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Nilavembu Kudineer, Evidence Based Siddha Anti-Viral and Immuno-modulating Drug, A Review

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Abstract
Siddha system offers a wide range of medicines including herbal, poly herbal, herbo-mineral, mineral and organic to treat and prevent the diseases. *Nilavembu kudineer* (NVK) is a poly herbal decoction, prescribed very commonly for viral fevers and found to be effective in curative and preventive aspects. It contains totally nine ingredients which are used in equal proportions while preparing decoction. NVK is categorized under the class *"kudineer (decoction)"* which is one among 32 classifications of internal medicine described in Siddha literatures. The people of South India particularly from Tamil Nadu and Kerala experienced the effectiveness of NVK during previous chickungunya, H1N1 and dengue episodes. In the current novel corona viral outbreak also Government of Tamil Nadu started the distribution of *Nilavembu kudineer* and *Kabajura kudineer* through government hospitals and primary health centers at free of cost to the public for preventive and immune boosting purpose. The efficacy and safety of NVK and its ingredients in this context have been reported by some of the researchers previously. This background, made the authors to review available research reports, compile here to explore NVK as evidence based anti-viral and immuno modulating agent. The information in this review article may give authenticity and scientific support in the usage of medicine during viral epidemics including COVID 19.

Keywords
Anti-viral, Chickungunya, Corona, Dengue, Immuno-modulator, Nilavembu kudineer.

Abbreviations
NVK-Nilavembu kudineer, NVKC- Nilavembu kudineer choornam.

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1. INTRODUCTION
Siddha system of medicine is one of the oldest medical systems originated in between 7000 BC and 5000 BC and it belongs to Dravidian tradition, practiced in southern states like Tamil Nadu and Kerala. Siddha advocates vaidhyam (treatment), vatham (alchemy), yogam (8 stages of yogic practices), jnanam (eternal knowledge) and offers medicines for 4448 diseases of mankind. Medicines in Siddha are grouped under 32 types of internal and 32 types of external medicines. *Nilavembu kudineer* (NVK) is an internal medicine under kudineer

(decoction/ concoction) category. It is a polyherbal formulation generally advised by Siddha practitioners for fevers of varied origin including viral fevers. The decoction was widely used by the people of Tamil Nadu and to some extent in Kerala during earlier chickungunya and dengue epidemic episodes. Both chickungunya fever and dengue fever was effectively treated with a common formulation, NVK [1]. Such experiences made the public to become more familiar towards NVK. In novel corona virus (COVID 19) outbreak also people started taking the medicine as preventive and immuno boosting agent based on government guidelines. It is noteworthy mention that NVK is being included in the advisory notified by Ministry of AYUSH, Government of India and state governments of Tamil Nadu and Kerala in connection with COVID19 for preventing and immune boosting purposes. In this background authors decided to review and compile the scientific information from available research reports in order to explore the antiviral and immunomodulating effect of NVK and its ingredients. This paper is also aimed to strengthen the scientific background in the usage of NVK during viral epidemics.

2. NILAVEMBU KUDINEER: COMPOSITION AND PREPARATION METHOD

NVK is available in the market in coarsely powdered form. It encompasses totally nine active ingredients in equal proportions. The chief ingredient of this formulation is Nilavembu (*Andrographis paniculata*), commonly known as King of Bitters which adds bitter taste to the decoction. This plant is native to India and Sri Lanka [2]. Other ingredients of NVK include Vettiver (*Vetiveria zizanioides*), Vilamichai ver (*Plectranthus vettiveroides*), Chandanam (*Santalum album*), Peipudal (*Trichosanthes cucumerina*), Koraikizhangu (*Cyperus rotundus*), Chukku (*Zingiber officinale*), Milaku (*Piper nigrum*) and Parpadagam (*Mollugo cerviana*) [3]. All nine ingredients are purified as per traditional purification methods, dried under shadow and ground into coarse choornam (powder) form. These ingredients are permissible for medicinal preparations as per the list given in the schedule E (1) of the Drug and Cosmetic Act 1940. Now a days NVK choornam is manufactured by GMP certified companies in Siddha by following SOP and other guidelines notified in Drug and Cosmetic Act 1940. The quality of the medicine is assessed with parameters and procedures as prescribed by Pharmaceutical Laboratories of Indian Medicine.

The preparation method of decoction is concerned, 25 grams of powder is taken and boiled with 500 ml of water till the decoction is reduced/concentrated to 125 ml then filtered [4]. The dose level of NVK for the adult is 30-60 ml, twice daily and shelf life for the decoction is only 3 hours as per Siddha guidelines [5]. It is given in the dosage of 20 ml bid for 3-5 years age group and 30 ml bid for 5-12 years [6].

3. TRADITIONAL USES OF NVK

Traditionally NVK is recommended for all kind of fevers [3], kulir juram (malarial fever), azhal juram (bilious fever) [4] and nadukku juram (fever with rigors). Ingredients in this formulation are indicated for fever, sinusitis, diabetes, hypertension, delirium, asthma, cough, indigestion, ascites, tuberculosis, diarrhoea, psychiatric diseases [7], inflammation, arthralgia, arthritis, gastric ulcer, jaundice and general debility [8]. Febrifuge (reducing fever), Diaphoretic (increasing perspiration) and Diuretic (increasing urinary output) are common therapeutic effects exhibited by the ingredients individually.

4. PHYTOCHEMICAL CONSTITUENTS

Therapeutic effect of every herb is confined to the bioactive compounds present in it. Screening of such compounds is crucial for standardization purpose and other scientific validations. Alkaloids, carbohydrates, glycosides, coumarins, phenols, quinones, flavonoids, steroids, tannins, terpenoids and saponins [9] are various important secondary metabolites there in water extract, ethanolic extract and fresh decoction of NVK. The ingredients of NVK contain important bioactive compounds like Andrographolide, β vetiverine, α-zingiberene, α-copaene, cyperene, 2-monolinolenin, limonene, β-pinene, β-caryophyllene, and α-santalol. Some other important phytoconstituents and class in each ingredient of NVK[10] is listed here: 1. *Andrographis paniculata* (andrographolide, a diterpene; terpenes like bis-andrographolide, 14-deoxy-11-12 didehyroandrographolide, 14 deoxyandrographolide, neoxyandrographolide, ninandrographolide; flavonoids like oxygenated flavones, wogonin, oroxylin A; carvacrol, a phenolic compound; ether alcohol like eugenol; fatty acid like myristic acid; phenolic acid like chlorogenic acid; alkanes like hentriacontane; hydrocarbon like tritriacontane; polyphenols like caffeic acid; carboxylic acid like dicaffeoylquinic acid; and phytosterols like b-sitosterol-d-glucoside) 2. *Vetiveria zizanioides* (sesquiterpenes like vetivone, α-cadinene, α-calacorene, zizanoic acid; and sesquiterpene alcohol like epikuisinol, khusol) 3. S*antalum album* (sesquiterpenes like α,β-santolol, α,β-santalals, α,β-santaldiols, 10(Z)-sandolnol, α-santalenoic acid, vanillic acid 4-o-neohesperidoside, 2α,12-dihydroxy10(Z)- campherene, 2β,12-

dihydroxy10(Z)- campherene, 2,12,13-trihydroxy-10-campherene, (Z)-lanceol, (Z)-7-hydroxynuciferol, 2*R*-(*Z*)-campherene-2,13-diol, (*Z*)-2β-hydroxy-14-hydro-β-santalol, (*Z*)-2α-hydroxy-albumol, (*Z*)-1β-hydroxy-2-hydrolanceol; glycosides like eugenol-4-o-rhamnosyl glucoside, methoxyeugenol-4-o-rhamnosyl glucoside) 4. *Trichosanthes cucumerina* (triterpenoids like bryonolic acid, cucurbitacin B, cucurbitacin E, isocucurbitacin B, 23, 24-dihydrocucurbitacin D; phytosterols like β-sitosterol, stigmasterol) 5. *Cyperus rotundus* (sesquiterpenes like cyperene, cyperenone, α-cyperone, copadiene, rotundone, cyperenol, cyperol, isocyperol, α-and β-rotunol, kobusone, isokobusone; hydrocarbon like β-selinene; 4α-5α, oxidoeudesm-11-en- 3α-ol; Epoxyguaiene; Eugenol) 6. *Zingiber officinale* (phenols like 6-shogaol, 6-gingerol, gingerdiols, 1,8 cineole, 6-gingesulphonic acid; sesquiterpenes like zingiberol, α-zingiberene, ar-curcumine, β-bisabolene, α-santalol, β-eudesmol, nerolidol; monoterpenes like β-phellandrene, α-pinene, β-pinene, camphene, sabinene, myrcene; glycerols like gingerglycolipids A, B & C; geraniol glycosides; cyclohexene like Limonene) 7. *Piper nigrum* (alkaloids like piperine, pipercide, feruperine, aldehydes like piperonal; monoterpenes like sabinene, d-limonene, p-cymene; pyrollidine alkamides like trachyone, isopiperolein B, pergumidiene, pellitorine; phenolic compounds like guaiacol, n-trans-feruloylpiperidine; phenole like 1,8 cineole, n-trans-feruloyl tyramine; amides like pipnoohine, pipyahyine, n-isobutyl-2E,4E-octadec adienamide, n-isobutyl-2E,4E,8Z-eico satrienamide, piperchabamide D, retrofractamide A, dehydroretrofractamide; alkene like guineensine; alcohol like δ-cadinol; organic compound like piperoleine B) 8. *Mollugo cerviana* (flavonoids like orientin, vitexin; glucosides like orientin-2'O-glucoside, vitexin-2'O-glucoside). Secondary metabolites of NVK are reported to possess many pharmacological characteristics.

5. PHARMACOLOGICAL PROFILE OF NVK AND ITS INGREDIENTS

5.1. Antipyretic, analgesic and anti-inflammatory effect

Fever, head ache and body pain are major complaints commonly seen in fevers, irrespective of aetiological factors. Hence prescribing medicine should comprise antipyretic, analgesic and anti-inflammatory properties to get relief from fever, pain and associated symptoms. Fever is the body's natural defensive mechanism leads to formation of pro-inflammatory mediators like cytokines like interleukin 1β, α and β, interleukin 6 (IL-6), tumour necrosis factor (TNF-α) which enhances prostaglandin E2 (PGE2) and triggers hypothalamus to elevate body temperature. It is reported that the extract of NVKC has equal and consistent efficacy to reduce fever compared to paracetamol. Inhibition of PGE2 synthesis by inhibiting cycloxygenase 2 expressions/ pathway (COX2) leads to reduction in the elevated body temperature has been reported as common mode of action of antipyretic agents [11]. The significant reduction of fever by ethanolic extract of NVKC on the brewer's yeast induced pyrexia in rat supporting the antipyretic potential of NVK. The mediators such as prostaglandins, bradykinins, and Substance-P are known to be the reasons for pain in fevers. NVK suppresses the formation of aforesaid substances or prevent their action to produce analgesic activity. The ethanolic extract of NVKC showed good anti-inflammatory activity at 1, 3 and 5 hours in carrageenin induced inflammation compared to control animals. Andrographolide and neoandrographolide, the diterpene compounds present in *Andrographis paniculata* and piperine content in *Piper nigrum* is producing anti-inflammatory effect of NVK. Administration of piperine dramatically reduces pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α. Likewise α-cyperone, isocyperol, kobusone, isokobusone content present in *Cyperus rotundus*, 6-shagaol, 6-gingerol, β-eudesmol, nerolidol, hexahydrocurcumin content in *Zingiber officinale*, bryonoli acid, 23,24-dihydrocucurbitacin D content in *Trichosanthus cucumerina* and the plant *Mollugo cerviana* are reported for its anti-inflammatory activities is an added value for the potency of decoction[10].

5.2 Anti-microbial effect

Secondary bacterial infection followed by viral infection might be the biggest medical concerns associated with elevated mortality rates. Available reports substantiate that NVK is effective not only against virus but also bacteria. NVK has potent broad spectrum anti-bacterial effect against both gram positive and gram negative and found to be effective for secondary infections. The bioactive constituents present in NVK such as glycosides and coumarins are said to be responsible for its antimicrobial activities [9]. The reviews of pharmacological actions of individual plants of NVK shows that the plant extracts exhibited antimicrobial activity against 28 pathogens that have been experimented [8]. Earlier studies affirms that Andrographolide, flavones, carvacrol, myristic acid present in *Andrographis paniculata*, vetivone, α-cadinene, zizanoic acid present in *Vetiveria zizanioides,* cyperene, β-selinene present in *Cyperus rotundus*, trachyone, isopiperolein B, pergumidiene, pellitorine, N-isobutyl-2E, 4E-

octadecadienamide present in *Piper nigrum*, β-phellandrone, gingeriols, β-pinene present in *Zingiber officinale*, (Z)-lanceol, (Z)-7-hydroxy nuciferol, 2R-(Z)-campherene-2,13-diol, (Z)2 β-hydroxy-14-hydro-β-santalool, (Z)-1β-hydroxy-2-hydrolanceol present in *Santalum album* are possessing significant anti-microbial properties[10]. All the available data endorses the antimicrobial activity of NVK and found to be useful in viral fever connected secondary infections.

5.3 Broad spectrum anti-viral activities

More evidences are available for nilavembu (NV), the key ingredient of NVK to substantiate its wide range of anti-viral properties. It is reported to be effective against Herpes Simplex Virus (HSV-1), Dengue Virus (DENV1)[7] and Chikungunya virus [1]. Another study states that NVK controls Human Immunodeficiency Virus (HIV) by inhibiting reverse transcriptase and Hepatitis B Virus (HBV) by inhibiting DNA polymerase [12]. NV is also proved to be effective against Influenza-A, Flavivirus, Pestivirus, Human Papilloma Virus (HPV), Epstain Barr Virus (EBV) [13] and H1N1[8]. Andrographolide is a diterpenoid content of NV inhibits HIV replication in HIV patients by interfering cyclin dependant kinase activity [14]. The other investigator reported that androgrphaloide may inhibit HIV induced cell cycle dysregulation leading to rise in CD4 (+) lymphocyte levels in HIV infected individuals [15].

Trichosanthen, a polypeptide constituent of *Trichosanthes cucumerina* exhibits various activities like anti-viral, immunomodulatory, anti-inflammatory, anti-tumour and anti-human immuno deficiency virus (anti-HIV) activities. The anti-HIV effect of Trichosanthen is attributed to inhibition of replication of HIV and cytotoxicity to HIV infected cells mainly macrophages and lymphocytes especially helper T cells ($CD4^+$T Cells) [16]. In an *in vitro* study, sandalwood oil demonstrated antiviral effect against herpes simplex virus (HSV-1 & 2) through inhibition of viral replication [17]. Sandalwood oil constituents α and β –santalols and derivatives have been implicated in the treatment of warts in human especially HPV and DNA pox virus that causes *Molluscum contagiosum* and speculated to be a cure against HIV and other RNA virus [18]. The methanol crude extract of *Zingiber officinale* was found to inhibit HCV protease [19]. The anti-viral activity of *Cyperus rotundus* against HSV-1, *Zingiber officinale* against HIV-1, CMV and *Andrographis paniculata* against rotavirus were also reported earlier [20].

5.4 Anti-dengue, anti-chickungunya activities

The medicine intended for treating Dengue and Chickungunya must possess properties like analgesic, anti-pyretic, anti-inflammatory and antiviral to alleviate the reported symptoms such as high fever, headaches, pain behind eyes, joint and muscle pain, fatigue, nausea, vomiting, skin rash, mild bleeding from nose/gums, bruises, damage to lymph/blood vessels, liver enlargement and circulatory system failure[10].The analgesic, anti-pyretic, anti-inflammatory and antiviral properties of NVK and its ingredients have been reviewed in this paper.

A study report justifies that NVK can be used as a potential anti-viral against dengue (DENV-2) and chickungunya (CHIKV) both as preventive medicine before the infection and as an anti-viral during active infection [1]. It is reported that suppression of histamine, serotonin, kinins and prostaglandins might be the reason for the anti-inflammatory, analgesic effects of NVK in chickungunya fever. The effectiveness of ethanolic extract of NVKC in carrageenin induced inflammation animal model supports the anti-inflammatory effect of NVK [11] in chikungunya. Persistent joint pain during chikungunya convalescence period may require long term treatment with analgesics and anti-inflammatory agents. Prolonged treatment with NSAID might leads to gastritis, peptic ulcer, cardiovascular risk etc. In such conditions, time tested herbal preparations like NVK, possessing analgesic and anti-inflammatory effects might be useful in chikungunya related post viral arthralgia/ arthritis. Inhibition of nitric oxide and prostaglandin production [15] *are* said to be the other reasons for its anti-inflammatory effect.

A case-control study report supports that consumption of NVK as a prophylactic measure prevents significantly the occurrence of viral fevers including dengue in all age groups invariably [21]. In an interventional cohort study conducted in dengue prevalent area by using NVK it was affirmed that the consumption of NVK and conduct of awareness programme among the public could impede the outbreak of dengue like illness in endemic areas [22]. The administration of NVK and *Adathodai manappagu* combindly for a period of seven days in dengue cases with clinical symptoms and thrombocytopaenia (reduce number of platelets), it was observed by the investigators that there is a drastic increase in platelet count on each day [6].

Many *invitro* and *invivo* studies were conducted with plant derived bioactive principles against dengue virus. Various flavonoid compounds from ethanol/ methanol derived extract of Andrographis paniculata have been described that they are possessing antiviral properties including dengue with 75% of inhibition [13]. In a study carried out for the preliminary screening for anti-dengue agent,

methanolic extract of *Andrographis paniculata* was found to maintain most of the normal cell morphologies without causing much cytopathic effect to the DEN-1 infected cells and shows high potential to be an anti-dengue agent, particularly towards DENV-1 serotype [23]. These findings suggested that the anti-dengue activity might be owing to the presence of flavonoid compounds or other compounds such as terpenes and polyphenols that were extractable by methanol. The role of diterpene such as andrographolide, 14-deoxyandrographolide and 14-deoxy-11,12-didehydroandrographolide present in methanolic extract of *Andrographis paniculata* against DENV-1 to be considered. The aqueous extract of *Zingiber officinale* may play an important role in the regulation of plasma leakage in dengue virus infection and decrease the chances of severe dengue complications by inhibiting the activity and expression of MMP-2 and MMP-9 while up regulating the expression of TIMP-1 and TIMP-2. Thus it can help in the development of new anti-dengue agents [24]. Inhibition of dengue NS2B-NS3 proteases and prevention of the viral assembly is the mechanism observed by the investigators as in the case of *Vetiveria zizanioides* [25]. Anti- dengue virocidal activity of *Santalum album* one among the ingredient of NVK also has been reported [26] earlier.

5.5 Immuno-modulatory effect

Viral infection is concerned, immunity of an individual is an important factor to fight against infection and prevent the incidence. All available reports support the immunomodulatory effect of NVK. The effect of *Andrographis paniculata, Piper nigrum, Santalum album, Zingiber officinale, Cyperus rotundus* and *Vetiveria zizanioides* (six out of nine ingredients of NVK) on immune response were already reported [27]. The polysaccharides present in NVK enhance the immune response by activation of complements, lymphocytes and macrophages [28] and flavonoid found in higher concentration stimulate the synthesis of interferons leading to immunomodulation [29]. Beside polysaccharides, flavonoids, the other secondary metabolites present in NVK such as alkaloids, glycosides, tannins and phenols also exhibiting immunomodulating effect [30]. It is understood that phytochemicals in NVK act synergistically and boost immune system significantly.

Andrographis paniculata exhibits immunomodulatory activity by increasing antibody production and decreasing delayed type hypersensitivity response, enhancing proliferation of blood lymphocytes and cytokines [31]. Another study stated that the immunomodulatory effect of *Andrographis paniculata* is attributed to the presence of andrographaloide, a diterpene compound which improves immunity by increasing CD4+ lymphocytes, cytotoxic T cells, natural killer cells, phagocytosis and antibody dependent cell mediated cytotoxicity [14]. It is also found that a significant increase in total WBC count and relative increase in weight of spleen and thymus in Andrographolide treated mice during 30 days of treatment [32]. The immunomodulatory effect of piperine content present in *Piper nigrum* [33], cucurbitacin E in *Trichosanthes cucumerina* [34] and gingeriols, shagaol present in *Zingiber officinale* [35] also have been reported earlier. The proliferation of lymphocytes in the absence and presence of mitogens was studied with *Cyperus rotundus* extract at the concentration range 1-1000 µg/ml and confirmed the significant increase in the lymphocyte proliferation [36]. As in the case of *Mollugo cerviana*, the phytochemical constituents present in it such as alkaloids, flavonoids and vitamin C and E that serve a defense mechanism against many microorganisms, insects and other herbivores [37].

5.6 Possible role of NVK against corona virus infection (SARS CoV-2)

Neither medicine nor vaccine has been developed until now in modern medicine against corona and related researches are intensified worldwide currently. However certain allopathic drugs are being tried across the world to combat corona importantly hydroxy chloroquine (HCQ), an anti-malarial drug. It is also known that there is a usage of anti-viral drug named “interferon α-2B” in COVID19 cases. By conceiving the above concepts, the merit of NVK is reviewed with available data. NVK has a wide range of secondary metabolites such as alkaloids, carbohydrates, glycosides, coumarins, flavonoids, phenolic compounds, quinones, steroids, phytosterols, tannins and terpenoids [7]. The flavonoid which was found in higher concentration in NVKC has more beneficial effect in immune system and exhibits immunomodulatory effect particularly by stimulating interferon synthesis [29]. Anti-malarial activity of synthetic quinones has already been reported [38,39]and interesting to note that NV possesses quinones also. Hence NVK is exhibiting immunomodulating effect by stimulating interferons and containing quinones naturally, it could be considered in the treatment of corona as like that of Interferon alpha-2B and HCQ. However scientific studies shall be carried out to elucidate whether the concentrations of such compounds in NVK are effective and adequate to combat SARS CoV-2.

6. CONCLUSION

Nilavembu kudineer is a well-known Siddha classical medicine used widely by the practitioners for viral fevers, having potent anti-pyretic, analgesic, anti-inflammatory, anti-viral and immunomodulatory activities. It is also used widely by public during each viral outbreak as a preventive/ prophylactic medicine. Though many research and review articles are published in research journals by various workers on traditional uses, phytochemistry and pharmacology of NVK and its ingredients individually, none of them described complete details on its anti-viral properties and immunomodulating effects collectively and exclusively. Hence a systematic review of NVK has been carried out and expressed here as it will facilitate the practitioners, researchers, teaching faculties, medical students, consumers and government health authorities for having updated knowledge about anti-viral and immuno modulating efficacy of NVK. Current review substantiates antiviral, anti-dengue, anti-chickungunya, immunomodulating activities and also possible role of NVK against novel corona virus. It is expected that this review may strengthen the scientific background in the usage of NVK as curative and preventive in this context.

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