REVIEW

Viral induced Pediatric Acute Respiratory Distress Syndrome (PARDS) and Siddha Herbs: A Narrative Review

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ABSTRACT

Introduction: Pediatric Acute Respiratory Distress Syndrome (PARDS) with acute pulmonary inflammation is one of the leading causes of death within pediatric intensive care unit. Although the mortality rate has reduced with the advent of lung protective ventilation and Extra Corporeal Membrane Oxygenation (ECMO), no specific effective pharmacological treatment is available. This study aims to explore and substantiate the anti-viral potential of Siddha herbs for PARDS. **Methods**: Thorough survey of research studies from electronic databases and literature analysis of the Siddha texts was performed. The Symptomatology of acute respiratory distress syndrome is comparable to *Vichinna Swasam* described in Siddha pathology. **Results**: The viral induced primary pneumonia, the predominant cause of PARDS, could be managed by the use of anti-viral Siddha herbs, known to have inhibitive effects on the cytokine storm in viral progressive states. Various experimental studies that analyze the anti-inflammatory activity of Siddha herbs and their mechanism of action in attenuation or reversal of the acute lung injury caused by pro- inflammatory mediators have been tabulated. **Conclusion**: The consolidation of experiment knowledge with ethnopharmacological evidence of Siddha plants-based drugs can offer a novel platform for development of integrated anti-viral treatment modules for treating PARDS.

KEY WORDS: ARDS, PARDS, Cytokines, Siddha.

1. INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS), first described in 1967 in adults presented with tachypnea, hypoxemia and decreased pulmonary compliance[1]. Recommendations of the PALICC (Pediatric Acute Lung Injury Consensus Conference, 2015) regarding Pediatric Acute respiratory Distress Syndrome (PARDS) has prompted for early recognition and diagnosing PARDS in clinical practice[2]. Although the outcomes for ARDS in pediatric population have improved with ventilator support, the rates of mortality and morbidity are significant[3]. Previous clinical and pre-clinical studies have revealed that alkaloids from natural plant sources have shown to have anti-viral, anti-inflammatory, antioxidant activity that attenuates the effect of inflammatory cells on lung tissue resulting in either through reduction or reversal of acute lung injury[4]. This review seeks to discuss about viral induced ARDS, its Siddha counterpart and identify herbs

through literature analysis of experimental studies.

The Respiratory Syncytial Virus (RSV) and Influenza A (HINI) virus significantly cause PARDS with the bacterial co infection playing a significant role[5,6]. According to Kinikar et al, an Indian study suggested that 18% of pediatric patients admitted with confirmed HINI (Influenza A) virus had developed ARDS[7]. The community acquired viral infections include both seasonal and pandemic pathogens playing a major role besides nosocomial infections[8]. Seasonal viruses, the most frequent cause of childhood community acquired pneumonia; include RSV, corona viruses, rhinoviruses, adenoviruses, para influenza viruses and human meta pneumo virus[9].

The Primary pneumonia triggered by viral infections is the most common etiology of PARDS[10]. Anatomic and physiological differences render children and infants more vulnerable to severe respiratory insult compared to adults necessitating the need for prevention with herbal strategies. In the delicate population timely intervention at lower threshold level itself is needed[11]. Cases of seasonal viruses typically causing severe infection in immunocompromised patients are being increasingly reported[12].

In 2015, World Health Organization developed a list of community acquired novel pathogens likely to produce severe outbreaks in the near future for which neither prevention nor specific treatments were available[13]. The list spoke of two novel corona viruses SARS-CoV and MERS-CoV, now SARS- CoV2 become a dangerous addition creating havoc around the world. About 20% of the SARS CoV-1 patients had developed ARDS, while 40% mortality rate were recorded in MERS CoV infections, COVID-19 pandemic has a mortality rate of 1.5%, confirming that corona virus continues to be the significant etiology of ARDS with high mortality[14-16] in the current age of epidemics.

This narrative review will lead to identification of the new areas of integration of Siddha with conventional therapy as a preventive and add-on therapy for at-risk pediatric population.

2. METHODS OF REVIEW

Survey of the Scientific Journals were done through electronic databases such as PUBMED, GOOGLE SCHOLAR, AYUSH RESEARCH PORTAL, TN DR. MGR university repository etc for literatures on PARDS and ARDS. The review of articles was done by analyzing the bibliography of references (backward Citation Chase done). The SEARCH terms used were "PARDS", "ARDS", "HERBS and ARDS", the preclinical study results and the narrative articles were screened for relevant information. An integrative literature review was carried out to narrate the empirical literatures of PARDS in comparison to Siddha science for bringing out a new perspective on effectiveness of Siddha herbs in management and prophylaxis of ARDS.

3. RESULTS

The symptomatology of the ARDS is compared with that of the "*Vicchinna Swasam*" for a clearer understanding of the diagnosis made in Siddha (Table 1). Following which various herbs used in the scope of respiratory distress, have been subjected to scrutiny whether there is anti-inflammatory action that can either attenuate or reverse the acute lung injury and damage caused by pro-inflammatory mediators of cytokine storm in viral progressive

states and immune conditions. The results of which are also tabulated (Table 2).

3.1 Symptoms of PARDS

PARDS may develop over a few days or worsen quickly. The most common symptoms are shortness of breath, fast breathing (tachypnea) or taking lots of rapid, shallow breath, fast heart rate, coughing that produces white frothy sputum, blue fingernails or blue tone to the skin or lips, fatigue, fever, crackling sound in the lungs, chest pain, especially when trying to breathe deeply, low blood pressure, confusion and rarely abdominal pain[17].

3.2 Siddha diagnosis "*Vichinna Swasam*" and the Concept of ARDS

The ARDS could be compared to *Vicciṉṉa cuvācam* in Siddha, also known as *aiya vaḷi iraippu, pēriraippu*. The signs and symptoms of *Vicciṉṉa cuvācam* show severe derangement of *aiyam* and *vaḷi*. It is caused by dietary, environmental/seasonal and behavioral factors that cause an aggravation of *aiyam* showing common premonitory symptoms of any viral respiratory infection[18]. This is followed by derangement of *vaḷi* associated with increase of *utāṉaṉ* from the *aṉākata cakkaram*. Then difficulty in breathing sets in with shallow and rapid breaths. The symptoms of hypercapnia that is caused by the rapid shallow breathing has been clearly reported in Siddha texts. The white frothy nature of the sputum indicates the derangement of *aiyam* and *vaḷi* corresponding to *aiya vaḷi iraippu*[19].

In respiratory distress disorders, along with the dietary, seasonal factors, the *iyarkai vaṉmai* (innate immunity) of the person play an important role in the viral replication and progression of pneumonia to ARDS. Since children have delicate balance of the tri-humors (*vaḷi*, *aḻal* and *aiyam*) hanging in balance, mild dietary, seasonal variations can cause profound effects in the lung tissues. Siddha system states the importance of history taking of consumption of *aiyam* aggravating foods (food allergies), periodical infections during seasonal changes and predisposed infections in treating any *aiya nōy* (phlegmatic disorder). Siddha advocates immunity in times of epidemics through various herbal decoctions as mark of preventive health termed as *ceyaṟkai vaṉmai* (immunity induced by immune-modulators/immune boosters)[20].

The analogue between the *Vicciṉṉa cuvācam* and ARDS have been given Table 1.

Table 1. Comparative signs and symptoms of ARDS with *Vicciṉṉa cuvācam* (*Aiya vaḷi iraippu*):

Features of *Vicciṉṉa cuvācam*	Presence in ARDS[21]
Inability to breathe in and out with intermittent dyspnea	+
Dryness of tongue, Sweating	+
Giddiness, sense of rotation of the body	+
Congestion of eyes with pain	+, severe ocular congestion, mucus, conjunctivitis and discomfort due to cytokine mediated inflammation mostly observed in RSV infections[22,23].
Incoherent talk, feeling sad, occasional behavioral disturbances	+
Pain in the genitalia	Not observed in literature review of ARDS
Abdominal distension (retention of urine and stools)	+ Abdominal pain as in case of pancreatitis in ARDS[24].

The symptomatology of *Vicciṉṉa cuvācam as* pointed out by Siddha is due to the pathophysiology of respiratory distress itself showing reduced alveolar ventilation, loading up of carbon dioxide - retention, central nervous system depression, fatigue of respiratory muscles, impairment of neuromuscular transmission, imbalance of energy demands and supplies and adaptation of central controllers[25].

Out of the 5 types of classical *iraippu nōy* in Siddha texts, *aiya vaḷi iraippu* is seen as the complication of the other respiratory illnesses. Differential diagnosis of *aiya vaḷi iraippu* includes *aiya iraippu* (*Tamaraka cuvācam*), *mantāra cuvācam, cuvāca kācam and cuvāca aiyam*. In Siddha therapeutics, some of the medicines used for respiratory distress are *tāḷicāti cūraṇam, tirikaṭuku cūraṇam, kōrōcaṉai māttirai, kastūri karuppu, cuvāca kuṭōri māttirai, tūtuvaḷai ney, pavaḷa paṛpam, tippili iracāyaṇam, kaṇṭaṅkattiri cūraṇam*[26,27].

3.3 Activities of Siddha herbs on Acute Lung Injury in Experimental models

Preclinical studies indicate pretreatment of the lung tissues to herbal constituents, prior to either acute injury or oxidative stress, produce attenuation of the inflammatory changes and the extant of remodeling of the lung tissues, further (when treated), there is significant reversal of the peroxidation induced changes[28]. This gives us hope that early intervention with Siddha herbal compound drugs can prove to attenuate the viral effects, inhibit viral replication, sequelae and oxidative damage therein. The details of these study results with reference to the anti-inflammatory effects is given in Table 2.

4. DISCUSSION

Herbal medicine is the third most popular choice of both adults (11%) and children (6%) suffering from asthma/respiratory distress. This is why there is a reason to believe the use of herbal medicines for ARDS, further more for prevention and attenuation of the condition in young children[39]. Four of the five classes of drugs currently used to treat either asthma or respiratory distress—namely, ß2 agonists, anticholinergics, methylxanthines and cromones have origins in herbal treatments going back at least 5000 years[40].

ARDS known to be Acute Lung Injury (ALI), Non-cardiac Lung edema is associated with high rates of morbidity and mortality with no accurate therapeutic agents/pharmacological treatment. Corticosteroids remain the mainstay of ALI treatment and for those at risk of ARDS but they cause significant side effects by increasing the risk of infections[41].

In Siddha, several herbal and herbo-mineral drugs have been used to treat respiratory illnesses. Various classifications of respiratory ailments have been explained in classical Siddha texts as *iluppu* or *iraippu nōy*. The symptoms of acute respiratory distress syndrome can be closely found to be similar to that of *vicciṉṉa cuvācam*, synonymous with *pēriraippu, aiya vaḷi iraippu* mentioned in Siddha Maruthuvam (Siddha General Medicine).

Table 2. Showing Evidence suggesting effects of Siddha herbal constituents in ALI in animal models

Name of the plant	Part used	Active constituent	Experimental model	Potential activities	Mechanism of AIA	Ref.
Berberis aristata DC.	Root	Berberine	LPS-induced acute lung injury	AIA	Berberine inhibits LPS-induced ALI through the PERK-mediated Nrf2/HO-1 signaling axis; inflammatory factor (IL-6 and IL-8) release and reactive oxygen species generation were significantly decreased	[29]
Curcuma longa L.	Root	Curcumin	Ischemia – reperfusion (I/R) induced lung injury in rats.	AIA	Curcumin attenuates acute lung injury, probably through improving oxidative stress and inhibiting nuclear factor-κB-mediated expression of inflammatory cytokines; down regulates the production of TNF-α	[30]
Glycyrrhiza glabra L.	Root	Glycyrrhizin	lipopolysaccharide-induced acute lung injury in a mouse model	AIA and lung protective effects	Inhibited pro inflammatory cytokines playing a key role in the initial phase of inflammatory response, which suggests that inhibition of the TLR-4/NF-κB signal pathway	[31]
Andrographis paniculata (Burm. fil.) Nees	Whole plant	Andrographolide	LPS induced inflammation in vivo and in vitro.	AIA and lung protective effects.	Andrographolide significantly inhibited the ratios of phospho-IKKβ/total IKKβ, phospho-IκBα/total IκBα and phospho-NF-κB p65/total NF-κB p65 and NF-κB p65 DNA binding activities, both *in vivo* and *in vitro*. *In vivo*, pulmonary inflammation, pulmonary edema, ultrastructure changes of type II alveolar epithelial cells, MPO activity, total cells, neutrophils, macrophages, TNF-α, IL-6 and IL-1β in BALF, along with the expression of VCAM-1 and VEGF were dose-dependently	[32]

					attenuated by andrographolide.	
Adhatoda vasica NEES	Leaf	Vasicine	Ovalbumin and aluminium hydroxide exposed wistar rats	AIA and Anti-oxidant against lipid peroxidation and related injury due to oxidative stress; reversal of injury	Significant reduction in the oxidative stress, marked recovery and reverse to normalcy of the histological findings of intra alveolar hemorrhage, interstitial pneumonitis, hyperplastic changes in the bronchial epithelium were reverted by vasicine. (Changes of lipid peroxidation reverted to normal)	[33]
Vitex negundo L.	Leaf	-	Guinea pig model	Anti-oxidant against lipid peroxidation and related injury due to oxidative stress	Reversal of increased lipid peroxidation and damage to lung tissues caused by ovalbumin and aluminum hydroxide and restoration of normal epithelial barrier	[34]
Zingiber officinale Roscoe	Rhizome	Zingerone and 6-shagoal	Murine acute lung injury model.	AIA and attenuates lipopolysaccharide-induced acute lung injury	Zingerone attenuates the mitogen-activated protein kinases (MAPK) and nuclear factor-kappa B (NF-κB) signaling pathways through blocking the phosphorylation of ERK, p38/MAPK and IκBα, NF-κB/P65; both 6-shogaol and zingerone significantly improved the histopathological lung conditions in a dose dependent manner and attenuated the LPS-induced neutrophils and macrophages in the bronchoalveolar lavage fluid (BALF) with a declined MPO activity, which serves as an important marker of neutrophil influx into the tissues	[35]
Nigella sativa L.	Seed	Thymoquinone	Murine acute lung injury model.	AIA and attenuates Lipopolysaccharide (LPS) induced lung	Pretreatment (3 mg/kg, i.p.) for 5 days prior to ovalbumin; sensitization showed a marked decrease in the response of the tracheal spirals	[36]

				injury; anti-oxidant, antispasmodic	to acetylcholine and histamine (Spasmogens); effectively reduced inflammatory cells infiltration, lipid peroxidation, glutathione depletion, TNF- α and IL-1β levels in both BALF and lung tissue homogenates, in response to the endotoxin LPS.	
Abies webbiana (Wall. ex D.Don) Lindl.	Leaf	Taxol	Model of murine lung injury induced by intratracheal lipopolysaccharide (LPS) administration.	AIA and anti-edemagenic effects; suppression of endotoxin LPS-induced inflammation and vascular leak in lung tissue and microtubule stabilization	Significantly reduced infiltration of proteins and inflammatory cells into bronchoalveolar lavage fluid, lung myeloperoxidase activity and significantly attenuated LPS-induced microvascular lung leakage; significantly decreased both TNF-α and IL-6 levels in BALF	[37]
Syzygium aromaticum (L.) Merr	Flower bud	Eugenol	LPS induced ALI in Rats	AIA and attenuates Lipopolysaccharide (LPS) induced lung injury in rats; anti-oxidant, antispasmodic	Eugenol inhibits the transcription of NF-κB and COX-2 stimulated by LPS in lung homogenate. Reduced the neutrophil recruitment, macrophages, TNF-*α*, and NF-*κ*B expression	[38]

AIA – Anti-inflammatory activity; BALF – Broncho alveolar Lavage Fluid; LPS – Lipopolysaccharides; LP - Lipid peroxidation; MPO - Myeloperoxidase; (Nrf2) - Nuclear factor-erythroid 2-related factor 2; PERK - Protein kinase-like ER kinase; NF-κB - Nuclear factor-kappa B; IκBα - Inhibitor of nuclear factor kappa B; IL-6 - Interleukin 6; IL-8 – Interleukin 8; TNF-α - Tumor necrosis factor-alpha; IL-1β- Interlukin-1 beta; ERK- Kinase activated by extracellular signal; MAPK- Mitogen-activated protein (MAP) kinase; PMN- Polymorphonuclear; COX-2 - Cyclooxygenase-2.

As cost of the therapeutic interventions on improving the oxygen levels during ARDS is very much higher, there is a dire need in developing countries for cost-effective ways to resolve the resultant inflammation in the lung tissues and reversal of the injury. As far as the pathogenesis of ARDS is concerned neutrophil infiltration contributes to tissue damage, interstitial edema and hypoxemia. The result is respiratory hypoventilation, hypoxemia and CNS depression. The persistence of neutrophils in large numbers leads to a poor ALI/ARDS prognosis. The resolution is characterized by removal of neutrophils in the lung tissue and restoration of epithelial barrier function i.e. its permeability[28].

There are evidences of potential effects of medicinal plants and their secondary metabolites reducing the lung edema by inhibiting neutrophil infiltration, reducing levels of leukocytes, clearing of macrophages, MPO, IL-6, TNF-α, NF-κB and other such cytokines and pro-inflammatory mediators, restoring balance between proteases and anti-protease in BALF thereby resolving acute inflammation and this comes together with their anti-viral effects as bonus. Andrographolide (*Andrographis paniculata* Burm. f. Nees), Curcumin (*Curcuma longa* L.) and glycyrrhizin (*Glycyrrhiza glabra* L.) have been proved to produce the effects[30-32]. Berberine, an alkaloid from *Berberis aristata* DC effectively alleviated lung injury by reducing lung edema and neutrophil infiltration. Berberine inhibits LPS-induced ALI through the PERK-mediated Nrf2/HO-1 signaling axis[29]. Studies reveal vasicine, a quinazoline alkaloid in *Adhatoda vasica* Nees reverses the hyperplastic changes in bronchial tubes, interstitial pneumonitis and intra alveolar hemorrhage[33]. Damage to the lung tissues caused by lipid peroxidation (oxidative stress) was found to be reversed by leaf extract of *Vitex negundo* L[34]. Zingerone and 6-shagaol from *Zingiber officinale* Roscoe, significantly improved the histopathological lung conditions by reducing the neutrophil influx and declined MPO activity apart from attenuating the cytokine induced inflammatory injury in the lung tissue[35]. Thymoquinone from *Nigella sativa* L. showed remarkable reduction in the spasmogenic response of the trachea when administered 5 days prior to the injury. It further prevented most of the pathological changes that occur by inhibiting pro-inflammatory mediators, lipid peroxidation, glutathione depletion by way of preventing oxidative stress in both the BALF and lung homogenates[36]. Taxol from *Abies webbiana* (Wall. ex D.Don) Lindl. significantly reduced inflammatory histological changes in lung parenchyma and parameters of LPS-induced inflammation, MPO activity, attenuated microvascular lung leakage, reduced both TNF-α and IL-6 levels in BALF[37]. Eugenol, a guaiacol phenolic compound in *Syzygium aromaticum* (L.) Merr. reduced the neutrophil infiltration, increased the lung permeability and prevented lipid peroxidation by inhibiting the formation of superoxide radicals from xanthine oxidase system and by generation of hydroxyl radicals. Thus, reducing oxidative stress has a major role play in resolving inflammation as it involves reducing the release of inflammatory mediators and attenuating the lung injury. Eugenol reduced the neutrophil recruitment, macrophages, TNF-α and NF-κB expression[38].

Urai māttirai, an age-long Siddha medicine commonly used in every household with infant is primarily administered to prevent recurrent respiratory infections. It consists of *Zingiber officinale* Roscoe, *Glycyrrhiza glabra* L,

Anacyclus pyrethrum (L.) Lag, *Acorus calamus* L., *Allium sativum* L., *Piper longum* L. and *Ferula assafoetida* L., hence is poised to play a role in prevention of viral PARDS[42,43].

As pointed out in Table 2 the plant-derivatives and Siddha drugs which includes them as ingredients can be considered as alternative therapeutics to deal with respiratory illnesses in at-risk persons who are prone to develop ARDS, vulnerable population and attenuation of ARDS alongside conventional therapies. Various compounds shown in the review have demonstrated considerable efficacy in inhibiting various inflammatory mediators and attenuating the inflammatory mechanism in ARDS, which is why they can also be employed in treating various other respiratory diseases such as chronic asthma, COPD and emphysema.

4.1 Research recommendations for future scope of siddha antivirals

The goal of therapy must focus on reducing infection burden and viral sequelae. While research is being thrust to find suitable antivirals (such as neuraminidase inhibitors) from various natural sources, investigators are focusing on potential benefits of immune modulation, Viral clearance and resolution of infection by initiation of adaptive immune cells in host must be target of intervention. The following aspects in Siddha research must be considered in management of ARDS.

4.1.1 Effects of various Siddha herbs and drugs could be investigated using Cigarette Smoke-induced mouse model and LPS (Lipo Poly Saccharides) induced Acute Lung Injury (ALI) models. These models are very similar to lung tissues in diseased conditions of ARDS, COPD and effectively emulate virus induced acute lung injury. This will seek to substantiate attenuation changes in pretreatment with medicinal extracts.

4.1.2 Assessing the modulation of inflammatory response and inhibition of subsequent fibrosis formation in mouse model.

4.1.3 Medicinal extracts are minimally cytotoxic and relatively innocuous; there is a need to test for viral inhibitions such as Hem agglutination (HA) and Neuraminidase (NA) protein to help reduce 90% of virus adsorption and penetration indicating potent action in the early stages of replication[44].

5. CONCLUSION

The burden of PARDS largely owing to the viral infections have been massive and a definite need to scale down the mortality and post viral sequelae of viral pneumonia. There is a paradigm shift towards prevention and treatment of early stages of acute lung injury prior to respiratory failure. The results table of the review elucidate proven effects on either attenuation or reversal of the acute lung injury models as part of the evidence-based data on Siddha plants' effects on ARDS. With respect to this, there remains a wide scope of research possibilities in Siddha from comprehending the epidemiology, viral specific- treatment options, medicine-host response (may be tēki -specific) onto generating evidence for traditionally versatile medicines. It is found that many Siddha drugs exist as nano-micellar formations by way of purification and drug preparation methods and are suitable for sustained drug delivery. The potential of Siddha drugs as prophylactic for those persons at risk for PARDS/ARDS has to be investigated for inhibitive effects on inflammatory response in different acute lung injury models, assays for Hem agglutination and FL based Neuraminidase inhibition. Further

substantiation through applied clinical trials will result in building a robust evidence-based treatment protocol for PARDS in Siddha for effective and safe early intervention.

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