Review Article

Pathophysiology of Covid-19 and host centric approaches in Ayurveda

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A B S T R A C T

The world is facing a global crisis and health emergency of COVID-19. Understanding of COVID-19 pathophysiology in ayurvedic host centric framework is prerequisite for apt use of Ayurveda. This paper reviews COVID-19 pathophysiology, clinical presentations and prognosis in ayurvedic perspective. Concept of exogenous pathogenic diseases can be traced in fever, microbes, toxins, epidemics and seasonal regimens chapters of Ayurveda. Such exogenous diseases later manifest multi-system presentation according to involvement of different ‘Dosha’ and derangement of ‘Agni’. The pathology of COVID-19 is primarily that of ‘Sannipata Jwara’ (fever) with involvement of respiratory system. Secondary manifestations include coagulopathies, cardiovascular, neural, and renal complications. Gastrointestinal system is closely associated with respiratory mechanism in ayurvedic pathophysiological conceptualization of Srotas. Abnormal immune responses in COVID-19 are result of abnormalities of Tridosha, Rakta (blood) and Ojas (Vital nectar). The initial phase is Vata-Kapha dominant whereas later stage of aggravated immune response is Vata-Pitta dominant. Alveolar damage, coagulopathies indicate Rakta dhatu vitiation. With this integrative understanding of COVID-19, we propose novel strategies for therapeutics and prophylaxis. Measures for ‘Conservation of Agni-bala’, ‘Attainment of Rakta- Pitta-Praja’ homeostasis and ‘Protection of Tri-Marma i.e. vital organs’ can be important host based strategies for reduction in the mortality in COVID-19 and for better clinical outcomes. This host centric approach can make paradigm shift in management of this epidemic.

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1. Introduction

The world is facing a never like pandemic of COVID-19 with its implications at economical, psychological and more levels in society. Pragmatic strategies are being proposed for possible role of Ayurved in management of COVID-19 [1]. Scientists are proposing need of ‘Systems approach’ as it can provide more comprehensive structure to manage disease as well as epidemic components, as society is itself a complex adaptive system [2]. Potential of Ayurvedic immunomodulators (Rasayana) medicines and need of host centric approaches are proposed by the time [3,4]. The need for ‘host centric approach’ gets underlined amidst recurrence (of infection and disease) in cured patients of COVID-19 [5].

Understanding COVID-19 Pathophysiology is basic prerequisite for deciding Ayurveda preventive and curative strategies. One cannot appropriately bridge Ayurveda with evidence based medicine without understanding epistemology of Ayurveda [6]. Ayurveda deals at more comprehensive levels of abstraction like Dosha and Dhatus (tissues). Thus an appropriate translation of COVID-19 in Ayurvedic anatomical and pathophysiological terminology is needed. This article reviews COVID-19 pathology and its Ayurvedic perspective and discuss host centric approach of Ayurveda for COVID-19.

2. Infectious diseases in Ayurveda

The concept of pathogenic agents and infectious disease was not unknown to Ayurveda. Fundamentally Ayurveda classifies diseases as Nija (from Intrinsic Causes), Agantuja (Extrinsic causes) and Manasa (Psychosomatic). Aupsargika (Infectious) and Sankramak (Contagious) are mentioned by Sushruta (7th century BC). The concept of infectious diseases is explained under five chapters Jwara, Krimi, Visha, Jana padodhwamsa and Ritucharya (Seasonal regimes). Jwara (Hyperthermia) is cardinal symptom in many of infectious diseases. Krimi is all encompassing term used for parasites, worms and microbes. Arundatta the commentator of Ashtang
Hridaya clarifies that pathogen of the blood is totally invisible to the human eye, their existence can be inferred [7]. Janapadodhwamsa is the concept of epidemics in Ayurveda. Ritu-charya is the season specific regimes where prophylaxis and management of seasonal flu can be seen. Autumn and spring fevers are associated with Pitta and Kapha dominance [8]. Role of seasonal changes in environment, particularly temperature and humidity are proven to be associated with modifications in host intrinsic, innate, and adaptive immune responses to viral infections in the respiratory tract [9] (Fig. 1).

‘Dosha’ and ‘Agni’ are the pivotal concepts as imbalance or balance of Dosha and Agni are synonymous with state of disease or being healthy. Even in exogenous diseases, there is the role of Dosha and Agni in disease manifestation and prognosis. Dosha, Dhatu, Malā, Srotas, Agni and Manas (mind) is the framework in which any disease is needed to be interpreted. Concept of diagnosis in Ayurveda is less about naming diseases but understanding the underlying in-equilibrium. Charaka says that innumerable diseases can origin from same vitiated Dosha according to variations in aetiology and involved body tissues [8]. With these insights COVID-19 is reviewed here.

3. Understanding COVID-19 disease & Ayurveda

3.1. The virus and Ayurveda

Coronaviruses is a genus in the Coronaviridae family (order Nidovirales) of pleomorphic and enveloped viruses. Three human coronaviruses HCoV-OC43, HCoV-229 E and SARS CoV-1 were acknowledged as pathogenic agents for upper respiratory tract coronaviruses HCoV-OC43, HCoV-229 E and SARS CoV-1 were Nidovirales) of pleomorphic and enveloped viruses. Three human infections [10]. Role of seasonal changes in environment, particularly temperature and humidity are proven to be associated with modifications in host intrinsic, innate, and adaptive immune responses to viral infections in the respiratory tract [9] (Fig. 1).

Janapadodhwamsa refers to particular geographic consideration. Interestingly there is mention of an epidemic fever with respiratory system presentation (fever, cough, breathing difficulty, rhinorrhea, headache and even anosmia) caused by entry of pathogenic agent through the nasal passages. This clinical presentation by Sushruta is amazingly analogous to epidemics like SARS, MERS, Swine Flu and even COVID-19 [13]. Contagious diseases and means of contagion as physical contact, inhalation, eating together, sleeping, sitting together and sharing used linens and garlands are well discussed by Sushruta.

3.2. The epidemics/contagious complement and ayurveda

According to few reports SARS-CoV-2 can be detected in the air, three hours after aerosolisation. WHO has issued guidelines for contact and droplet precautions for healthcare workers working for suspected COVID-19 patients, also USA-CDC has recommended airborne precautions [12].

Janapadodhwamsa is the Ayurvedic term for epidemics. Janapada refers to particular geographic consideration. Interestingly there is mention of an epidemic fever with respiratory system presentation (fever, cough, breathing difficulty, rhinorrhea, headache and even anosmia) caused by entry of pathogenic agent through the nasal passages. This clinical presentation by Sushruta is amazingly analogous to epidemics like SARS, MERS, Swine Flu and even COVID-19 [13]. Contagious diseases and means of contagion as physical contact, inhalation, eating together, sleeping, sitting together and sharing used linens and garlands are well discussed by Sushruta.

3.3. Stage wise disease progression, immune response, lung events and ayurveda

There are four stages of Disease progression viz Asymptomatic Stage, Stages with upper and Lower Respiratory tract involvements and last Stage of ARDS/MODS. The disease progression and stage-wise Immune Responses are summarised in Table 1.

Events in Lung and Ayurveda Perspectives (Table 2).

3.4. Symptomatology, cytokine storm and Ayurveda

Symptoms include aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell. A rash on skin and discoloration of fingers or toes are less common symptoms. Serious symptoms include difficulty breathing or shortness of breath, chest pain or pressure, loss of speech or movement. Nasopharyngeal swab Polymerase chain reaction analysis confirms the disease.

3.4.1. Respiratory symptoms in Sannipata Jwara

Abhishangaja Jwara, Bhootopasangaja Jwara is Vishama Jwara according to Vagbhata. Sanapikata is a disease variant with vitiation of all three Dosha in pathogenesis. Agantuja varieties of any diseases can complicate into Sanapikata state with severe prognosis. The viral or bacterial fevers, along with malignancy, auto immune diseases, etc. are needed to be considered as Sanapikata state. In COVID-19 Primary manifestations are seen at Pranava Srotas as virus enters through nasal passage (Table 3).

Respiratory symptoms are seen in different types of Sannipata jwara.

The most mimicking ‘Kanthhakajja Sanapikata’ symptoms include throat pain, dyspnoea, tastelessness, delirium, Malaise, dehydration, head ache, shaking [25]. Out of the 29 Lakshanas of Sarvaloshan Sanapikata, 25 Lakshanas are found in the COVID-19 infection [26].

To summarize, the early presentation of COVID-19 is ‘Kapha Vata’ dominant whereas late phase of complications is ‘Vata Pitta’ dominant. The later phase of secondary infections, sepsis & multi organ failure is indicative of involvement of ‘Marma-Asthhi-Sandhi Roga Marga’ (disease pathway).

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Fig. 1. Concept of Infectious diseases in Ayurveda

Jwara later complicates with involvement of multiple tissues and organs.

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### Table 1
COVID-19 Disease Progression: Pathophysiology and Immune Response.

| Disease progression       | Local pathophysiology                                                                 | Stage wise immune response                                                                 |
|---------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Stage 1 Asymptomatic stage| Entry of virus in nasal passage Epithelial cells (particularly Ciliated cells) get affected [14]. ACE2 is important receptor along with TMPRSS2 [15,16]. Although less viral load, individuals are infectious. | Mild Innate immune response. TH1 response by host is crucial to decide fate of infection. |
| Stage 2 Upper Respiratory Tract involvement | Sputum swab exhibit SARS COV-2 In few Cough, sore throat starts here. In most cases progression ends here. | Strong Innate immune response. Increased plasma IP-10,MIG, IL-8 and MCP levels during the first week are considered independent predictor of outcome & with adverse outcome. (Intensive care unit admission or death) [17,18] |
| Stage 3 Lower Respiratory Tract involvement | Virus starts affecting alveoli. It affects type II pneumocytes (responsible for production of surfactant and are precursor for type I pneumocytes) than type I pneumocytes (responsible for gaseous exchange). Type II pneumocytes undergo apoptosis and die due to viral particles [19]. DAD: Diffuse alveolar lung damage: This is most commonly seen histopathologic feature [21]. Histologically: Injury to the alveolar epithelial cells, Hyaline membrane formation, Hyperplasia of type II pneumocytes, Consolidation by fibrinolastic proliferation with extracellular matrix and fibrin forming clusters [22]. Alveolar macrophages affected: Alveolar macrophages expressing ACE2 are again target cells for SARS CoV-2 infection. Alveolar condensation, Ground glass infiltrations, Hypoxia | Crucial role of T cells: Another study reported that CD4+ T cells, CD8+ T cells, and natural killer cells were reduced in severely ill patients compared with those with mild disease symptoms. Moreover, a substantial reduction of CD4+ T cell and CD8+ T cell counts in the peripheral blood was also observed in a patient who died [23]. |
| Stage 4 ARDS, MODS          | Acute Respiratory Distress SyndromePulmonary thrombosis HLH-like (haemophagocytic lymphohistiocytosis) cytokine storm with characteristics of HLH, including hypercytokinemia, unremitting fever, cytopenias, hyperferritinemia, and multi-organ damage, are commonly seen in seriously ill patients with COVID-19 [20]. | Raised Serum Ferritin (doubling in 24 h) and raised IL-6, LDH, D-dimer, C-reactive Protein (CRP) levels mark severe condition. |

3.4.2. Understanding Cytokine storm in Ayurveda Perspectives

Cytokine storm is overreaction of immune system exhibiting numerous cytokines and resulting in inflammation/necrosis of internal organs, and organ failure. It can be tempting for Ayurveda authors to compare cytokine storm with aggravated Vata, Kapha, and Pitta, which are symptoms in Vata Kapha Pitta (VKP) tridosha dysregulation. Patients with severe condition will exhibit Vayu and Prana Vyana both will be increased. It is essential to suppress the pathophysiologic interpretations of cytokine storm in Ayurveda pathophysiology interpretation.

| Lung pathology                              | Ayurveda pathophysiological interpretations                                                                 |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Diffuse Alveolar Lung Damage: Type II pneumocytes hyperplasia Diffuse alveolar damage with presence of multinucleated pneumocytes. Fibrogranulation tissue proliferation in small airways and airspaces (organizing pneumonia-like lesions) in subpleural locations in some patients [23]. Some studies report along with classical DAD, there are evidences of: Capillary injury Mural and luminal fibrin deposition Infusion of the inter-alveolar septa by Neutrophils/macrophages. Hyaline membrane formation: A membrane composed of proteins and dead cells lines the alveoli, making gas exchange difficult or impossible, Alveolar condensation | Embryologically lungs are made of bubbling in Rakta (blood) Dhatu. The airsacs represent bubbles, whereas the alveolar composite structure is made from Rakta. COVID-19 is Alveolar disease and thus ‘Rakta Dhatu’ remains pivotal in pathology. Type II pneumocytes which serve as precursor for Type I pneumocytes and those produce surfactants get affected. This Regenerative ability of cells/tissue is attributed to Baha & Shukra Dhatu the first and last tissue in hierarchy of body tissues. Ayurvedic Rasayan & Vajikarana medicines have regenerative efficacies. The word exudate is derived from latin “exsudare”, literally meaning ‘to sweat out’. Exudative inflammation is like Vishyandana. Ayurvedic term indicating phenomenon of liquefaction. This further result in alveolar condensation. The hyaline membrane formation and obstruction is nothing but Avarodha (Obstruction) by Kapha in turn leading to further vitiation of Vata. Only Kapha is not necessarily responsible for obstructive phenomena. Even Vata subtypes may obstruct each other. COVID-19 symptoms like anosmia, ageusia and impaired Baha (immunity) are seen as symptoms of ‘Prana Avrata Vyana’ [24]. ‘Prana Avrata Vyana’ is condition when Prana Vata (Vata subtype responsible for pulmonary and nervous and cognitive functions) obstructs Vyana Vata (Vata subtype for cardio-pulmonary pumping and Baha i.e. strength and immunity) This can be Upadra (complication) or Udakara (residual effect) Khora Puka I.e. abnormal metabolism leads to hardening of tissues/fibrotic changes. It will be interesting to see if these post COVID-19 fibrotic changes are therapeutically reversible or not. They can be called as upadara (Complications) or Udakara (residual effect of the disease that is not relieved by the specific treatment) of COVID-19 |
| Interstitial widening and patches of Lung fibrosis |                                                                                                             |
aggravated Agni, Dhatu paka (Body tissue disintegration as result of aggravated Agni), Shotha (Inflammation) or diseases like Jwara and Visarpa where the involvement of body tissues can become fatal very rapidly. There cannot be one single comparable phenomenon in Ayurved for cytokine storm. The very rapidly. There cannot be one single comparable phenomenon in Ayurved for cytokine storm. The speediness is important as there is speedy and lethal pathogenesis that affects vital organs. The speediness is important virtue of pathogenesis in COVID-19.

3.5. Complications & multi-organ involvement in COVID-19 and Ayurveda

ACE2 receptors are there in many tissues and thus COVID-19 presents as Multi-systemic disease [29].

3.5.1. Gastrointestinal complications

Abundant amount of ACE2 is present in the small intestine and colon, which can be the probable reasoning for gastrointestinal symptoms like diarrhea, nausea, vomiting, and abdominal discomfort or pain. Mild to moderate liver injury (elevated amino transferases, hypoproteinemia, and prothrombin time prolongation) has been reported. Analysts have suggested that abdominal pain can be used as a clinical predictor of more severe disease and be involved in future risk stratification algorithms [30].

3.5.2. Neural complications

Agitation, confusion, diffuse corticospinal tract signs with enhanced tendon reflexes, ankle clonus, bilateral extensor plantar reflexes, disorientation, and poorly organized movements in response to command were reported during and or at the time of discharge [31].

3.5.3. Cardiac complications

After respiratory system, the second most affected body system known by COVID-19 is the cardiovascular system [32]. Patients with cardiovascular risk factors are at increased risk to develop severe complications. Some cardiovascular diseases associated with COVID-19 include myocarditis, heart failure, cardiac arrhythmias, and acute coronary syndrome as direct consequences of systemic inflammation [33].

3.5.4. Vascular complications

Reports about association of coagulopathies with poor prognosis and probable role of anti-coagulants like low molecular heparin are published [34]. Elevated D-dimer and FDP (Fibrin Degradation products) are common in deaths with COVID-19. Poor prognosis is also associated with disseminated intravascular coagulopathy (DIC) [35].

In Ayurveda terminology coagulopathies are ‘Kapha dominant Rakta pitta’. Charaka has mentioned Rakta pitta as complication of Jwara. Rakta pitta represents a group of pathologies including coagulopathies, vascular complications etc.

3.5.5. Renal complications

The ACE2, is abundant in renal tubular epithelial cells. This can be linkage for some associations between COVID-19 and acute kidney injury (AKI), proteinuria, microhematuria and raised serum creatinine. Acute kidney injury is more common among patients with more severe disease, and is considered a negative prognostic factor with respect to survival [36]. Perhaps a maladaptive systemic inflammatory immune response, cytokine storm may contribute to hypoperfusion and thus result in injury to the renal tubules. Systemic hypoxia, abnormal coagulation are causes and diffuse proximal tubule injury with frank necrosis was evident. There were prominent erythrocyte aggregates obstructing the lumen of capillaries without platelet or fibrinoid material [37].

3.5.6. Sepsis/MODS (Multi Organ Dysfunction Syndrome)

Critically ill COVID-19 patients are reported to develop typical clinical manifestations of shock, with severe metabolic acidosis, indicating possible microcirculation dysfunction and impaired liver and kidney functions [38]. Sepsis in COVID-19 cases have wide range of signs and symptoms of multi-organ involvement, including respiratory manifestations, hypoxemia, renal impairment with reduced urine output, tachycardia, altered mental status, and functional alterations of organs expressed as laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia [39].

Ayurveda scholars have mentioned similarities between Sama Jwara with ‘sepsis/septic shock/systemic inflammatory response syndrome (SIRS)/multiple organ dysfunction syndrome (MODS)/septic encephalopathy/delirium’ [40].

Cardiac, Renal and Neural presentations indicate involvement of Tri Marma (three most vital organs). Hepatic derangements and coagulopathies underline vitiation of Rakta. Involvement of all three Roga marga (Ayurveda diseases pathways) is seen (Fig. 2).

4. COVID-19 in Ayurvedic model of Hetu (Etiology) - Linga (Symptomatology) - Samprapti (Pathogenesis)

4.1. Etiology factor (Hetu) and probability of disease progression

The COVID-19 pathogen is Agantuj (exogenous) 80% patients of COVID-19 remain asymptomatic. Contact with viral material can be
considered as Pradhanik Hetu (etiological factor weak enough to cause disease at its own). SARS CoV-2 can be better interpreted as Vyanjaka Hetu (etiological factor acting at time of genesis of disease), whereas Utpadak Hetu are etiological factors are mainly diet and lifestyle leading to accumulation of Dosha. In Ayurvedic conceptualization accumulated Dosha makes the body susceptible to disease. Even in an exogenous disease, there is involvement of Dosha and the role of Agni in prognosis of disease. As COVID-19 prognosis is associated with comorbidities, this concept of Utpadaka Hetu becomes important. Original retrospective studies of non survivors or critically ill cases of COVID-19 can contribute as evidence for these lifestyle factors as Utpadaka Hetu for bad prognosis of COVID-19.

4.2. Linga

The symptoms of COVID resemble with sannipatika jwara as reviewed earlier. COVID-19 symptoms are summarized here in Table 4.

Thus there are variety of symptoms showing involvement of Pranavaha, Rasavaha, Raktavaha and Majjavaha Srotas and Marma involvement. Symptoms are from

Table 4
Analysis of Symptoms in Ayurvedic terminology.

| Common symptoms | Dosha status | Srotas |
|-----------------|--------------|--------|
| Fever           | Vata dominant| Pranavaha Srotas |
| Dry cough       | Kasa         | Rasavaha Srotas |
| Tiredness       | Related with Jwara | Pranavaha Srotas |
| Aches/Pains     | Angamarda    | Pranavaha Srotas |
| Sore throat     | Galadhwnasa  | Pranavaha Srotas |
| Conjunctivitis  | Pratishyay   | Pranavaha Srotas |
| Headache        | Netrabhashyanda | Pranavaha Srotas |
| Diarrhoea       | Shirashoola  | Pranavaha Srotas |
| Loss of taste   | Atisara      | Pranavaha Srotas |
| Loss of smell   | Arrochi      | Pranavaha Srotas |
| Discoloration of fingers | Anosmia | Pranavaha Srotas |
| Difficulty breathing or shortness of breath | Shwasa | Pranavaha Srotas, Marma |
| Chest pain or pressure | Ura Shool | Pranavaha Srotas, Marma |
| Loss of speech or movement | Vakgraha, Varayadhi | Pranavaha Srotas, Marma |

Less common symptoms

| Vata dominant | Pranavaha Srotas |
| Vata, Kapha | Pranavaha Srotas |
| Kapha, (and Rakta vitiation) | Pranavaha Srotas |
| Kapha dominant triDosha | Pranavaha Srotas |
| Kapha dominant (and Rakta vitiation) | Pranavaha Srotas |
| Vata dominant Tridosha | Pranavaha Srotas |
| Kapha, Pitta, Vata | Pranavaha Srotas |

Serious symptoms

| Vata, Kapha and Pitta as Shwasa is originated from Anashaya | Pranavaha Srotas, Marma |
| Vata dominant | Pranavaha Srotas, Marma |
| Vata dominant | Pranavaha Srotas, Marma |

Fig. 2. Primary and secondary manifestations of COVID-19 in Ayurveda perspective.
Jwara, Shwasa, Pratishtay, Vatavyadhi, HrudRoga, TriMarma chapters again implying COVID-19 as multi-systemic disease.

4.3. Samprapti

Initial pathogenesis is of Agantu (exogenous) Jwara and thus exhibit symptoms of Rasavaha Srotas i.e. tastelessness, headache, nausea, bodyache. This is followed by symptoms of Pranavaha and Raktavaha Srotas. Udana Dushti is evident as there is extreme loss of Bala i.e. deterioration of immune response, speech related symptoms in few. Raktavaha Srotodusthi is also evident from coagulopathies and extremity discolorations. Fatal complications are possible because ‘Prana’ (vitality or oxygen in this context) follows ‘Rakta’ (blood). In Ayurveda embryological view point Fuffusa (lungs) are made up of Rakta only. In context with respiratory mechanism Ayurveda considers the cardiopulmonary unit as a whole without differentiating heart and lungs. Mahasrotas (gastrointestinal tract) is also associated with Pranavaha Srotas as moolasthana. The pathogenesis later involves heart and kidney which are considered as third ‘Roga marga’ (disease pathway). In Ayurveda, hematuria is seen as associated symptom under Kasa Roga (Many Bronchial conditions) indicating involvement of urinary system as complication of respiratory pathologies. Pathogenesis worsens and complicates in ARDS (if there is kha-vaigunya i.e. susceptibility in lungs), or involves Heart or Kidney (according to kha-vaigunya). Interestingly Hiccup, dyspnea, cough and complications in vital organs are symptoms when fever pathogenesis invades Majja Dhatu according to Charaka and Sushruta [8,41]. Thus the later stage of COVID-19 with aggravated immune response indicates invasion of fever in Dhatu hierarchy (Fig. 3).
Table 5
Contemporary and Novel approaches (Preventive and Therapeutic) based on Ayurvedic Pathophysiology of COVID-19.

| Pathogen centric approaches | Host centric approaches | Rationale |
|-----------------------------|-------------------------|-----------|
| Hygiene, Sanitization, Physical Distancing and other measures to avoid possibility of infection. | 7–8 H of sleep. Vitamin C, D3 and other supplements. Yoga and Respiratory Exercises. Interventions of Pulmonary Function improving agents | Evidences of immunomodulatory mechanisms of exercise, micronutrients and sleep |
| Ayurveda Immunomodulator Herbs for minimizing virus replication and to arrest Cytokine syndrome. | | |

Proposed Novel Approaches based on Host centric Approach and Ayurveda Pathophysiology of COVID-19

| Nassya, Gandusha can be local measures for care of pathogen entry points. | Conservation of Agni-Bala & maintenance of Agni (Digestive and metabolic equilibrium). Attainment of ‘Rakta–Pitta–Prana’ homeostasis with specific dietary, lifestyle modifications and therapeutic interventions. Protection of Murma (Vital organs, the dedicated sites of Prana) with specific dietary, lifestyle modifications and interventions ‘Prana Kamya Rasayana’ (Rasayana medicines particularly for vitals). Basti (Medicated enema) and Other relevant measures for protection of Heart, Brain and kidney from relevant chapters like Visha Chikitsa. | As MahaSrotas is associated with Pranavah Srotas as moolasthana. According to Ayurveda Physiology Prana (not mere oxygen but vitality) follows Rakta and both are interdependent [8]. The Inflammatory Responses, Sepsis as well as Coagulopathy are result of Rakta and Pitta vitiation Cytokine storm results in Inflammation and even necrotic changes in vital organs [45]. Basti is recommended as best measure for protection of vital organs [8]. |

Ayurveda Immunomodulator Herbs for arresting viral load in different organs. This can be decided (from variety of Rasayana Herbs having efficacy on different systems and Organs) on basis of involvement of Organs and Tissues in the patient.

5. **Ayurvedic host centric approach in COVID-19 and remarks**

The ‘Germ theory’ received more importance and was followed by development of Medical Microbiology and anti-microbial medicines in last century. With these advances infectious diseases were treated far well. So far as Host-Germ approach is concerned ‘virusence factor theory’ was later followed by concept of ‘Damage response framework’. DRF is an approach for incorporation of range of host responses to microbes with a parabolic curve in which host damage is plotted as a function of the host response. Importantly neither host nor microbial properties, are adequate to predict the outcome of host–microbe interaction because this outcome exhibits emergent properties [42].

In ayurvedic epistemology, microbe is viewed as nimitta karana (instrumental cause), contact of microbe with receptors as esamayavey karana (non-intimate cause) and host internal milieu as samayaveey karana (intimate cause). As reviewed earlier the dynamic status of Dosh, Dhatu, mala and Agni the physiological elements of internal milieu are important in fate of exogenous and pathogenic diseases like COVID-19. The disease presentation is a dynamic phenomenon. Bala (body strength), Agni (digestive power) and Pradnya (mental ability) are as markers for prognosis, and Charaka has recommended continuous assessment of these three [43]. Thus it is host internal milieu in totality that is important for the immune response and prognosis.

Bala is often considered as body strength but is inclusive of various activities such as immunomodulator, bulk promoting, nutritional etc. Pathophysiology and Immune responses in COVID-19 are important to be discussed in Ayurveda perspectives. Immunity is popularly imitated as ‘Vyadhikshmatwa’ in Ayurveda which is an incomplete translation. Prana/vitality is an important consideration. Rakta (Blood), Shukra (Reproductive tissues and Reproductive hormones) and Ojus (Quintessence of the seven body tissues) are the body tissues responsible for immune functions and appropriate immune responses. In fact it is not only immunity but a holistic network of Bala, Agni, Dosa, DhatuBala, Vaya and many more factors that decide the immune responses and fate of disease progression.

Pathophysiology of COVID-19 is primarily that of Respiratory system. Gastrointestinal, cardiac, renal, neural and coagulative complications follow. Pranavah Srotas (Cardiopulmonary apparatus), MahaSrotas (Gastrointestinal tract) with Agni and RaktaVah Srotas (Blood and liver) are vitiated. Earlier presentation of COVID-19 is Vata-Kapha dominant whereas later stage of cytokine storm is Vata-Pitta dominant. Rakta (Blood) is most important Dhatu because lung alveolar tissues are made from Rakta only, coagulopathy are related with Rakta and immune responses too are also associated with Rakta Dhatu. COVID-19 affects Pneumocytes type II which are precursor for Type I pneumocytes. Thus reproductive/tissue repairing mechanism of body is another important factor. This reproductive ability is associated with Shukra Dhatu. Ojus is next important body tissue as vital organs are affected in COVID-19. Thus Prana- Rakta- Shukra-Ojus is the pathophysiological quadrant in Ayurvedic perspective of COVID-19.

This proposed integrative understanding of Pathophysiology and holistic quadrant of Prana-Rakta-Shukra-Ojus can give novel leads for Preventive and Therapeutic approaches for COVID-19. Here we propose Novel approaches (Preventive and Therapeutic) based on this integrative understanding. They are summarized in Table 5.

Last few decades there is a good amount of research on virus–host interactions, particularly with approach of systems biology. Virus-host systems biology can make predictions on host responses and dynamic interactions between viruses and hosts by computational modelling. It is interesting to note that modelling are expected to be done at different levels of abstraction like genes, proteins, cells, and organisms [46]. Ayurvedic foundational framework of ‘Dosa-Dhatu-Mala-Agni-Srotas’ can serve as a model for these proposed studies. Ayurvedic foundational concepts have great potential and hence such studies can indeed make paradigm shift. Conservation of Agni-Bala and homeostasis of Prana-Rakta-Shukra-Ojus quadrant can be best host centric approach to improve clinical outcomes in COVID-19.

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