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THERAPEUTIC EFFECTIVENESS OF THE SIDDHA IMMUNO MODULATORY POLYHERBAL FORMULATION NELLIKAI LEGIYAM AGAINST COVID-19 PANDEMIC- A REVIEW

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ABSTRACT

In Siddha system of medicines, Nellikai legiyam is significantly used as immunomodulatory drug. The current outbreak of coronavirus (COVID-19) is one of the immunosuppressive or immunomodulatory diseases. According to WHO, the serious symptoms of COVID-19 are shortness of breath, chest pain and loss of speech. This review article focuses on the phytochemicals and pharmacological activities of prior study work on each of its herbal ingredients i.e., *Phyllathus emblica* (Nellikkai vatral), Zingiber officinalis (Chukku), Piper nigrum (Milagu), Piper longum (Thippili), Piper longum root (Thippili Moolam), Carum copticum (Omam), Syzygiyum aromaticum. Linn (Lavangam), Elattaria cardamomum. Maton (Elarisi), Illicium verum (Thakkolam), Cuminum cyminum. Linn (seeragam), Coriandrum sativum. Linn, (Kothumalli), Maranta arundinacea (Koogai neer), Glycirrhiza glabra (Athimathuram), Embelia ribes. Burn.f (Vayuvidangam). Nellikai legiyam is concluded to have Immunomodulatory, antioxidant, anti-inflammatory and antimicrobial action after analysis of the bioactive constituents and pharmacological action for the treatment of COVID-19.

KEYWORDS: COVID-19, Nellikai legiyam, Siddha, Immunomodulator drug.

INTRODUCTION

An outbreak of pneumonia in December 2019 in Wuhan, China, has now been determined to be caused by a novel coronavirus. The virus has been named as SARS-CoV-2 and the disease is now called COVID-19.[1] As per WHO reports, the disease has spread globally with more than 5.93 million confirmed cases and 0.36 million deaths as of May 31, 2020.[2] The common symptoms are fever, dry cough and tiredness. The cause of death in almost all patients is respiratory failure, shock, acute respiratory distress syndrome (ARDS), and cardiac arrhythmia, or irregular heartbeat. Apparently, there is no clear antiviral or vaccine available or approved, to combat the COVID-19, and the possible treatment is still symptomatic. The utilization of Traditional Chinese Medicine (TCM) in Wuhan to treat COVID-19 is an example of how traditional health care can lead to the effective treatment of these patients.[3] Siddha system of medicine is traditional healing system, one of India's oldest holistic system. It originates from Lord Shiva and the Siddhar's inherited his wisdom. This system features a large source of drugs from four types namely herbals, metals, minerals and animal. In that one of the excellent immunomodulator drugs said in the text `The Pharmacopoeia of siddha research medicine' was nellikai legiyam and its therapeutic usage is dysmenorrhoea, dyspepsia, hyper acidity, indigestion etc.

MATERIALS AND METHODS

INGREDIENTS

According to the text the ingredients of the nellikai legiyam is given below:

S.No	Tamil Name	Botanical Name	Parts Used	Quantity
1	Nellikai vatral	Phyllanthus emblica Linn	Dried fruit	5.4 kg
2	Nattu sarkarai	Saccharum officinarum Linn	Jaggery powder	7 kg
3	Chukku	Zingiber officinale, Rose	Dried rhizome	144 g
4	Milagu	Pipper nigrum	Dried unripe fruit	144 g
5	Thippili	Piper longum Linn	Dried unripe fruit	144 g
6	Thippili moolam	Root of Piper longum Linn	Root	144 g
7	Omam	Carum copticum Benth & Hook.f	Fruit	144 g
8	Jeeragam	Cuminum cyminum.Linn	Fruit	144 g
9	Lavangam	Syzygiyum aromaticum.Linn	Flower buds	144 g
10	Elarisi	Elattaria cardamomum.Maton	Seed	144 g
11	Thakkolam	Illicium verum	Seed	144 g

12	Kothumalli	Coriandrum sativum.Linn	Fruit	144 g
13	Kugaineer	Maranta arundinacea	Rhizome	144 g
14	Athimathuram	Glycyrhiza glabra.Linn	Root	144 g
15	Vayuvidangam	Embelia ribes.Burn.f	Fruit	144 g
16	Cow's ghee			1 kg
17	Honey			½ litre

STANDARD OPERATING PROCEDURE FOR THE PREPARATION OF NELLIKKAI LEGIYAM

COLLECTION AND AUTHENTIFICATION

The raw drugs were purchased from the Chennai raw drug store and authenticated by Dr.Aravind, Assistant Professor, Department of medicinal botany, National institute of siddha, Tambaram Sanatorium, Chennai-47.

PURIFICATION OF RAW DRUGS

*1***.** Nellikkai (*Phyllathus emblica.Linn)*

Clean in water and removed the seed.

2. Chukku (*Zingiber officinale, Rose*)

Double the proportion of lime stone [calcium carbonate] solution is poured and boiled for three hours, then wash it, dry and remove the peel.

3. Milagu (*Pipper nigrum*)

Soak it in sour butter milk for three hours.

4. Thippili (*Piper longum.Linn*)

Soak it in plumbago zeylanica,Linn (Kodiveli) leaf juice for twenty-four minutes (1 Nazhigai) and dry it sun.

5. Thippili moolam (*Root of Piper longum.Linn*)

Dried under shade.

6. Omam (*Carum copticumBenth&Hook.f*)

Dried under shade.

7. Jeeragam (*Cuminum cyminum.Linn*)

Dried in sunlight and fried it like as golden yellow colour.

8. Lavangam (*Syzygiyum aromaticum.Linn)*

Dried under shade.

9. Elarisi (*Elattaria cardamomum.Maton*)

Remove the peel, take the seeds and dried under shade.

10. Thakkolam (*Illicium verum*)

Dried under shade.

11. Kothumalli (*Coriandrum sativum.Linn)*

Boil with Hotwater & dry it in sunlight

12. Athimathuram (*Glycyrhiza glabra.Linn)*

Scraped the outer layer and cut in to small pieces then dried into sun light.

13. Vayuvidangam (*Embelia ribes.Burn.f*)

Cleaned and dried under shade.

14. Kugaineer (*Maranta arundinacea*)

PREPARATION OF NELLIKAI LEGIYAM

STEP 1

Nellikai vatral is added with 8 parts of water and reduced into 1/8 parts of decoction.

STEP 2

The decoction is added with Nattu sarkarai and boiled until it reaches kambi patham.

STEP 3

The paagu is added with other powdered drugs and stirred till it attains legiyam patham.

STEP 4

Finally add cow's ghee and honey.

DOSE:

½ thola(6g)

REFERENCE

Dr. M.Shanmugam & G.D.Naidu -The Pharmacopoeia of siddha research medicines Page no-219

DATA ON INGREDIENTS AS PER THE GUNAPADAM MOOLIGAI VAGUPPU SIDDHA TEXT[2]

S.No	Name	Taste	Potency	Division	Action
1	Nellikai vatral	Sour, Stringent, Sweet	Cold	Sweet	Refrigerant, Diuretic, Laxative
2	Chukku	Pungent	Hot	Pungent	Stimulant, Stomachic, Carminative
3	Milagu	Bitter, Pungent	Hot	Pungent	Acrid, Carminative, Anti periodic, Rubefacient, Stimulant, Resolvent, Anti vadha, Antidote
4	Thippili	Pungent	Hot	Sweet	Stimulant, Carminative
5	Thippili moolam	Pungent	Hot	Pungent	Stomachic
6	Omam	Pungent	Hot	Pungent	Stomachic, Anti

					spasmodic, Carminative, Antiseptic, Stimulant, Tonic, Sialogogue
7	Jeeragam	Pungent, Sweet	Cold	Sweet	Carminative, Stimulant, Stomachic, Astringent
8	Lavangam	Pungent	Hot	Pungent	Anti-spasmodic, Carminative, Stomachic
9	Elarisi	Pungent	Hot	Pungent	Stimulant, Carminative, Stomachic
10	Thakkolam	Astringent	Hot	Pungent	Anti vadha, astringent, Febrifuge, Nutritive
11	Kothamalee	Bitter	Hot	Pungent	Anthelmintic, deobstruent, diuretic, emmenagogue
12	Kugaineer	Sweet	Hot	Sweet	Refrigerant, Demulcent, Nutrient
13	Athimathuram	Sweet	Cold	Sweet	Emollient, demulcent, mild expectorant, laxative, tonic
14	Vayuvidangam	Bitter	Hot	Pungent	Anthelmintic, Carminative, Stomachic, Stimulant

PHYTOCHEMICALS OF INGREDIENTS OF NELLIKAI LEGIYAM

S.No	Name	Phytochemicals
1	Nellikai vatral	Higher number of polyphenols like gallic acid, ellagic acid, tannins like Pedunculagin, Chebulinic acid (Ellagitannin), Chebulagic acid (Benzopyran tannin), Corilagin (Ellagitannin), Geraniin (Dehydroellagitannin), Ellagotannin, Alkaloids like Phyllantine, Phyllembein, Phyllantidine. flavonoids like rutin and quercetin, saponins and Emblicanin A and B, Punigluconin, minerals, vitamins, amino acids, fixed oils.[4]
2	Nattu sarkarai	Fatty acid, alcohol, phytosterols, higher terpenoids, flavonoids, -O- and -C-glycosides, and phenolic acids.[5]
3	Chukku	Cardiac glycosides, alkaloids, saponins, tannins, flavonoids, polyphenol and reducing sugars in both aqueous and petroleum ether extracts. Mainly sesquiterpenoids, bisapolene, zingiberene, and zingiberol (Connel D), 6-Shogaol.[6]
4	Milagu	Propanedioic acid, dimethyl ester, Bicyclo heptane,3-Carene, Cyclohexene, Piperine, Ursodeoxycholic acid, piperidine, piperettine and piperanine, Stigmasterol.[7]
5	Thippili	N-5-(4-hydroxy-3-methoxyphenyl)-2E-pentenoyl piperidine, piperolactam A, 1-[1-oxo-5 (3,4-methylenedioxyphenyl) -2E,4E-pentadienyl] -pirrolidine, 1-[1-oxo-5 (3,4-methylenedioxyphenyl) -2E-pentenyl] -pirrolidine, 1-[1-oxo-9 (3,4-methylene dioxyphenyl)-2E, 8E-nonadienyl] -pyrrolidine, (R)-(-) -turmerone, octahydro-4-hydroy-3alpha-methyl-7-methylene-alpha-(1-methylethyl)-1H-indene-1-methanol, (+) -aphanamol I , bisdemethoxycurcumin, demethoxycurcumin.[8]

6	Thippili moolam	Piperine, piplartine, triacontane, dihydro-stigmasterol, an unidentified steroid, reducing sugars, glycosides, sesamin and methyl-3,4,5-trimethoxycinnamate.[9]
7	Omam	carbohydrates, glucosides, saponins and phenolic compounds (carvacrol), volatile oils (thymol), terpiene, paracymene and beta-pinene, protein, fat, fiber, and minerals including calcium, phosphorus, iron, and nicotinic acid (niacin).[10]
8	Jeeragam	cuminaldehyde, limonene, α- and β-pinene, 1,8-cineole, *o*- and *p*-cymene, α- and γ-terpinene, safranal and linalool.[11]
9	Lavangam	monoterpenes, sesquiterpenes, phenolics and hydrocarbon compounds, eugenol (70-85%) followed by eugenyl acetate (15%) and β-caryophyllene (5-12%).[12]
10	Elarisi	carbohydrates, proteins, minerals, lipids, essential oils, flavonoids, terpenoids and carotenoids.[13]
11	Thakkolam	lignans, sesquiterpenes, flavonoids, alkaloids, essential oil, and tannins (9% to 10%), both cis- and trans-anethole (85% to 90%), limone, α-pinene, safrol, β-phellandrene, α-terpineol, and farnesol.[14]
12	Kothumalli	linalool(60-70%), monoterpenes hydrocarbons viz. α-pinene, limpnene, γ-terpinene, p-cymene, borneol, citronellol, camphor, geraniol geraniol acetate, heterocyclic components like pyrazine, pyridine, thiazole, furan and tetrahudrofuran derivatives, isocoumarins, coriandrin, dihydrocoriandrin, coriandronsA-E, flavonoids, pthlides, neochidilide, digustilide phenolic acids and sterols.[15]
13	Kugaineer	alkaloids, carbohydrate, cardiac glycosides, proteins, amino acids, phenolic compounds, terpenoids, saponins, flavones and gum.[16]
14	Athimathuram	Triterpenoid saponins (4–20%), mostly glycyrrhizin, a mixture of potassium and calcium salts of 18β-glycyrrhizic acid, triterpenes included liquiritic acid, glycyrretol, glabrolide, isoglaborlide and liquorice acid. 18β-glycyrrhizic acid (3-O-(2-O-β-d-glucopyranuronosyl–α-d-glucopyranurosyl)-3-β-hydroxy-11-oxo-18β,20β-olean-12-en-29-oic acid).[17]
15	Vayuvidangam	embelin, volatile oil, fixed oil, resin, tannin, christembine (alkaloid), phenolic acids like caffeic acid, vanillic acid, chrorogenic acid, cinnamic acid, o-cumaric acid.[18]

PHARMACOLOGICAL ACTIVITIES OF INGREDIENTS OF NELLIKAI LEGIYAM

NELLIKAI VATRAL (Phyllanthus emblica Linn.)

1. Antioxident

*Phyllanthus emblica Linn***.** is one of the richest sources of vitamin-C and low molecular weight hydrolysable tannins. The tannins like emblicanin-A (37%), emblicanin-B (33%), punigluconin and pedunculagin are reported to provide protection against oxygen radical included haemolysis of rat peripheral blood erythrocytes. The powerful antioxidant ellagic acid inhibits mutations in genes and repairs the chromosomal abnormalities. Reddy et al.,

suggested that the amelioration of alcohol-induced oxidative stress might be due to the combined effect of phytophenols such as tannins, flavonoid compounds and vitamin C.[19]

2. Anti-inflammatory

Reduced inflammation by Carrageenan induced rat paw edema method. Rexin pellet granuloma method (Chronic). In this in vivo study, fruit of *Phyllanthus emblica* showed significant anti-inflammatory activity, in both acute as well as chronic model of inflammation comparable to diclofenac was proved.[20]

3. Immuno modulatory

Sai Ram et al., investigated the anti-oxidant and immunomodulatory properties of *Phyllanthus emblica* using chromium (VI) as an immunosuppressive agent. Cytotoxicity, free radical production, lipid peroxidation, decreased GPx activity and diminished GSH levels is caused by chromium. Both lipopolysaccharide and concanavalin-A-stimulated lymphocyte proliferation was also significantly inhibited. Chromium also inhibited concanavalin-A stimulated interleukin-2 and gamma-interferon production. Presence of Cr enhanced apoptosis and DNA fragmentation. *Phyllanthus emblica* significantly inhibited Cr-induced free radical production, and restored the anti-oxidant status back to control level. E. officinalis also inhibited apoptosis and DNA fragmentation induced by Cr. Interestingly E. officinalis relieved the immunosuppressive effects of Cr on lymphocyte proliferation and even restored the IL-2 and gamma-IFN production considerably.[21]

3. Anti-cancerous and Anti proliferative

Yang et al., investigated the beneficial effect of pyrogallol on human lung cancer cell lines-H441 (lung adenocarcinoma) and H520 (lung squamous cell carcinoma). Results from both in vitro and in vivo studies together indicate that pyrogallol can be developed as a likely anti-lung cancer drug, particularly for the non-small cell lung cancer.[22]

4. Anti-diabetic

In in vivo study phyllanthus emblica extracts reduced the oxidative markers (SOD, CAT, GSH, GPx, LPO) and biochemical parameters (plasma insulin, Serum creatinine, urea, glucose, SGPT, SGOT, ALP) in streptozotocin induced diabetic rats.[23] Prevent hyperglycemia-induced lens opacification, aggregation and insolubilization of lens proteins on streptozotocin (STZ)-induced diabetic cataract in rats.[24]

CHUKKU (Zingiber officinale Roscoe**)**

1. Antioxidant

In vitro, ginger has been shown to exhibit antioxidant effects. Nunes et al., (2012). Jhambh et al., (2015) studied that ethanolic extract of Zingiber officinale orally at dosage of 50, 100 and 200 mg/kg b.wt. for 30 days respectively and found that dosage of 50 mg/kg to be safest and protective to rats that may be used in various disease conditions in animals for its antioxidant potential.[25]

2. Anticancer

The effect of 6-SHO on the growth of prostate cancer cells was investigated. 6-SHO effectively reduced survival and induced apoptosis of cultured human (LNCaP, DU145, and PC3) and mouse (HMVP2) prostate cancer cells. Mechanistic studies revealed that 6-SHO reduced constitutive and interleukin (IL)-6–induced STAT3 activation and inhibited both constitutive and TNF-a–induced NF-kB activity in these cells.[26]

3. Anti-inflammatory

Ginger has been reported to be effective in alleviating joint pain from osteoarthritis and rheumatoid arthritis possibly because of its anti-inflammatory effects.[27]

4. Anti-hyperglycemic

Hypoglycemic potential of 6-gingerol in STZ induced diabetes rats was proven.[28]

5. Anti-hyperlipidemic

Ginger will also help to minimize high cholesterol and keep the heart safe (Akoachere et al., 2002).

6. Antiplatelet activity

In vitro study, Srivastava (1984) found that aqueous ginger extract prevented the aggregation of platelets caused by ADP, epinephrine, collagen, and arachidonic acid.

MILAGU (Piper nigrum)

1. Antioxidant activity

In vitro studies, revealed that piperine inhibited free radicals and reactive oxygen species, therefore known to possess protective effects against oxidative damage. piperine also found to decrease lipid peroxidation in vivo.[29]

2. Anti-asthmatic activity

Kim et al. reported that oral administration of piperine in different proportion to mice suppressed and reduced the infiltration of eosinophil, hyper responsiveness and inflammation due the suppression of the production of histamine, interleukin- 5, immunoglobulin E and interleukin-4.[30]

3. Anticancerous

Piper nigrum was found to prevent the oxidative stress by inhibiting lipid peroxidation, human lipoxygenase and arresting hydroxyl and superoxide free radicals, decrease lung carcinogenesis in animal studies.[31] Landscron et al. reported that piperine inhibits some of the pro-inflammatory cytokines that are produced by tumour cells, there by interfering with the signalling mechanisms between cancer cells, thereby reducing the chances of tumour progression.[32]

THIPPILI (Piper longum Linn.)

1. Anti-oxidant

The petroleum ether extract of the fruit decrease lipid peroxide levels and maintain glutathione content, demonstrates antioxidant activity.[33]

2. Anti-cancerous

The alcoholic extract of Piper longum (10mg/dose/animal) and piperine (1.14mg/dose/animal) inhibits solid tumor development in mice induced with Daltons lymphoma ascites cells and increases the life span of mice. Piperine also shows cytotoxic towards Doltons lymphoma ascites and Ehrlichascites carcinoma cells at 250mg/ml.[34]

3. Anti-inflammatory

The piper extract and piperine possess inhibitory activities on prostaglandin and leukotrienes Cox-1 inhibitory effect and thus exhibit anti-inflammatory activity.[35]

4. Anti-asthmatic

The ethanolic extract of Piper longum in milk reduced passive cutaneous anaphylaxis in rats and protected gunia pigs against antigen-induced bronchospasm.[36]

5. Anti-microbial

Trivedi et al. reported that 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. It was found that piperlonguminine has a potent action against bacillus subtilis.[37]

THIPPILI MOOLAM (Piper longum Linn.)

1. Analgesic activity

P. longum root for opioid type analgesia using rat tail-flick method and for NSAID type analgesia using acetic-acid writhing method by using pentazocine and ibuprofen as drug controls. An aqueous suspension of P. longum root powder was given orally to mice and rat. The study accomplished that P. longum root had weak opioid but potent NSAID type of analgesic activity.[38]

2. Antiamoebic activity

root and fruit of P. longum possess antiamoebic activity approximately to the same extent48. The ethanolic extract, hexane fraction, n-butanol soluble fraction exerted in vitro amoebicidal action at 1000 micrograms/mL and the chloroform fraction showed the same at 500 micrograms/mL. The ethanolic extract and piperine, a pure compound, from this plant material cured 90% and 40% of rats with caecal amoebiasis respectively.[39]

OMAM (*Carum copticumBenth&Hook.f*)

1. Antiulcer effect

Aqueous extract from C. Copticum (125, 250, and 500 mg / kg) treatment for two weeks improved ibuprofen-induced peptic ulcer in rats that was comparable to omeprazole effect.[40]

2. Lithotripsic action

In an *in vivo* study, the effect of the extract of *C. copticum* seeds on urinary stone of 350 patients was investigated. According to data of this study, Ca oxalate, Ca oxalate/uric acid, and Ca-oxalate/hydroxyapatite stones were treated by 100%, 53%, and 31.25%, respectively, with the extract.[41]

3. Antiparasitic Effects

C. copticum, thymol, and carvacrol have macrofilaricidal properties against adult bovine filarial worm *S. digitata in vitro*. In addition, the plant increased mortality and infertility of female worm of human filarial worm *Brugia malayi in vivo.*[42]

JEERAGAM (*Cuminum cyminum.Linn*)

1. Antimicrobial effect

Through microdilution process, ethanol extracts of Cyminum cuminum seed were tested for antimicrobial activity in vitro. Ethanol extract of seed exhibited antimicrobial activity against biofilm Escherichia coli.[43] The in vitro antifungal activities of essential oil from Cuminum cyminum were studied against C. albicans ATCC 14053, C. dubliniensis ATCC CD60, C. glabrata ATCC 90030, C. krusei ATCC 6258 and C. parapsilosis ATCC 22019. The best minimal inhibitory concentration (MIC) of Cuminum cyminum oil was recorded against C. albicans and C. dubliniensis (289 mg/l).[44]

2. Hypotesive effect

The anti-hypertensive potential of standardized aqueous extract of Cuminum cyminum seeds and its role in arterial endothelial nitric oxide synthase expression, inflammation, and oxidative stress were evaluated in renal hypertensive rats. Cuminum cyminum seed was administered orally (200 mg/kg bw) for a period of 9 weeks, it improved plasma nitric oxide and decreased the systolic blood pressure in hypertensive rats.[45]

3. Anticancer

Cumin seeds also decreased significantly the incidence of both B[a]P-induced neoplasia and 3'MeDAB induced hepatomas in Wistar rats.[46]

LAVANGAM (*Syzygiyum aromaticum.Linn)*

1. Antimicrobial activity

Rana et al. documented the antifungal efficacy of clove oil towards *Trichophyton rubrum*, *Microsporum canis*, *T. mentagrophytes*, *Fusarium monoliforme*, *M. gypseum*, *F. oxysporum*, *Epidermophyton floccosum*, *Mucor* sp., *M. gypseum*, *T. rubrum*, and *Aspergillus* sp.[47]

Eugeniin, the compound isolated from *S. aromaticum* extract has been documented for its antiviral efficacy towards various herpes virus strains and the hepatitis C virus by its action on the synthesis of the viral DNA by inhibiting the viral DNA polymerase enzyme.[48]

2. Anticancerous activity

Ethyl acetate extract of clove inhibits tumor growth and promotes cell cycle arrest and apoptosis. Oleanolic acid one of the components of ethyl acetate extract of clove was found

to be responsible for its antitumor activity. Its mechanism was attributed to the promotion of Go/G1 cell cycle arrest and induction of apoptosis in a dose-dependent manner.[49]

Hussain et al. studied the effect of eugenol combined with gemcitabine on cervical carcinoma and found that the combination of eugenol and gemcitabine can inhibit cancer cell growth, even in low concentrations.[50]

3. Anti inflammatory activity

Clove exerted anti-inflammatory and immunomodulatory activities by suppressing the lipopolysaccharide (LPS) action as well as the nuclear factor-κB (NF-κB) pathway. Han and Parker reported that the anti-inflammatory activity of clove may be related to the active compound, eugenol.[51]

ELARISI (*Elattaria cardamomum.Maton*)

1. Anti oxidant

Antioxidant activity of seeds and pods of green cardamom against inhibition of linoleic acid peroxidation, thiocyanide method as reported by Shi *et al*. (2011).[52]

2. Antimicrobial activity

According to Mejdi et al. (2015), it has potential broad-spectrum antibacterial and antifungal activities that could be used to prevent damage from food-borne pathogens and food spoilage organisms.[53]

3. Anticancerous activity

Bhattacharjee et al. (2007) reported that the constituents of phytochemicals of CEOs such as 1, 8-cineole and limonene demonstrated a protective role against cancer development. Further they said aqueous cardamom extract could improve the activity of the detoxifying enzyme glutathione S-transferase and reduce lipid peroxidation.[54]

THAKKOLAM (*Illicium verum*)

1. Antioxidant

Yadav *et al*. demonstrated that treatment with star extracts reduced the mean nodular volume as well as the development of nodules in the liver of rats with induced carcinogenesis, and that the nodule incidence was significantly lowered after star treatment in rats.[55]

2. Anti-inflammatory activities

I. verum extracts (IVE) were investigated for the anti-inflammatory effects in the human keratinocyte HaCaT cell line. IVE successively exerted anti-inflammatory effects by suppressing the expression of TNF-α/IFN-γ-induced chemokines, pro-inflammatory cytokines, and adhesion molecules via blockade of NF-κB, STAT1, MAPK, and Akt activation, suggesting that IVE may be a useful therapeutic candidate for inflammatory skin diseases, such as atopic dermatitis.[56]

3. Antimicrobial activity

The preliminary studies of crude ethanolic extract from the fruit of I. verum Hook showed antimicrobial activity against S. aureus ATCC 25923, E. coli ATCC 25922, P. aeruginosa ATCC 27853, C. albicans, A. flavus and T. mentagrophytes, which was determined by the agar diffusion method.[57]

KOTHAMALEE (*Coriandrum sativum.Linn)*

1. Diuretic action

The aqueous extract of coriander seed possesses diuretic and saluretic activity. Aqueous extract of coriander seed was administered by continuous intravenous infusion at two doses (40 and 100 mg/kg) to anesthetized Wistar rats. Furosemide (10 mg/kg), a standard diuretic was used as the reference drug. Excretion of water and electrolytes in urine was measured, and glomerular filtration rate was determined. The crude aqueous extract of coriander seeds increased diuresis, excretion of electrolytes, and glomerular filtration rate in a dose-dependent way. The mechanism of action of the plant extract appears to be similar to that of furosemide.[58]

2. Antimicrobial Activity

The antimicrobial activity of ethanol, methanol, acetone, chloroform, hexane and petroleum ether extracts of Coriandrum sativum was investigated against infectious pathogenic bacteria such as E. coli, Pseudomonas aeruginosa, Staphylococcus aureus and Klebsiella Pneumonia; and many fungi including Aspergillus niger, Candida albicans, Candida kefyr and Candida tropicalis using agar well diffusion method. Methanol extract showed a varying degree of antibacterial and antifungal effects more than ethanol, acetone, chloroform, hexane and petroleum ether extracts.[59]

ATHIMATHURAM (*Glycyrhiza glabra.Linn)*

1. Effect on memory and learning

The effect of Glycyrrhiza glabra root extract (75, 150 and 300 mg/kg for 2 weeks) was evaluated on learning and memory in three months old male rats. Elevated plus-maze and Morris water maze tests were conducted to evaluate the learning and memory parameters as exteroceptive behavioral model and Diazepam induced amnesia as interoceptive behavioral model. The aqueous extract of root of Glycyrrhiza glabra showed improvement in learning and memory in a dose dependent manner. However, 150 mg/kg dose significantly ($P<0.01$) enhanced learning and memory.[60]

2. Anti-ulcer activity

Carbenoxolone a glycyrrhizate analog was effective in clinical trials in the treatment of gastric and duodenal ulcer at the medium dose of 100 mg three times a day. Liquorice can raise the concentration of prostaglandins in the digestive system that promote mucus secretion from the stomach, it was also prolonged the life span of surface cells in the stomach and has an anti-pepsin effects.[61]

VAYUVIDANGAM (*Embelia ribes.Burn.f*)

1. Anthelminthic activity

Embelia ribes seed oil when administered at different doses like 10 mg/ml, 50 mg/ml and 100 mg/ml reported death of the worms (Pheretima posthuma). Embelia ribes fruit extract in combination with Veronica anthelmintica seed extract administered at 1g / kg exerted a considerable decrease in the fecal eggs per gram (EPG) count in goats suffering from mixed gastrointestinal nematode infections.[62]

2. Antidiabetic Activity

Administration of ethanolic extract of Embelia ribes berries orally for 6 weeks at a dose of 100 mg/kg and 200 mg/kg significantly ($p<0.01$) reduced the levels of blood glucose, heart rate and systolic blood pressure in streptozotocin induced diabetic Wistar albino rats.[63]

KOOGAI NEER

1. Anti-oxidant

The ethanolic extract of M. arundinacea exhibited high antiradical activity against DPPH, ABTS, hydrogen peroxide and nitric oxide radicals with IC50 value of 293.4, 297.4, 336.1 and 258.7 µg/ml respectively. Thus, the results indicate that M. arundinacea extract

attenuated oxidative stress via its antioxidant properties and was found to be an effective scavenger of ABTS, H2O2 & NO.[64]

2. Immunostimulatory effect

BALB/c mice were fed the arrowroot powder to examine the immunostimulatory effect in vivo. Feeding of the arrowroot tuber powder for 14 days significantly enhanced IgG, IgM, and IgA levels in serum. The arrowroot tuber powder might contain resistant starch acting as dietary fibers that could stimulate the immune system.

CONCLUSION

The ingredients of nellikkai legiyam are having antioxidant, anti-inflammatory, immuno modulatory, anti-asthmatic, anti-microbial and anti-cancerous activities. Hence, it can be prescribed as immuno modulatory drug for the COVID-19 pandemic. And also, this review focused on the immuno modulating activity of various phytochemicals such as alkaloids, polysaccharides, lectins, glycosides, phenolic compounds, flavonoids, tannins and saponins present in the nellikkai legiyam. Thus, the prophylactic and therapeutic potential of siddha poly herbal formulation nellikkai legiyam is proven effective prophylaxis and adjuvant therapy of COVID-19.

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