Pathophysiology of COVID-19 and Host centric approaches of Ayurveda

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Title: Pathophysiology of Covid-19 and Host centric approaches in Ayurveda

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Abstract:

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 Ojus (Vital nectar). The initial phase is Vata-Kapha dominant whereas later stage ofagrivated immune response is Vata-Pitta dominant. Alveolar damage, coagulopathies indicate Rakta dhatu vitiation. This integrative understanding of COVID-19, we can propose novel strategies for therapeutics and prophylaxis. Measures for ‘Conservation of Agni-bala’, ‘Attainment of Rakta- Pitta-Prana 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.

Key words: complimentary medicine, Physiopathology, Ayurveda, SARS COV-2, Host centric, prophylaxis

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 Ayurveda 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 Dhatu (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, Janapadodhwansa 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]

Janapadodhwans is the concept of epidemics in Ayurveda. Ritucharya is the seasonal 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]
‘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, Mala, 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.[10] 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-229E and SARS CoV-1 were acknowledged as pathogenic agents for upper respiratory tract infections. [11]

Although not mentioned as virus but microbes and pathogenic agents are described in *Ayurveda* as reviewed earlier. The initial stage of COVID-19 is exogenous (*Agantu*) disease which later converts into systemic (*Nija*) disease.[12] *Abhishangaja Jwara* is the term for those caused by the contact of the poisonous air or toxic plants or other such toxins.[13] However this *Abhishangaja Jwara* later complicates with involvement of multiple tissues and organs.

3.2 **The epidemics/ contagious complement and Ayurveda:**

According to few reports SARS-CoV-2 can be detected in the air, 3 hours after aeroslisation. 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.[14]

*Janapadodhwansa* 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.[15] 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:**
<table>
<thead>
<tr>
<th>Disease Progression</th>
<th>Local Pathophysiology</th>
<th>Stage wise Immune response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1</strong>&lt;br&gt;Asymptomatic stage</td>
<td>Entry of virus in nasal passage&lt;br&gt;Epithelial cells (particularly Ciliated cells) get affected. [16]&lt;br&gt;ACE2 is important receptor along with TMPRSS2. [17][18]&lt;br&gt;Although less viral load, individuals are infectious.</td>
<td>Mild Innate immune response. &lt;br&gt;Th1 response by host is crucial to decide fate of infection.</td>
</tr>
<tr>
<td><strong>Stage 2</strong>&lt;br&gt;Upper Respiratory Tract involvement</td>
<td>Sputum swab exhibit SARS CoV-2&lt;br&gt;In few Cough, sore throat starts here. &lt;br&gt;In most cases progression ends here.</td>
<td>Strong Innate immune response. &lt;br&gt;Increased plasma IP-10 ,MIG, IL-8 and MCP levels during the first week are considered independent predictor of outcome &amp; with adverse outcome. (intensive care unit admission or death) [19] [20]</td>
</tr>
<tr>
<td><strong>Stage 3</strong>&lt;br&gt;Lower Respiratory Tract involvement</td>
<td>Virus starting affecting alveoli. &lt;br&gt;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). &lt;br&gt;Type II pneumocytes undergo apoptosis and die due to viral particles. [21] &lt;br&gt;DAD: Diffuse alveolar lung damage: This is most commonly seen histopathologic feature.[23]&lt;br&gt;Histologically: &lt;br&gt;Injury to the alveolar epithelial cells, Hyaline membrane formation, Hyperplasia of type II pneumocytes, Consolidation by fibroblastic proliferation with extracellular matrix and fibrin forming clusters in.[24] &lt;br&gt;Alveolar macrophages affected: &lt;br&gt;Alveolar macrophages expressing ACE2 are again target cells for SARS-CoV-2 infection. &lt;br&gt;Alveolar condensation &lt;br&gt;Ground glass infiltrations &lt;br&gt;Hypoxia</td>
<td>Aggravated immune response: Cytokine storm: lower lymphocyte counts and higher plasma concentrations of a number of inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF). [22]&lt;br&gt;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. [25]</td>
</tr>
</tbody>
</table>
| **Stage 4**<br>Acute Respiratory Distress Syndrome | Raised Serum Ferritin (doubling in
ARDS, MODS

HLH-like (haemophagocytic lymphohistiocytosis) cytokine storm with characteristics of HLH, including hypercytokinaemia, unremitting fever, cytopenias, hyperferritinaemia, and multi-organ damage, are commonly seen in seriously ill patients with COVID-19.[22] 24 hours) and raised IL-6, LDH, D-dimer, C-reactive Protein (CRP) levels mark severe condition.

**Lung Events and Ayurveda:** Importantly COVID-19 lung pathology is more restrictive than obstructive as it is more an alveolar diseases than airway disease, the basic lung pathology classification. Pathological events in lungs and *Ayurveda* Perspectives are summarized in table no.2

**Table no. 2 : Events in Lung and *Ayurveda* Perspectives:**

<table>
<thead>
<tr>
<th>Lung Pathology</th>
<th><em>Ayurveda</em> Pathophysiological Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse Alveolar Lung Damage:</td>
<td>Embryologically lungs are made of bubbling in <em>Rakta</em> (blood) <em>Dhatu</em>. The airsacs represent bubbles, whereas the alveolar composite structure is made from <em>Rakta</em>. COVID-19 is Alveolar disease and thus ‘<em>Rakta Dhatu</em>’ remains pivotal in pathology.</td>
</tr>
<tr>
<td>Type II pneumocytes hyperplasia</td>
<td>Type II pneumocytes which serve as precursor for Type I pneumocytes and those produce surfactants get affected.</td>
</tr>
</tbody>
</table>
| Diffuse alveolar damage with presence of multinucleated pneumocytes. Fibro-granulation tissue proliferation in small airways and airspaces (organizing pneumonia-like lesions) in subpleural locations in some patients.[25] | This Regenerative ability of cells/ tissue is attributed to *Rasa & Shukra Dhatu* the first and last tissue in hierarchy of body tissues. 
*Ayurvedic Rasayana & Vajikarana* medicines have regenerative efficacies. |
| 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:                          | 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. |
| A membrane composed of proteins and dead cells lines the alveoli, making gas exchange difficult or impossible, |                                                                                                               |
| Alveolar condensation                                | The hyaline membrane formation and obstruction is nothing but *Avarodha* (Obstruction) by *Kapha* in turn leading to further vitiation of *Vata*. |

*Journal Pre-proof*
Only *Kapha* is not necessarily responsible for obstructive phenomena. Even *Vata* subtypes may obstruct each other. COVID-19 symptoms like anosmia, ageusia and impaired *Bala* (immunity) are seen as symptoms of ‘*Prana Avruta Vyana*’.[26] ‘*Prana Avruta 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 *Bala* i.e. strength and immunity)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial widening and patches of Lung fibrosis</td>
<td>This can be <em>Upadrava</em> (complication) or <em>Udarka</em> (residual effect)</td>
</tr>
<tr>
<td>Khara <em>Paka</em> i.e. abnormal metabolism leads to hardening of tissues/ fibrotic changes.</td>
<td>It will be interesting to see if these post COVID-19 fibrotic changes are therapeutically reversible or not. They can be called as <em>upadrava</em> (Complications ) or <em>Udarka</em> (residual effect of the disease that is not relieved by the specific treatment) of COVID-19</td>
</tr>
</tbody>
</table>

### 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.

**Respiratory symptoms in *Sannipata Jwara*:**

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

Respiratory symptoms are seen in different types of *Sannipata jwara*.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Variant of <em>Sannipata Jwara</em></th>
<th>Classic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pratishyay</em></td>
<td>Diminished <em>Kapha</em>, moderate <em>Pitta</em> &amp; increased <em>Vata Sannipata</em></td>
<td><em>Charaka Samhita</em></td>
</tr>
<tr>
<td>(Rhinorrhoea)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Kasa</em></td>
<td>Increased <em>Kapha</em> –diminished <em>Vata</em> and <em>Pitta Sannipatika</em>, Increased <em>Vata</em> and <em>Kapha</em> &amp; diminished <em>Pitta Sannipata</em> Diminished <em>Kapha</em>, moderate <em>Pitta</em> &amp; increased <em>Vata Sannipata</em></td>
<td><em>Charaka Samhita</em></td>
</tr>
<tr>
<td>(Cough)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Shwasa</em></td>
<td>Diminished <em>Kapha</em>, moderate <em>Pitta</em> &amp; increased <em>Vata Sannipata</em></td>
<td><em>Charaka Samhita</em></td>
</tr>
<tr>
<td>(Dyspnea)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural pain</td>
<td>Diminished <em>Kapha</em>, moderate <em>Pitta</em> &amp; increased <em>Vata Sannipata</em></td>
<td><em>Charaka Samhita</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>BhavaPrakasha</em></td>
</tr>
</tbody>
</table>

The most mimicking ‘*Kanthkubja Sannipata*’ symptoms include throat pain, dyspnoea, tastelessness, delirium, Malaise, dehydration, head ache, shaking.[27] Out of the 29 *Lakshanas* of *SarvaDoshaSannipata*, 25 *Lakshanas* are found in the COVID-19 infection.[28]

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-Asthi-Sandhi Roga Marga*’ (disease pathway).

*Abhishangaja Jwara, Bhootopasangaja Jwara* is Vishama *Jwara* according to Vagbhata, *Sannipatika* is a disease variant with vitiation of all three *Dosha* in pathogenesis.[29] Agantuja varieties of any diseases can complicate into *Sannipatika* state with severe prognosis. The viral or bacterial fevers, along with malignancy, auto immune diseases, etc. are needed to be considered as *Sannipatika* state.[30] Primary manifestations are seen at *Pranavaha Srotas* as virus enters through nasal passage.
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, 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 Ayurveda cytokine storm. The ‘effect’ of cytokine storm is seen on vital organs, quoted as Marma in Ayurveda. Heart brain and kidney are three important Marmas i.e. vital organs which are accounted into Madhyama Rogamarga (middle pathway for manifestation of disease), amongst three Roga marga (three broad based groups of disease pathways).

In Ayurvedic epistemology vyavayee guna (the important attribute of Visha) makes pathogenesis rapid. Gara Visha is the relevant Ayurveda concept of toxins where Gara literally means the one digluted. Ashtang Sangraha has mentioned that Gara Visha (A group of poisons where one can find ‘Combination of parts of the body and excreta of different animals enlisted) can be fast acting. Thus Visha is an important consideration as there is speedy and lethal pathogenesis that affects vital organs. The speediness is important virtue of pathogenesis in COVID-19. In Ayurvedic epistemology it is vyavayee guna (the important attribute of Visha) that makes pathogenesis rapid. Gara Visha is the relevant Ayurveda concept of toxins where Gara literally means the one digluted. Ashtang Sangraha has mentioned that Gara Visha (A group of poisons where one can find ‘Combination of parts of the body and excreta of different animals enlisted) can be fast acting. Thus Visha is an important consideration as there is speedy and lethal pathogenesis that affects vital organs.

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.[31]

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 aminotransferases, 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.[32]

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.[33]

3.5.3 Cardiac complications: After respiratory system, the second most affected body system known by COVID-19 is the cardiovascular system.[34] 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.[35]

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.[36] 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).[37]

In Ayurveda terminology coagulopathies are ‘Kapha dominant RaktaPitta’. Charaka has mentioned RaktaPitta as complication of Jwara. RaktaPitta 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.[38] 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.[39]

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.[40] 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.[41] Ayurveda Scholars have mentioned similitudes between Sama Sannipatika Jwara with ‘sepsis/septic shock/systemic inflammatory response syndrome (SIRS)/multiple organ dysfunction syndrome (MODS)/septic encephalopathy/delirium’.[42]

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

### Diagram 2: Primary and Secondary Manifestations of COVID-19 in Ayurveda perspective
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% of patients of COVID-19 remain asymptomatic, the Contact with the 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 life style 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 no.4

<table>
<thead>
<tr>
<th>Table no. 4 Analysis of Symptoms in Ayurvedic terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common Symptoms</strong></td>
</tr>
<tr>
<td><strong>Ayurvedic name</strong></td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Dry cough</td>
</tr>
<tr>
<td>Tiredness</td>
</tr>
<tr>
<td><strong>Less Common Symptoms</strong></td>
</tr>
<tr>
<td>Aches/Pains</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Rhinorrhea</td>
</tr>
<tr>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>loss of taste</td>
</tr>
<tr>
<td>loss of smell</td>
</tr>
<tr>
<td>discoloration of fingers</td>
</tr>
<tr>
<td><strong>Serious Symptoms</strong></td>
</tr>
<tr>
<td>Difficulty breathing or shortness of breath.</td>
</tr>
<tr>
<td>Chest pain or pressure</td>
</tr>
<tr>
<td>Loss of speech or movement</td>
</tr>
</tbody>
</table>

Thus there are variety of symptoms showing involvement of Pranavaha, Rasavaha, Raktavaha and Majjavaha Srotas and Marma involvement. Symptoms are from Jwara, Shwasa, Pratishyay, Vadavyadhi, 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 Srotodusthti* 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.[43] [44] Thus the later stage of COVID-19 with aggravated immune response indicates invasion of fever in *Dhatu* hierarchy.
Diagram 3: Stage wise Disease Progression in Covid-19 Integrated approach

Diagram 3- Stage Wise disease Progression in Covid-19 (Integrated Approach):

- **Srotas/Dhatu involvement**
  - Pranavaha Srotas
  - Cytokine Storm involving tissue and organs
  - Cardio Pulmonary Apparatus
  - MahaSrotas Gastrointestinal System
  - Nidanarthakara Roga Raktapitta
  - Liver Impairment

- **Stage Of Complications**
  - Mild Pneumonia
  - GI Symptoms (Anorexia, Vomiting, Diarrhea, Hepatic Dysfunction)
  - Severe Pneumonia
  - Dhatu Paka And or Secondary Infection making prognosis worst
  - Raised Creatinine Kidney; Renal Tubules function Affected
  - Septic shock, Majja gata jwara and Cold Extremities

- **Vital Complication stage**
  - ARDS
  - Myocardial Complications
  - Coagulopathies And Vascular Complication
  - Appropriate management & Successful outcome Or Death
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 ‘virulence 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.[45]

In ayurvedic epistemology, microbe is viewed as *nimitta karana* (instrumental cause), contact of microbe with receptors as *asamavyeekarana* (non-intimate cause) and host internal milieu as *samavyeekarana* (intimate cause). As reviewed earlier the dynamic status of *Dosha, 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.[46] Thus it is host internal milieu in totality that is important for the prognosis.

*Bala* is often considered as body strength but is inclusive of various activities such as immunomodulator, bulk promoting, nutritional etc.[47] 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, hormones and ability) 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, Dosha, Dhatu, Bala, 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. *Pranavaha Srotas* (Cardiopulmonary apparatus), *MahaSrotas* (Gastrointestinal tract) with *Agni* and *Raktavaha 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, coagulopathies are related with *Rakta* and immune responses too are associated with *Rakta Dhatu* only. COVID-19 affects Pneumocytes type II which are precursor for Type I pneumocytes. Thus reproductive / tissue repairing mechanism of body are 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 no. 5.

<table>
<thead>
<tr>
<th>Pathogen centric Approaches</th>
<th>Host Centric Approaches</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hygiene, Sanitization, Physical Distancing and other measures to avoid possibility of infection.</td>
<td>7-8 Hours of sleep. Vitamin C, D3 and other supplements. Yoga and Respiratory Exercises. Interventions of Pulmonary Function improving agents</td>
<td>Evidences of immunomodulatory mechanisms of exercise, micronutrients, sleep</td>
</tr>
<tr>
<td>Ayurveda Immunomodulator Herbs for minimizing virus replication and to arrest Cytokine syndrome.</td>
<td></td>
<td>Evidences of Ayurveda immunomodulatory herbs/formulations mechanisms in biomedical terminology</td>
</tr>
<tr>
<td><strong>Proposed Novel Approaches based on Host centric Approach and Ayurveda Pathophysiology of COVID-19</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathogen Centric Approaches</td>
<td>Host Centric Approaches</td>
<td>Rationale</td>
</tr>
<tr>
<td>Nasya, Gandusha can be local measures for care of pathogen entry points.</td>
<td>Conservation of Agni-Bala &amp; maintenance of Agni (Digestive and metabolic equilibrium).</td>
<td>As MahaSrotas is associated with Pranavaha Srotas as moolasthana</td>
</tr>
<tr>
<td></td>
<td>Attainment of ‘Rakta – Pitta’ homeostasis with specific dietary, lifestyle modifications and therapeutic interventions.</td>
<td>According to Ayurveda Physiology Prana (not mere oxygen but vitality) follows Rakta and both are interdependent.[48]</td>
</tr>
</tbody>
</table>

The Inflammatory Responses,
| Protection of *Marma* (Vital organs, the dedicated sites of *Prana*) with specific dietary, lifestyle modifications and interventions | Sepsis as well as Coagulopathy are result of *Rakta* and *Pitta* vitiation |
| ‘*Prana Kamiya Rasayana*’ (*Rasayana* medicines particularly for vitals). | Cytokine storm results in Inflammation and even necrotic changes in vital organs.[50] |
| *Basti* (Medicated enema) | *Basti* is recommended as best measure for protection of vital organs.[51] |
| Other relevant measures for protection of Heart, Brain and kidney from relevant chapters like *Visha Chikitsa*. [49] | |

**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.

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.[52] *Ayurvedic* foundational framework of ‘*Dosha-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.

Acknowledgement: Authors are thankful to Dr Supriya Bhalerao & Prof Asmita Wele for inputs on scientific writing.


## Table no. 1 Analysis of Symptoms in Ayurvedic terminology

<table>
<thead>
<tr>
<th>Common Symptoms</th>
<th>Ayurvedic name</th>
<th>Dosha status</th>
<th>Srotas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Jwara</td>
<td>Pitta dominant tridosha</td>
<td></td>
</tr>
<tr>
<td>Dry cough</td>
<td>Vata dominant</td>
<td>Viloma Vata</td>
<td>Pranavaha Srotas</td>
</tr>
<tr>
<td>Tiredness related with Jwara</td>
<td>Vata dominant</td>
<td>Rasavaha Srotas</td>
<td></td>
</tr>
</tbody>
</table>

### Less Common Symptoms

<table>
<thead>
<tr>
<th>Less Common Symptoms</th>
<th>Ayurvedic name</th>
<th>Dosha status</th>
<th>Srotas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aches/Pains</td>
<td>Angamarda</td>
<td>Vata dominant</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>Galadhwanaa</td>
<td>Kapha, (and rakta vitiation)</td>
<td>Pranavaha srotas</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>Pratishyay</td>
<td>Vata, Kapha</td>
<td>Pranavaha Srotas</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Netrabhishtyanda</td>
<td>Kapha dominant tridosha</td>
<td>Majja vaha srotas</td>
</tr>
<tr>
<td>Headache</td>
<td>Shirashoola</td>
<td>Kapha dominant ( and rakta vitiation)</td>
<td>Raktavaha srotas</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Atisara</td>
<td>Vata dominant tridosha</td>
<td>Purishavaha srotas</td>
</tr>
<tr>
<td>Loss of taste</td>
<td>Aroochi</td>
<td>Kapha, Pitta, Vata</td>
<td>Annavaha srotas</td>
</tr>
<tr>
<td>Loss of smell</td>
<td>Anosmia</td>
<td>Vata</td>
<td>Pranavaha srotas</td>
</tr>
<tr>
<td>Discoloration of fingers</td>
<td>Araktata, Karshnya</td>
<td>Pitta (and Rakta vitiation)</td>
<td>Raktavaha srotas</td>
</tr>
</tbody>
</table>

### Serious symptoms

<table>
<thead>
<tr>
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<th>Ayurvedic name</th>
<th>Dosha status</th>
<th>Srotas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty breathing or shortness of breath, Shwasa</td>
<td>Vata- Kapha And Pitta as Shwasa is originated from Amashaya</td>
<td>Pranavaha srotas, Marma involvement</td>
<td></td>
</tr>
<tr>
<td>Chest pain or pressure, Ura shoola</td>
<td>Vata dominant</td>
<td>Pranavaha srotas, Marma involvement</td>
<td></td>
</tr>
<tr>
<td>Loss of speech or movement, Vakgraha, Vatavadyahi</td>
<td>Vata dominant</td>
<td>Marma involvement</td>
<td></td>
</tr>
<tr>
<td>Table no.2 : Novel approaches (Preventive and Therapeutic) based on this integrative understanding of Covid-19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
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<td><strong>Contemporary Approaches</strong></td>
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<td>Hygiene, Sanitization, Physical Distancing and other measures to avoid possibility of infection.</td>
<td>7-8 Hrs of sleep. Vitamin C, D3 and other supplements. Yoga and Respiratory Exercises. Interventions of Pulmonary Function improving agents</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>As the critical stages of vital organ involvement, Inflammatory Responses, Sepsis as well as Coagulopathy/ Vasculopathy are understood as imbalance in Rakta and Pitta Physiology.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protection of Marma (Vital organs the dedicated sites of Prana) with specific dietary, lifestyle modifications and interventions</td>
<td>Cytokine storm results in Inflammation and even necrosis in vital organs.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>‘Prana Kamiya Rasayana’ are mentioned by Charaka specifically for protection of Vitality and thereby</td>
<td>The phenomenon of Vital organ complications is discussed in TriMarma Chikitsa chapter of charaka.</td>
<td></td>
</tr>
</tbody>
</table>
| **vital organs.**  
| Basti is recommended as best measure for protection of vital organs.[55]  
| Also sections in Visha Chikitsa are for Protecting Heart and Brain.[56]  
| **One must consider measures and dietary and lifestyle recommendations and interventions mentioned specifically for protection of Marma.**  

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.
Pathophysiology of Covid-19 and Host centric approaches in Ayurveda

Diagram 1: Concept of Infectious diseases in Ayurveda
Diagram no. 2: Primary and secondary Manifestations of Covid-19

- Myocardial (Hridaya)
- Neural (Shira)
- Renal (Vrikka)
- JWARA WITH Upper & Lower Respiratory (Primary Manifestations)
- PRANAVAHA SROTOMOOLA

- Coagulopathies
- Vasculopathies
- Gastrointestinal PRANAVAHA SROTOMOOLA and Liver

- Sepsis
- MODS
Diagram 3: Stage wise Disease Progression in Covid-19 Integrated approach

Diagram 3- Stage Wise disease Progression in Covid-19 (Integrated Approach):
Diagram 1: Concept of Infectious diseases in Ayurveda

- Jwara (Fever)
- Visha (Toxins)
- Krimi (Microbes)
- Concept of Infectious diseases in Ayurved
- Epidemic (Janapado Dhwansa)
- Seasonal Regimes & Diseases
Diagram 2: Primary and Secondary Manifestations of COVID-19 in Ayurveda perspective

**JWARA with Upper and Lower Respiratory Involvement** (Primary Manifestations)

**PRANAVAHA STROTAS**

- Myocardial (Hridaya)
- Neural (Shira)
- Renal (Vrikka)
- Coagulopathies Vasculopathies (Rakta)
- Sepsis (Visha)
- Gastrointestinal PRANAVAHA STROTOMOOLA and Liver
Diagram 3: Stage wise Disease Progression in CoVID-19 Integrated approach

Diagram 3: Stage Wise Disease Progression in CoVID-19 (Integrated Approach):
Pathophysiology of Covid-19 and Host centric approaches in Ayurveda

Conflict of interest:

None

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