Asian Journal of Advances in Medical Science

3(1): 273-284, 2021

POTENTIAL OF URAI MATHIRAI (PEDIATRIC SIDDHA FORMULATION) FOR THE PROPHYLAXIS AND MANAGEMENT OF COVID-19 IN CHILDREN

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Received: 30 July 2021
Accepted: 23 September 2021
Published: 25 September 2021

Review Article

ABSTRACT

The World Health Organization (WHO) data proposes that 8.5% of reported COVID-19 cases belong to pediatric population who are aged less than 18 years. Supportive care alone is recommended in asymptomatic, mild, or moderate pediatric COVID-19 patients by the panel of pediatric infectious diseases physicians and pharmacists from 20 geographically diverse North American institutions. This review article focuses on the prophylactic and therapeutic potential of Urai mathirai in the management of pediatric COVID-19 patients. The literature was looked, in databases such as Medline/PubMed Central/PubMed, Google Scholar, Science Direct, Web of science, Directory of open access journals (DOAJ), and reference lists to distinguish published manuscripts relevant to the use of Urai mathirai to prevent or treat COVID-19 in children. The herbs found in Urai Mathirai and their bioactive phytoconstituents possess antiviral, anti-inflammatory, antioxidant, immunomodulatory, bronchodilatory and other pharmacological effects relevant to the management of signs and manifestations of COVID-19. The viability of Urai Mathirai in the prophylaxis and management of pediatric COVID-19 patients could further be established by future clinical studies.

Keywords: SARS CoV-2; COVID-19; pediatric siddha formulations; urai mathirai; herbal formulations.

1. INTRODUCTION

The current pandemic Coronavirus disease 2019 (COVID-19) is a viral illness, recognized to begin with in Wuhan, China in December 2019 and is caused by a novel coronavirus, which has been named later as Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. Around 212 million of worldwide populace have become SARS-CoV-2 positive and 4.43 million among them lost

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their lives as of 23rd August 2021, as indicated by the World Health Organization (WHO) novel Coronavirus (COVID-19) Situation Board [2].

Mainly adults and elderly people were affected in the initial months of COVID-19 pandemic. However, the available data suggests that 8.5% of reported COVID-19 cases belong to pediatric population who are aged less than 18 years, as per WHO [3]. Majority of children with SARS-CoV-2 infection were asymptomatic or seen with mild symptoms including headache, fever, dry cough, fatigue, diarrhea, abdominal discomfort, nausea and vomiting [4,5].

Low prevalence of COVID-19 among children presumably because of the reasons like lower exposure to SARS-CoV-2 virus, coinfections with other viruses, protective role of Bacillus Calmette-Guérin (BCG) vaccine, more active innate and adaptive immunity, healthier respiratory tracts, differences in microbiota, immaturity of angiotensin converting enzyme 2 (ACE2) receptors, higher levels of melatonin, normal level of lymphocytes (especially natural killer (NK) cells), and the development of less intense cytokine storms [6,7]. Moreover, severe or critical COVID-19 illness were less observed among children.

Abnormality in laboratory parameters including leukopenia, lymphopenia, thrombocytopenia, transaminitis, elevated levels of ferritin, C - reactive protein (CRP), interleukin-6 (IL-6), procalcitonin, and others were observed commonly in children with moderate-severe COVID-19 [8-10]. The children with pre-existing medical conditions including neurological, cardiac and gastrointestinal disorders, and those aged less than 1 year commonly needed hospitalizations and pediatric intensive care unit (PICU) admissions [11-13].

Few of the children with COVID-19 were observed with a hyper inflammatory syndrome named multisystem inflammatory syndrome in children (MIS-C), which has many similarities to Kawasaki Disease (KD), Toxic Shock Syndrome (TSS), and macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) [14-18]. The characteristics of MIS-C may include persistent fever, skin rash, conjunctivitis, diarrhea, elevated inflammatory biomarkers, shock, extremity edema, multisystem organ dysfunction and many other symptoms and MIS-C most commonly affects young and school-aged children [19-23].

Generally, the adult patients with SARS-CoV-2 infection could be managed by utilizing the drugs having the potential of restraining viral entry and/or viral fusion including umifenovir, Baricitinib, camostat mesilate, and Nafamostat mesilate and the drugs having the potential of inhibiting viral replication like remdesivir, favipiravir, Lopinavir/ritonavir, Ribavirin, Sofosbuvir, chloroquine and Hydroxychloroquine [24]. Whereas, the asymptomatic, mild, or moderate pediatric COVID-19 patients to be managed with supportive care only as per the recommendation from panel of pediatric infectious diseases physicians and pharmacists from 20 geographically diverse North American institutions. Moreover, the panel recommends against the use of Lopinavir/ritonavir, Ribavirin, Sofosbuvir, chloroquine and Hydroxychloroquine in pediatric COVID-19 patients. However, the severe or critical pediatric COVID-19 patients could be managed by the administration of Remdesivir [25].

In addition, the adult patients with COVID-19 might also be managed by using some adjuvant therapies including corticosteroids, monoclonal antibodies, interleukin-1 (IL-1) inhibitors, anticoagulants, interferons, TNF-α inhibitors, colchicine, etoposide, ruxolitinib, convalescent plasma, immunoglobulins, mesenchymal stem cells, natural killer (NK) cells, and inhaled nitric oxide (iNO) [26]. The pediatric patients with severe or critical COVID-19 illness might be managed using adjuvant therapies like corticosteroids (methylprednisolone), interleukin inhibitors (Tocilizumab or Anakinra) and anticoagulants (low molecular weight heparin) [27].

The use of traditional medicine is very common among global population especially in underdeveloped or developing countries, nowadays. Similarly, many patients with COVID-19 from different parts of the world are using various traditional medicines including Siddha, Ayurveda, Traditional chinese medicine, Traditional african medicine, Traditional persian medicine, etc. alone or along with repurposed antiviral drugs and standard care. The ministry of AYUSH (Government of India) recommends the use of siddha formulations such as Kabasura Kudineer, Nilavembu Kudineer and others to manage adult patients with COVID-19 [28]. Moreover, the efficacy of other siddha formulations such as Kabasura Kudineer [29], and Nilavembu Kudineer [30] were demonstrated against COVID-19 in various clinical and in-silico studies. In addition, the ministry of AYUSH (Government of India) recommends the use of 50 mg of Urai Mathirai in pediatric COVID-19 patients depending upon age [28]. Hence, this review focuses on the use of Urai Mathirai for the prophylaxis and management of children with COVID-19.

2. METHODS

The literature search was carried out in databases such as Medline/PubMed Central/PubMed, Google Scholar, Science Direct, EBSCO, Scopus, Web of science, EMBASE, Directory of open access journals (DOAJ), and reference lists to identify relevant articles, using terms like SARS CoV-2, COVID-19, Urai Mathirai, Pediatric Siddha formulation and Herbal preparation. This review includes the articles that assessed the safety and efficacy of individual ingredients of Urai mathirai, the pediatric siddha formulation. The articles written in English have been considered for the review, whereas the duplicate publications are excluded.

3. RESULTS AND DISCUSSION

Urai Mathirai is a polyherbal, pediatric siddha formulation, which has been used traditionally and is recommended usually as an immunomodulatory agent, to prevent recurrent respiratory infections in children [31]. Recently, the ministry of AYUSH (Government of India) recommends the use of 50 mg of Urai Mathirai to manage pediatric COVID-19 patients depending upon age [28].

Urai mathirai contains various herbal ingredients (Table I) including *Acorus calamus* (Vasambu/ Sweet flag), *Myristica fragrans* (Jathikkai/ Nutmeg), *Terminalia chebula* (Kadukkai/ Chebulic myrobalan), *Quercus infectoria* (Maasikkai/ Oakgall), *Piper longum* (Thippili/ Long pepper), *Allium sativum* (Poondu/ Garlic), *Zingiber officinale* (Sukku/ Dried Ginger), *Glycyrrhiza glabra* (Athimathuram/ Liquorice), *and Ferula asafoetida (*Perunkayam / Asafoetida*) and Anacyclus pyrethrum* (Akkrakaram / Pellitory) [32].

3.1 Acorus Calamus (Vasambu/ Sweet Flag)

Acorus calamus is an herb used traditionally in various systems of medicine including Siddha, Ayurveda, Unani, Traditional Chinese medicine and others, to manage conditions such as bronchitis and other inflammatory conditions, cramps, flatulence, diarrhea, appetite loss, nervous disorders, vascular disorders, and many others, since ancient times [33]. Several phytochemical studies of *Acorus calamus* identified the presence of flavonoids, volatile oil, glycosides, saponins, tannins, and polyphenolic compounds. Moreover, the bioactive phytoconstituents of *Acorus calamus* include β- asarone, α- selinene, camphene, s- cadinol, calarene, calamen, clamenol, calameon, and sesquiterpenes [34,35].

Acorus calamus has antioxidant, anti-iflammatory, antiviral, bronchodilatory, CNS depressant, antidiarrheal, anticonvulsant, antispasmodic, antimicrobial and many other pharmacological activities [36,37]. In addition, *Acorus calamus* helps to improve the immune system and hence it is used widely in pharmaceutical sector [38]. However, the major bioactive phytoconstituent of *Acorus calamus* determined to be β- asarone (isoasarone), which has analgesic, spasmolytic, antisecretory, sedative and CNS depressant activities [39].

3.2 Myristica Fragrans (Jathikkai/ Nutmeg)

Myristica fragrans is used commonly as a spice and flavoring agent in food preparations. It is also used in traditional medicines including Ayurveda, Siddha, Ethnomedicine (Tribal medicine) and others as aphrodisiac, astringent, digestive tonic, carminative, anti-flatulent, and others. The phytochemical analysis of *Myristica fragrans* revealed that it contains myristicin, myrislignan, myrcene, macelignan, elemicin, terpinene, limonene, α-pinene, camphene, p-cymene, sabinene, 4-terpineol, eugeunol, and others [40-42]. The pharmacological properties of *Myristica fragrans* include antioxidant, anti-inflammatory, antimicrobial, antithrombotic, antiplatelet, hypoglycemic, hypolipidemic and others [43,44].

3.3 Terminalia Chebula (Kadukkai/ Chebulic Myrobalan)

Terminalia chebula is an herb, which is traditionally used for decades to manage conditions like asthma, sore throat, diarrhea, dysentery, vomiting, ulcers, bleeding piles, gout, heart and bladder diseases [45]. The chemical composition of *Terminalia chebula* include hydrolysable tannins (chebulic acid, gallic acid, ellagic acid), gallotannins (1, 6 di-O-galloyl-β-D-glucose, 3, 4, 6 triO-galloyl-βD-glucose, 2,3,4,6 tetra-O-galloyl-β-D-glucose, 1, 2,3,4,6 penta-Ogalloyl-β-Dglucose), ellagitannins (corilagin, punacalagin, casurarinin and terchebulin), glycosides (arjun glucoside I, arjungenin, and chebulosides I and II), and flavonoids (luteolin, rutins, and quercetin) [46-48].

The pharmacological and medicinal activities of the plant include antiviral, antioxidant, anti-inflammatory, immunomodulatory, antidiabetic, antihyperlipidemic, hepatoprotective, antimutagenic, antiproliferative, antispasmodic, wound healing, retinoprotective, and chemopreventive [49-51]. Moreover *Terminalia chebula* has been identified with potential antiviral efficacy against both DNA and RNA viruses. The tannins of *Terminalia chebula* of determined to prevent viral entry, resulting in minimized release of virions [52].

Table 1. Composition of *Urai Mathirai*

S. No	Herb	Major Phytoconstituents	Pharmacological Activities Relevant to Signs and Symptoms of COVID-19
1	*Acorus calamus* (Vasambu/ Sweet flag)	β- asarone, α- selinene, camphene, s- cadinol, calarene, calamen, clamenol, calameon, and sesquiterpenes [34,35]	Antioxidant, anti-iflammatory, antiviral, bronchodilatory, CNS depressant, antidiarrheal, anticonvulsant, antispasmodic, antimicrobial effects [36, 37]
2	*Myristica fragrans* (Jathikkai/ Nutmeg)	Myristicin, myrislignan, myrcene, macelignan, elemicin, terpinene, limonene, α-pinene, camphene, p-cymene, sabinene, 4-terpineol, eugeunol, and others [40-42]	Antioxidant, anti-inflammatory, antimicrobial, antithrombotic, antiplatelet, hypoglycemic, hypolipidemic and others [43, 44]
3	*Terminalia chebula* (Kadukkai/ Chebulic myrobalan)	Hydrolysable tannins (chebulic acid, gallic acid, ellagic acid), gallotannins (1, 6 di-O-galloyl-β-D-glucose, 3, 4, 6 triO-galloyl-βD-glucose, 2,3,4,6 tetra-O-galloyl-β-D-glucose, 1, 2,3,4,6 penta-Ogalloyl-β-Dglucose), ellagitannins (corilagin, punacalagin, casurarinin and terchebulin), glycosides (arjun glucoside I, arjungenin, and chebulosides I and II), and flavonoids (luteolin, rutins, and quercetin) [46-48]	Antiviral, antioxidant, anti-inflammatory, immunomodulatory, antidiabetic, antihyperlipidemic, hepatoprotective, antimutagenic, antiproliferative, antispasmodic, wound healing, retinoprotective, and chemopreventive [49-51]
4	*Quercus infectoria* (Maasikkai/ Oakgall)	Tannins such as syringic acid, β-sitosterol, amentoflavone, hexamethyl ether, isocryptomerin, methyl betulate, methyl oleanate and hexagalloyl glucose, gallic and ellagic acid	Antiviral, anti-inflammatory, astringent, antidiabetic, antibacterial, and antifungal effects [53,54]
5	*Piper longum* (Thippili/ Long pepper)	Alkaloids like piperine, methyl piperine, piperlongumine, piperlonguminine, pipernonaline, pipercide, piperderidine, dehydropipernonaline piperidine, tetrahydro piperine, trimethoxy cinnamoyl-piperidine, longamide, piperettine, asarinine, pellitorine, piperundecalidine, retrofractamide A, pergumidiene, brachystamide-B, N-isobutyl decadienamide, brachyamide-A, and brachystine [55,56]	Antioxidant, anti-inflammatory, immunomodulatory and antimicrobial effects [57,58]
6	*Allium sativum* (Poondu/ Garlic)	Organosulfur compounds (allicin, alliin, diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), methyl allyl trisulphate, diallyl thiosulfonate (allicin), S-allyl-cysteine (SAC), and S-allyl-cysteine sulfoxide (alliin)), phenolic compounds (β-resorcylic acid, followed by pyrogallol, gallic acid, rutin, protocatechuic acid, and quercetin), alkaloids, saponins, tannins, and polysaccharides along with numerous vitamins, minerals, and trace elements (germanium and selenium) [59-61]	Antioxidant, anti-inflammatory, anti-atherosclerotic, antihypertensive, antidiabetic, antibacterial, antifungal, anticarcinogenic, cardiovascular protective, hepatoprotective, renoprotective, and neuroprotective effects [62,63]

S. No	Herb	Major Phytoconstituents	Pharmacological Activities Relevant to Signs and Symptoms of COVID-19
7	*Zingiber officinale* (Sukku/ Dried Ginger)	Essential oils (Camphene, zingiberene, phellandrene, cineol, borneol, limonene, linalool, geraniol and nerolidol), non-volatile constituents (gingerol, shogoal, gingeberol, gingerine), resin and starch [64-66]	Antiviral, anti-inflammatory, antioxidant, antispasmodic, circulatory stimulant, expectorant, anti-emertic, carminative, digestive aid, etc. [67-69]
8	*Glycyrrhiza glabra* (Athimathuram/ Liquorice)	Saponins (glycyrrhizin (glycyrrhizic acid or glycyrrhizinic acid),alkaloids, phenolic compounds (formononetin, hemileiocarpin, hispaglabridin B, isoliquiritigenin, glabrene, glabridin, 4′-O-methylglabridin, paratocarpin B, phaseollinisoflavone (phytoalexin), glabrol, salicylic acid, and O-acetyl salicylic acid), flavonoids (glucoliquiritin apioside, prenyllicoflavone A, shinflavone, shinpterocarpin and 1-methoxyphaseollin), cardiac glycosides, carbohydrates, tannins, phlobatannins, anthraquinones, anthocyanin, terpenoids, glycosides, and sterols [72-74]	Antioxidant, anti-inflammatory, antiviral, antibacterial, and antidiabetic activities [75-77]
9	*Ferula asafoetida* (Perunkayam / Asafoetida)	Resins (ferulic acid, umbelliferone, asaresinotannols, farnesiferols, and coumarins), gum (glucose, galactose, l-arabinose, rhamnose, and glucuronic acid), and volatile oil (monoterpenes, sulfur-containing compounds (2-butyl 1-propenyl disulfide, 1-(methylthio) propyl 1-propenyl disulfide, and 2-butyl 3-(methylthio)-2-propenyl disulfide), and other volatile terpenoids) [79-81]	Antioxidant, anti-inflammatory, antiviral, antimicrobial, antispasmodic, hypotensive, hypolipidemic, hypoglycemic, anticarcinogenic, antiulcer, hepatoprotective, and neuroprotective effects [82-84]
10	*Anacyclus pyrethrum* (Akkrakaram / Pellitory)	Alkaloids (pellitorine), flavonoids, tannins, N-alkylamides, reducing compounds, coumarins, saponins, gum and traces of essential oil [85,86]	Antioxidant, anti-inflammatory, antiviral, immunostimulant, antimicrobial, anticonvulsant, antidiabetic, aphrodisiac, antidepressant and others [87,88]

3.4 Quercus Infectoria (Maasikkai/ Oakgall)

The galls from *Quercus infectoria* is used traditionally to tighten the vagina after childbirth. Naturally, it contains highest level of tannins (approximately 50-70%) such as syringic acid, β-sitosterol, amentoflavone, hexamethyl ether, isocryptomerin, methyl betulate, methyl oleanate and hexagalloyl glucose, gallic and ellagic acid. The tannins of *Quercus infectoria* identified to possess various pharmacological activities including antiviral, anti-inflammatory, astringent, antidiabetic, antibacterial, and antifungal effects [53,54].

3.5 Piper Longum (Thippili/ Long Pepper)

Piper longum is traditionally used to treat conditions like respiratory tract infections, tuberculosis, arthritis, menstrual pain, gonorrhea, and sleeping problems. The most abundant alkaloid of *Piper longum* is identified as piperine and it also contains other alkaloids including methyl piperine, piperlongumine, piperlonguminine, pipernonaline, pipercide, piperderidine, dehydropipernonaline piperidine, tetrahydro piperine, trimethoxy cinnamoyl-piperidine, longamide, piperettine, asarinine, pellitorine, piperundecalidine, retrofractamide A, pergumidiene, brachystamide-B, N-isobutyl decadienamide, brachyamide-A, and brachystine [55,56]. *Piper longum* has been observed with promising antioxidant activity and marked anti-inflammatory potential along with immunomodulatory and antimicrobial effects [57,58].

3.6 Allium Sativum (Poondu/ Garlic)

Allium sativum is a commonly used spice and condiment; the phytochemical analysis of *Allium sativum* revealed the presence of organosulfur compounds (allicin, alliin, diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), methyl allyl trisulphate, diallyl thiosulfonate (allicin), S-allyl-cysteine (SAC), and S-allyl-cysteine sulfoxide (alliin)), phenolic compounds (β-resorcylic acid, followed by pyrogallol, gallic acid, rutin, protocatechuic acid, and quercetin), alkaloids, saponins, tannins, and polysaccharides along with numerous vitamins, minerals, and trace elements (germanium and selenium) [59-61].

Various studies have shown that *Allium sativum* can enhance immunity and it also observed with different pharmacological activities including antioxidant, anti-inflammatory, anti-atherosclerotic, antihypertensive, antidiabetic, antibacterial, antifungal, anticarcinogenic, cardiovascular protective, hepatoprotective, renoprotective, and neuroprotective effects [62,63].

3.7 Zingiber Officinale (Sukku/ Dried Ginger)

Zingiber officinale (Dry ginger) is also a commonly used spice and condiment, which is used for many decades in traditional system of medicines including Siddha, Ayurveda, Unani and others to manage various conditions such as throat complaints, cough, vomiting, morning sickness, travel sickness, headache, fever, asthma, colic pain, flatulence, dyspepsia, indigestion, stomachache, spasms, fainting, gout, and chronic rheumatism. The bioactive phytoconstituents of *Zingiber officinale* include essential oils (Camphene, zingiberene, phellandrene, cineol, borneol, limonene, linalool, geraniol and nerolidol), non-volatile constituents (gingerol, shogoal, gingeberol, gingerine), resin and starch [64-66]. The biological and medicinal properties of *Zingiber officinale* include expectorant, anti-emertic, carminative, digestive aid, antiviral, anti-inflammatory, antioxidant, antispasmodic, circulatory stimulant, and others [67-69].

3.8 Glycyrrhiza Glabra (Athimathuram/ Liquorice)

Glycyrrhiza glabra is a perennial herb and it has been used traditionally to treat various conditions including respiratory disorders, sexual debility, stomach ulcers, rheumatism, skin diseases, epilepsy, hemorrhagic diseases, fever, paralysis, and jaundice [70,71].

The phytochemical analysis of *Glycyrrhiza glabra* revealed the presence of various bioactive components including saponins (glycyrrhizin (glycyrrhizic acid or glycyrrhizinic acid),alkaloids, phenolic compounds (formononetin, hemileiocarpin, hispaglabridin B, isoliquiritigenin, glabrene, glabridin, 4′-O-methylglabridin, paratocarpin B, phaseollinisoflavone (phytoalexin), glabrol, salicylic acid, and O-acetyl salicylic acid), flavonoids (glucoliquiritin apioside, prenyllicoflavone A, shinflavone, shinpterocarpin and 1-methoxyphaseollin), cardiac glycosides, carbohydrates, tannins, phlobatannins, anthraquinones, anthocyanin, terpenoids, glycosides, and sterols [72-74]. Several Pharmacological experiments have demonstrated that *Glycyrrhiza glabra* exhibited a variety of biological activities including antioxidant, anti-inflammatory, antiviral, antibacterial, and antidiabetic activities [75-77].

3.9 Ferula Asafoetida (Perunkayam / Asafoetida)

Ferula asafoetida is a perennial herb that has been consumed for centuries as a condiment and a traditional medicine as respiratory medicine (asthma, bronchitis, and whooping cough), aphrodisiac,

expectorant, anthelmintic, stimulant, analgesic, and many others [78].

The phytochemical analysis of *Ferula asafoetida* observed with various phytoconstituents including resins (ferulic acid, umbelliferone, asaresinotannols, farnesiferols, and coumarins), gum (glucose, galactose, l-arabinose, rhamnose, and glucuronic acid), and volatile oil (monoterpenes, sulfur-containing compounds (2-butyl 1-propenyl disulfide, 1-(methylthio) propyl 1-propenyl disulfide, and 2-butyl 3-(methylthio)-2-propenyl disulfide), and other volatile terpenoids) [79-81]. Various studies have determined that *Ferula asafoetida* has diverse pharmacological activities such as antioxidant, anti-inflammatory, antiviral, antimicrobial, antispasmodic, hypotensive, hypolipidemic, hypoglycemic, anticarcinogenic, antiulcer, hepatoprotective, and neuroprotective effects [82-84].

3.10 Anacyclus Pyrethrum (Akkrakaram / Pellitory)

Anacyclus pyrethrum is a traditionally used herb to manage conditions like toothache, digestive problems, salivary secretion, angina, female infertility, lethargy, and others. Several phyotoconstituents including alkaloids (pellitorine), flavonoids, tannins, N-alkylamides, reducing compounds, coumarins, saponins, gum and traces of essential oil, have been identified in phytochemical screening of *Anacylcus pyrethrum* [85,86]. The pharmacological and biological activities of *Anacyclus pyrethrum* include antioxidant, anti-inflammatory, antiviral, immunostimulant, antimicrobial, anticonvulsant, antidiabetic, aphrodisiac, antidepressant and others [87,88].

Diverse literature have reported that SARS-CoV-2 infection is associated with dysregulation of immune system (excessive activation of innate immunity (monocyte/macrophage), increased neutrophil/lymphocyte ratio (NLR), dysregulation of adaptive immunity (CD4+ T lymphopenia, CD8+ T lymphopenia, reduced NK cells, decreased levels of regulatory T cells), exacerbated inflammatory response (cytokine release syndrome, cytokine shower, and cytokine storm), hyper oxidative stress, acute lung injury, acute respiratory distress syndrome, hypoxemia, tissue hypoxia, sepsis and septic shock, multiple organ failure and eventual death based on the severity of infection [89-94]. Hence, the patients with COVID-19 are managed with antivirals, monoclonal antibodies, corticosteroids, antioxidants, anticoagulants and other supportive therapies as per patients' conditions.

The herbs found in Urai Mathirai and their bioactive phytoconstituents possess antiviral, anti-inflammatory, antioxidant, immunomodulatory, bronchodilatory and other pharmacological effects relevant to the management of signs and symptoms of COVID-19. In addition, an experimental animal study demonstrated the anti-inflammatory efficacy of Urai Mathirai in albino rats [95]. The acute toxicity study of Urai Mathirai revealed that there was no mortality observed in animals treated with 100 mg/kg of Urai Mathirai (10 times of therapeutic dose). In addition, the sub-acute toxicity study of Urai Mathirai determined no significant hormonal, biochemical, and histological changes and there was no significant alterations in body weight and water/feed consumption as well [96]. Moreover, the chronic toxicity study of Urai Mathirai demonstrated that the oral administration of 10, 50 and 100 mg/kg of Urai Mathirai did not cause any toxicity among treated animals [97].

4. CONCLUSION

Urai Mathirai may help to prevent or manage SARS-CoV-2 infection among children along with standard of care, as it has been used for decades in children as an immunomodulatory preparation. Moreover, the herbs found in Urai Mathirai and their bioactive phytoconstituents possess antiviral, anti-inflammatory, antioxidant, immunomodulatory, bronchodilatory and other pharmacological effects relevant to the management of signs and symptoms of COVID-19. In addition, the ministry of AYUSH (Government of India) recommends the use of 50 mg of Urai Mathirai to manage pediatric COVID-19 patients depending upon age. The patients or caregivers of pediatric COVID-19 patients should seek medical attention and avoid self-medication. The efficacy of Urai Mathirai in the prophylaxis or the management of pediatric COVID-19 patients could further be established by future clinical studies.

NOTE

The study highlights the efficacy of "Siddha" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an

avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSEN AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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DOI: 10.22541/au.158765852.23761913