bark	Alterative Vermifuge Febrifuge Expectorant Diuretic
2	<i>Piper nigrum</i> (<i>Milagu</i>)	Bitter Pungent	Air+Space Air+Fire	<i>Veppam</i>	Pungent	Seed Tendrils	Acrid Carminative Antiperiodic Rubefacient Stimulant Resolvent Antivatha Antidote
3	<i>Allium sativum</i> (<i>Vellai Poondu</i>)	Pungent	Air+Fire	<i>Veppam</i>	Pungent	Rhizome	Carminative Stomachic Tonic Alterative Stimulant Expectorant Diuretic

							Anthelmintic
4	<i>Piper betle</i> (Kammaaru vetrilai)	Pungent	Air+Fire	Veppam	Pungent	Leaf	Stimulant Carminative Astringent Aphrodisiac Antiseptic Febrifuge Stomachic Galactagogue Sialogogue

Different Therapeutic Activities of ingredient herbs of *Notchi kudineer*

Vitex negundo

Anti-pyretic Activity

The study of Naveen Pokala *et al* evaluated and compared the antipyretic activity of aqueous leaf extracts of *V. negundo* and *A. paniculata* in rabbits. The study had Aspirin as the comparison. Aqueous extracts of *V. negundo* and *A. paniculata* produced highly significant ($P < 0.001$) antipyretic effect in 400 and 800mg/kg doses. However, the onset of action was fast with *V. negundo*. The study concludes that aqueous extract of *V. negundo* has fast onset and sustained antipyretic action in New Zealand rabbits, whereas *A. paniculata* has delayed onset and sustained antipyretic effect^[12].

In Siddha materia medica, (medicinal plant section) decoction of *Notchi* leaves is indicated for *Murai suram* (intermittent fever as in Malaria). Various phytochemical constituents present in leaves of *Vitex negundo linn* are potent Antipyretic agents^[13].

Anti-inflammatory activity

The ethanolic roots extract of *Vitex negundo* by Plethysmometer method showed more considerable anti-inflammatory effect by using carrageenan induced rat paw edema method (Gangwar AK *et al*)^[14]. In another study of Singh P *et al*, ethanolic extract of *Vitex negundo* showed exhibited remarkable anti-inflammatory activity to standard drug of Indomethacin^[15].

Anti-tussive activity

Vitex negundo Linn (family: Verbenaceae) is used in traditional medical system for respiratory disorders. The antitussive effect of the butanolic extract of *V.negundo* (Vn) on Sulphur dioxide (SO₂)-induced cough was examined in mice. At 1000mgkg⁻¹, Vn caused maximum cough-suppressive effects i.e. cough inhibition at 60 min was 67.4% as compared to codeine (10mg kg⁻¹), dextromethorphan (10mgkg⁻¹) and saline having cough –inhibitory potential 75.7%, 74.7% and 0%, respectively. Regarding toxicity, no signs of neural impairment and acute behavioral toxicity were observed at antitussive doses^[16].

Analgesic Activity

Ethanolic extract of *Vitex negundo* flowers was evaluated by Maniyar YA and Sriraj D for peripheral analgesic activity by the acetic acid (0.7%) induced writhing test and central analgesic activity by the tail flick method respectively using aspirin as the standard drug. Extract significantly decreased the number of writhing in writhing test at all the doses ($p < 0.001$) and increased the reaction time in tail-flick method ($p < 0.001$) at all the doses when compared to control. The analgesic effects were comparable with that of the standard drug aspirin at dose 100mg/kg b.w in writhing test and produced greater analgesic activity than that of standard drug aspirin at dose 300mg/kg b.w in tail flick method. In the study flavonoids, tannins and alkaloids might be attributed to the peripheral and central analgesic activities^[17].

In addition to the above activities, the leaves of *V. negundo* may serve as an important source of natural antioxidant and immunomodulatory agent to protect the cells by mitigating oxidative stress induced toxicity to the biomolecules in experimental arthritis^[18].

Piper nigrum

Anti-inflammatory and Analgesic Activity

Piperine– an important alkaloid of *Piper nigrum* revealed to possess significant analgesic and anti-inflammatory properties^[19]. In a study performed using tail immersion method, analgesy-meter, hot plate, acetic acid induced writhing test and carrageenan- induced paw inflammation in rats, piperine at a dose of 10mg/kg completely terminated the writhes in mice. In the evaluation of anti-inflammatory effect using plethysmometer, piperine at doses of 10 and 15mg/kg started producing anti-inflammatory effect after 30 min, which lasted till 60 min, whereas hexane and ethanol extracts also produced a similar activity at a slightly low dose (10 mg/kg) but lasted for 120 min.

Anti-pyretic Activity

Piper nigrum at doses 250 and 500mg/kg significantly reduced the body temperature on yeast induced pyrexia and was comparable with standard.

Alcoholic extract of *piper nigrum* is having anti-pyretic activity. The active constituents such as alkaloids, flavonoids and sterols of alcoholic extract of *Piper nigrum* may be responsible for this Anti-pyretic Activity^[20].

Anti-tussive and bronchodilator activity

P.nigrum is widely used in many herbal cough syrups due to its potent anti-tussive and bronchodilator properties^[21]. Many traditional practices prove it as well.

Anti-histaminic Activity

Oral administration of piperine in different proportion to mice suppressed and reduced the infiltration of eosinophil, hyper responsiveness and inflammation due to the suppression of the production of histamine-5, immunoglobulin E and interleukin-4^[22].

Immunomodulatory

The research work of Amin F. Majdalawieh and Ronald I. Carr established that black pepper and cardamom extracts exert anti-carcinogenic effects via promoting the cytotoxic activity of NK cells. Black pepper and cardamom exert immunomodulatory roles and antitumor activities, and hence they manifest themselves as natural agents that can promote the maintenance of a healthy immune system. Black pepper and cardamom constituents can be used as potential therapeutic tools to regulate inflammatory responses and prevent/attenuate carcinogenesis^[23].

Allium sativum

Analgesic Activity

Mathew J et al have demonstrated that Garlic extract (GE) treatment (200mg/kg and 300mg/kg) reduce writhing episodes significantly as compared to control indicating its analgesic effect. The highest percentage inhibition of pain was seen with 300mg/kg of GE. GE treatment, in hot plate and Tail-clip methods significantly prolonged the reaction time at 60 min & 90 minutes. Though less potent than standard analgesics, GE was found to be effective in all three models of experimental pain^[24].

Anti-inflammatory Activity

The Anti-inflammatory activity exhibited by garlic oil is mainly through inhibiting the assembly-disassembly processes of the cytoskeleton^[25]. In a study by Sankhadip Bose *et al*, the isolated allicin from fresh garlic cloves showed anti-inflammatory activity and compared with standard drug which was assessed by difference in paw edema volume, after oral administration of allicin in rats. These observations helped us to ascertain the effective dose of allicin which was isolated with effect of post-acoustic waves and microwave radiation. The

methods ruled out possibilities of degradation of organo-sulfur compounds and showed a challenging result against inflammation and arthritis as well^[26].

Allium sativum may be an acceptable preventive measure against COVID-19 infection to boost immune system cells and to repress the production and secretion of proinflammatory cytokines as well as an adipose tissue derived hormone leptin having the proinflammatory nature^[27].

Uses

Leaves and bulbs are considered to have hypotensive, carminative, anti-septic, anthelmintic, diaphoretic and expectorant properties^[28]. Garlic offers antibiotic and antiviral benefits that make antibacterial properties make garlic a wonderful treatment for cough and cold. It may also reduce the severity of upper respiratory infections. It is also highly beneficial in treating various respiratory conditions such as asthma and bronchitis. It promotes expectoration with coughs, making it irreplaceable for those with chronic bronchitis. Garlic supplements can be taken on a regular basis to reduce the frequency of upper respiratory infections^[6].

Immunomodulatory

Studies have proved the Selenylation modification of garlic polysaccharides significantly improves its immune-enhancing activity, and selenizing garlic polysaccharides promote lymphocyte proliferation, enhances interferon- γ and IL-2, and increases the serum antibody titer in 14-day-old chicken^[29].

Piper betel

Analgesic and Anti-inflammatory activity

As shown by Reddy PS *et al*, the betel leaf hydroalcoholic extract HEPBL showed significant analgesic activity and significant anti-inflammatory activity in wistar rats. The sub-therapeutic dose of HEPBL at 50mg/kg also strengthens the sub-therapeutic effect of the standard analgesic dose. The analgesic and anti-inflammatory activity of *P.betle* can be attributed to the presence of phytochemical compounds, namely flavonoids, tannins, phenols and glycosides.^[30]

Anti-histamine Activity

Rahul Hajare *et al* have also proved that ethanolic extract and essential oil extract of leaves of *P. betel* Linn. showed Anti-histamine activity on guinea pigs. In isolated guinea pig tracheal chain preparation, there was a right side shift of dose response curve (DRC) of histamine. Chlorpheniramine maleate was used as a standard drug. Moreover extracts of *P. betel* disturbed histamine aerosol induce broncho constriction in

whole guinea pig, where essential oil was more effective comparatively to ethanolic extract. Thus from the results obtained in the present investigation, it can be concluded that ethanolic extract and essential oil of *P. betel* Linn possess Antihistaminic activity^[31].

Immunomodulatory

The immunomodulatory activity of methanolic extract of *Piper betel* L. consisting of mixture of phenols, flavonoids, tannins and polysaccharide produced decrease in antibody titre and increased suppression of inflammation suggesting possible immunosuppressive effect of extract on cellular and humoral response in mice^[32].

Traditional uses of Betel leaves^[33]

Sore Throat

Betel leaf is an excellent household remedy in the treatment of cough and sore throat. Local application of the leaves is effective in treating sore throat. The crushed fruit or berry should be mixed with honey and taken to relieve irritating cough.

Respiratory Disorders

Betel leaves are useful in pulmonary infection in childhood and old age. The leaves, soaked in mustard oil and warmed, may be applied to the chest to relieve cough and difficulty in breathing.

In-vitro Screening of "Notchi kudineer"^[34]

A descriptive in-vitro anti-inflammatory method by protein denaturation was performed from the extract of "Notchi kudineer". A statistically significant anti-inflammatory activity was from the aqueous extracts of *Notchi kudineer* and it may be developed as a potential lead to combat the inflammatory disorders.

Phytochemical investigations on the *Notchi kudineer* revealed the presence of various phytoconstituents such as triterpenoids, steroids, flavonoids, tannins, saponins, vitamins, sugars, vanillin, and ursolic acid. These phytochemicals have various health benefits such as antioxidant, antimicrobial, anti-inflammatory, cancer preventive, Anti-diabetic and Anti-hypertensive effect. For example, saponins have hypotensive and cardio-depressant properties. Glycosides are naturally cardio active drugs used in the treatment of congestive heart failure and cardiac arrhythmia.

DISCUSSION

The Siddha system of medicine has diverse and extensive use of natural resources for the prevention and management of seasonal epidemic diseases and comorbid conditions. Considering the basic idea of Siddha concept of preparing the sufferer (diseased person) to manage the disease by himself in the way of enhancing the internal atmosphere and

immunity, it can be assumed that the formulations have been created in such a way that they can be repurposed even against a new pathogen or new diseases. The pharmacological activities provide additional support to the use of *Notchi Kudineer* in COVID-19. The drugs used for COVID-19 management is categorized into four classes Anti-viral, Anti-inflammatory drugs, Anti-malaria drugs and traditional medicine. As COVID-19, is considered as a *Thottru noi* having similar symptoms as that of *Kabasuram* in Siddha literature, the effective management may be acquired by the use of drugs having Anti-pyretic, Anti-inflammatory and Anti-viral Activity to control the symptoms. From this literature review it is evident that all the four ingredients of *Notchi kudineer* possess pharmacological activities like Anti-pyretic, Anti-inflammatory, Analgesic, Antihistamine and Immunomodulatory activities. Further clinical trials would establish scientific evidence for the uses of 'Notchi kudineer' for treating the disease COVID-19 and its associated symptoms of fever and respiratory disorders.

CONCLUSION

As per Siddha system, medicines against a particular disease are formulated based on the fundamental principles like five basic elements (*Pancha mahaboothangal*), three bio-humors, six tastes etc. Many times the clinically effective Siddha medicines fail to show supportive evidence when it comes to Pharmacological activities done in animal models- as the core principles differs widely. However in case of *Notchi Kudineer* the Pharmacological studies collected from the available literature are in support of the claim that *Notchi Kudineer* is clinically effective in COVID-19 based on the traditional use since many decades. These facts indicate that further levels of clinical studies may be carried on with *Notchi Kudineer* on patients suffering from the pandemic of COVID-19.

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