



**Review Article**

**SCIENTIFIC UNDERSTANDING OF CYTOKINE STORM IN PERSPECTIVE OF AYURVEDA: A REVIEW**

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**ABSTRACT**

Cytokine storm also known as cytokine releasing syndrome is due to elevate level of circulating cytokine and hyper action that can be triggered by some factor like virus, bacteria or other epigenetic factors. In this era of communicable disease, COVID-19 is such a disease which shows manifestation in the form of cytokine storm. Increase level of cytokine like interleukin-6 etc in the blood causes destruction of normally functioning cell leads to dangerous life-threatening condition like ARDs. Cytokines are immunomodulating agents composed of soluble proteins, peptides and glycoproteins secreted by haemopoietic and non-haemopoietic cells in response to various stimuli. Their main role is in molecular interaction between various cells of the immune system. Cytokines are nothing but just the immune markers which hyperactivation leads to cytokine storm. There is not any description of such pathogenesis in Ayurveda. But Ayurveda clearly defined some concepts of immunity such *Asvyadhikshamatva*, *Oja*, *Bala*, *Vyadhibhatakarabhava* and *Rasayana*. In Covid-19, researcher found that such people are more vulnerable to disease and its severity. Such vulnerability depends upon person response to illness. Ayurveda may explain this vulnerability through its concepts of preventive, personalized and rejuvenation. The present review focused on cytokine storm and its understanding in perspective of Ayurvedic concepts of immunity.

**INTRODUCTION**

Cytokine storm refers to exaggerated immune response towards triggering factors by release of huge number of cytokines like in COVID-19 infection. Increase level of cytokine in the blood causes destruction of normally functioning cell leads to dangerous and potentially life-threatening condition, like acute respiratory distress syndrome and multiple organ failure.<sup>[1]</sup>

Cytokine storm play a major role in mortality of individuals infected with COVID 19. In case of covid 19, cytokines like interferons, interleukins, chemokines, colony stimulating factors (CSFs) and tumor necrosis factors (TNFs) are associated with cytokine storm.<sup>[2]</sup>

Covid 19 was 1<sup>st</sup> reported in Wuhan, China at the year 2019 and spread rapidly to whole world and became the reason of worldwide mortality and morbidity. It was designated as a global pandemic by WHO in march 2020 and still in 2022, its presence in the environment afraid the human population.<sup>[3]</sup> In ancient text of medical sciences called Ayurveda, there is no such description about such pathogenesis. Ayurveda described various titles like the concept of *Vyadhikshamatva*, *Bala* (*Sahaja*, *Kalaja*, *Yuktikrit*), *Oja*, *Vyadhivighatakar bhavas*, *Ahaarasampat*, *Sharirsampat*, and *Rasayana* to understand the immunity and its components. All these concepts of Ayurveda help to understand the modern understanding of immunity relating to disease defense mechanism. This review focused on Ayurvedic perspective of cytokine storm and understanding of predictive medicine approach against cytokine storm.

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## MATERIAL AND METHODS

This topic is examined using a variety of Ayurvedic classic literatures. Materials on immunity, its importance, and other relevant topics were gathered, examined, and debated to get a comprehensive grasp of the concept of immunity in connection to cytokine storm.

### Concept of Vyadhikshamatva

*Vyadhikshamatva* has a direct relation to disease incidence and manifestation. When certain foreign body comes and invades the body, it causes some form of diseases. At that particular time the body tries to fight against the disease by certain barrier to avoid its manifestation or to suppress its intensity. This power of body resistance against the development of disease (*Vyadhi- Utpadakpratibandhakatva*) or resist the *Bala* of disease (*Vyadhi- Balavirodhatva*) collectively called as *Vyadhikshamatva*.<sup>[4]</sup>

*Acharya Charak* has told that the resistance power of a disease varies from individual to individual (i.e., *Vyadhikshamatva*) according to their body constitution i.e., *Prakriti*.<sup>[5]</sup>

It is seen that with the same etiological factor disease manifestation is not the same i.e. some get diseased with mild cause and some does not get disease even after close contact with relevant causative factor. This is due to the difference in their ability to resist disease and suppress the dominance of the invaded cause, it is otherwise called as natural strength or the *Swabhavikbala* is directly proportional to *Deha prakriti*.<sup>[6]</sup>

**Understanding the Prakriti:** *Dosas* dominating the sperm and the ovum during the time of conception and also those inhibiting the uterus at that time determine the *Prakriti* (physical constitution) of the individual.<sup>[7]</sup> At the time of conception, in certain individuals, there is equilibrium of *Vata*, *Pitta* and *Kapha*. Some are dominated by *Vata*, some are dominated by *Pitta* and some are *Kapha*. Some are dominated by two *Dosha* and manifested as *Vata-Pitta*, *Vata-Kapha* and *Pitta Kapha*. Out of these categories, individual to be healthy only when *Vata*, *Pitta* and *Kapha* in his body are in a state of equilibrium and health represents the natural state of the body. Those belonging to the other categories always suffer from one or other of the bodily defects, although they might apparently be having normal health. It might be argued that the various types of natural conditions (*Prakriti*) of the body as produced at the time of conception are invariable and as such continue for the whole life. Such conditions are changed in certain individuals only to indicate imminent death.<sup>[8]</sup> *Acharya Susruta* has been stated that the *dosas* relating to the natural conditions of the body (*Prakriti*) get never enhanced, transformed or diminished.<sup>[9]</sup> *Prakriti* of the individuals defines the individual susceptibility based on immunity status and

response towards disease pathogenesis. Study on *Prakriti* and immunophenotyping revealed that the increased level of CD25 and CD56 in *Kapha Prakriti* may indicate ability to elicit better immune response, which is in conformity with textual references in Ayurveda.

**Concept of Agni:** The regular functioning of *Agni* is completely dependent on the normal functioning of all of the body's systems. If *Agni* becomes vitiated as a result of any etiological source, whatever it is, pathological processes begin, finally leading to the sick state of the body. Almost all ailments, according to Ayurveda. The development of *Ama Dosha* is the outcome of *Agni's* vitiation (undigested food). Products undergo poisonous modifications known as *Ama* as a result of faulty food digestion in *Amashaya* (due to the hypofunction of *Jatharagni*). Intestinal dysgenesis, infection, and a leaky gut, according to contemporary research, are responsible for the development of immunological dysregulation or autoimmunity, which is the cause of the illness and can be linked to *Ama*. This *Ama* generation creates *Srotorodha*, or channel blockage, which is the most prevalent factor in the onset of any illness. This entire pathogenic occurrence obstructs the digestion and absorption process, resulting in a variety of gastrointestinal problems.<sup>[10]</sup> In modern science, *Ama* production results in the generation of free radicals, which are referred to as hazardous elements. As a result, hypo functioning of *Agni* and *Ama* development is a primary role in the presentation of most illnesses, including gastrointestinal problems, allergy and auto-immune diseases, and numerous metabolic disorders. This demonstrates the importance of *Agni* vitiation in disease onset.

**Bala (strength):** The constitutional strength is present in every being from every time of birth. This is because of natural growth of the *Dhatus*. Thus, the natural strength does not require any extraneous factor for its growth but depends upon some inherent independent factors called as *Balavidhikar Bhava*. Strength is categorized into three types- *Sahaja* (constitutional), *Kalaja* (depends upon time) and *Yuktikrit* (acquired). Ayurveda defined the *Bala* of *Kapha prakriti* individuals are more as compared to *Vata* and *Pitta*.<sup>[11]</sup>

**Oja:** *Oja* is an essential and important element of the human body without which life is impossible to live, according to Ayurvedic literature. The majority of the actions that occur in the human body throughout one's life are dependent on *Oja*. The perpetual *Oja*, which is the essence of all the *Dhatus*, is responsible for *Bala* and immunity in the body. The *Ojas* is primarily responsible for internal immunity.<sup>[12]</sup> The cause-and-effect relationship between the *Ojas* and resistance power or immunity is demonstrated. The two tasks of *Ojas* are to supply sustenance and strength to the

body. *Ojas* can be compared to the immune system because their tasks are similar, such as protecting the body from infections and maintaining physical strength. Lysozyme, antibodies, white blood cells, complement complex, properdin, and other components of the immune system protect the body from microbes. *Ojas* also refers to a collection of body elements including *Kaphadosha*, *Raktadhatu*, and the essence of the seven *Dhatus*. All of these elements contribute to body strength. *Ojas* is the stuff that is stored in the body and used as energy to continue general living activities as well as to combat various ailments. Then any impairment in the elements that cause *Oja* to diminish leads to the same of *Oja kshaya* (defective immune system). As a result, it is critical to store and safeguard the existing *Oja*-related materials in the body in order to maintain the immunological response and the body's defensive system. Both the *Ojas* and the immune system require nutritional diet to function properly.

## DISCUSSION

Cytokine storm is a fatal condition in which there is danger to life due to elevated level of circulating cytokine and hyper action that can be triggered by pathogens COVID-19, bacterial sepsis, Epstein Barr virus (EPV) associated as LH, cancer, auto-immune disorder and monogenic disorder.<sup>[12]</sup>

It is very important to recognize cytokine storm as soon as possible by certain investigation and clinical findings because it has prognostic and therapeutic implication if not treated adequately it leads to multi organ failure.<sup>[13]</sup> In cytokine storm there is elevated level of cytokine which cause major damage to the cell. Cytokines are a diverse group of small nonstructural like molecular weight protein and glycoprotein that are secreted by cell that have a complex regulatory influence on immunity and inflammation. Cytokines involved in cytokine storm mainly are interleukin (1,2,3,4,6), interferon  $\chi$ , TNF ( $\alpha, \beta$ ), CSF (colony stimulating factor) etc.<sup>[14]</sup>

The immune system of the body is designed in a beautiful way that a respond to the pathogen and destroy it and return to homeostasis. So there is a balance between sufficient cytokine production in order to eliminate the pathogen and over production of cytokine which produces hyper inflammatory production.<sup>[15]</sup>

Inappropriate triggering factor or initiator like pathogen induced triggers leads to stimulation of driver cell like CD4 and CD8 T-cell, macrophages, dendritic cell which causes inappropriate or ineffective amplitude of response leads to immune hyper activation. In each of the above condition there is a failure of negative feedback mechanism that are mean to check hyper inflammation that tends to occur a very large production of inflammatory cytokine and

mediators. If untreated for prolonged period leads to multi organ failure followed by death.<sup>[16]</sup>

In patient with severe COVID-19 the immune related symptoms are more as compare to the asymptomatic or mild. Symptomatic patient, which suggest that host immune dysregulation contribute to the pathogenesis in some cases. It is seen that patient with co-morbid condition like hypertension, diabetes, asthma and obesity are associated with severe cases of COVID-19. It may be due to pre-existing chronic inflammatory phase or more chance of development of organ dysfunction from the immune response.<sup>[17,18]</sup>

COVID-19 infection mainly spread through inhalational root (droplet infection) where virus directly goes into lungs and caused viral pneumonia.<sup>[19]</sup> In early stages proper anti-viral which recommended rather than immunosuppressive gradually with progress of disease. There is increase level of cytokine producing cytokine storm role of immune suppressant is more than any anti-viral and anti-microbial.<sup>[20]</sup>

Ayurveda defines that *Kapha prakriti* individual are high immune status and BMI as compare to other *Prakriti* individuals whom may became more susceptible to disease like COVID-19 and show more hyperimmune response in the form of cytokine storm as compare to others. Modern scientific studies also revealed the role of BMI in severity of disease in case of COVID-19. More mortality or morbidity were seen in obese or overweight individuals as compare to normal weight individuals. Cytokine syndromes were more seen in person having metabolic disorders which also confirm the literature of Ayurveda. Ayurveda defined various principles for in depth understanding of immunity. *Kapha prakriti* individuals also have lower BMR due to *Mandagani* which made them more vulnerable to any disease. Agni is the metabolic power of the body help in maintaining the homeostasis in every pathway of the body. The failure of negative feedback mechanism to check the hyper inflammation also hampers due to low *Agni* status in *Kapha prakriti* individuals.

## CONCLUSION

This review article revealed that *Kapha dosha* either in *Prakriti* or *Agni* or *Bala* etc., become more vulnerable to cytokine storm in respect to other *Dosha* or *Prakriti*. This also will shed more light on cytokine storm interpretation in terms of Ayurvedic concepts of immunity with understanding of *Prakriti* and *Agni*. This review will also be useful to future research on cytokine storm in terms of *Prakriti* and *Agni bala* assessment.

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