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Manuscript Title:**Immunity Against COVID-19: Potential Role of Ayush Kwath**

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Immunity Against COVID-19: Potential Role of Ayush Kwath

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Abstract:

SARS-CoV-2 infection associated respiratory disease- COVID-19 has evolved into a pandemic but, being a new form of virus, pathogenesis of disease causation is not fully understood and drugs and vaccines against this virus are still being tested so that no effective drugs or vaccines have been advised by regulatory authority. In this context, the Ministry of AYUSH, Government of India has recommended 'Ayush Kwath' to improve the immunity and combat the infection. Our objective of this literature review is to review the role of immunity in pathogenesis of COVID-19 and role of *Ayush Kwath* against the virus and regulation of immunity. Current review was conducted using a search of available literature on COVID-19 and immunity, *Vyadhikshamatwa*, Ayurveda and COVID-19, *Rasayana*, Coronavirus, SARS-CoV-2, immunomodulatory effects of medicinal plants; *Tulsi*/ Holy Basil/ *Ocimum sanctum*, *Dalchini* /Cinnamon/ *Cinnamomum zeylanicum*, *Sunthi*/ Ginger/ *Zingiber officinale* and *Marich*/ Black Pepper/ *Piper nigrum*. Ayurveda, being an ancient science have both medicinal and cultural values and had stimulated our kitchen and influenced what we ate in different seasons and the remedies we used for common ailments. Herbs such as *Tulsi*, *Marich*, *Sunthi*, *Dalchini* are the most commonly used and easily available drugs in home. Thus, *Ayush Kwath* due to its immune-modulatory, antiviral, anti-oxidant, anti-inflammatory, anti-platelet, anti-atherosclerotic, hepato-protective, reno-protective properties; seems to be effective in immuno-regulation for controlling viral infections like COVID-19. Further pre-clinical and clinical trials need to be done for the evaluation of safety and efficacy of this polyherbal formulation.

Keywords: Ayurveda; COVID-19; SARS-CoV-2; Coronavirus; Immunity; *Ayush*.

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Immunity Against COVID-19: Potential Role of Ayush Kwath

1. Introduction:

COVID-19, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an infectious disease believed to be originated from bats and transmitted to human beings [1]. Being a new form of virus, pathogenesis of disease causation is not fully understood and drugs and vaccines against this virus are still being tested so that no effective drugs or vaccines have been advised by regulatory authority. Not only for Coronavirus, have many other viruses also lack preventive vaccines and effective antiviral medications. Studies have explored that these viruses can form drug-resistant mutants, which decrease the existing drug's efficacy. So, these viruses can be a threat to the mankind for long time [2].

High mortality among immune-compromised and those with some underlying pathology implies that the factors that improve immunity can prevent serious manifestations due to COVID-19 infection [3]. Many herbal products are found to have immune-modulatory and antiviral property, so their discovery can be a milestone in the prevention and control of COVID-19 [2]. In this context, the Government of India has recommended to take "*Ayush Kwath*" in order to boost the immunity. As this is a new formulation, this needs to be validated scientifically. We have made an attempt to review the immune-pathogenesis of COVID-19 and the role of each herb over it.

2. Immunopathogenesis of COVID-19:

The 'S' protein of coronavirus can bind to host cells through the ACE2 receptor found in the oral and nasal mucosa [4,1]. Other sites where ACE2 receptors are found are lungs, stomach, intestine, bladder, heart, and kidney [5]. Variable presentation of disease in different age groups, serious manifestations that are seen more commonly in immune-compromised, old aged and in those with underlying pathology, many asymptomatic cases in pediatric age group, and presence of lymphopenia in the majority of the cases; these factors implies that immunity has a vital role in the pathogenesis of COVID-19 [6,1,7,8]. It is assumed that our immune system has lack of memory against such a virus that gave it an edge over humans [3].

Viruses cause cell destruction mainly in two ways; direct cytopathic effects of the virus and immune response mediated destruction [9]. COVID-19 cannot lyse the cells it entered so the

major pathway of cell destruction is due to immune-mediated destruction [10,11]. It has been mentioned that unlike adults, less vigorous cell-mediated immune response in alveoli of children results in being asymptomatic in the majority of cases [3].

The pathogenesis can be split into two stages: Non-severe and Severe [12].

2.1. Non-severe stage:

The virus fuses with the host cell membrane and enters inside the host cell through airway epithelium [13,14]. The virus propagates and multiplies inside the host cell and can reach lower airway and alveoli. In adults with good innate cellular and humoral immunity propagation of virus can be limited and viral load reaching alveoli can be reduced thus recovery can take place within 2-3 weeks with mild symptoms [3].

Humoral immunity prevents the viruses to enter new cells while cell-mediated immunity targets on eradicating virus-infected cells [15,1]. In this stage, a strong immune system can be helpful in preventing the propagation of the virus thus reducing the severity of the disease [12].

2.2. Severe stage:

Once the immune system is breached, the virus propagates and reaches the lower respiratory tract and alveoli. Then the virus can penetrate alveoli and reaches systemic circulation causing viremia [3]. The virus binds to multiple organs having ACE2 receptor protein. During this stage, cell-mediated immunity becomes robust and starts releasing various pro-inflammatory cytokines (IFN- α , IFN- γ , IL-1B, IL-6, IL-12, IL-18, IL-33, TNF- α , etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) causing damage to multiple organs known as Cytokine storm [16,17]. We may need to suppress the inflammation for improvement during this severe stage [12]. IL-6 receptor antagonist (Tocilizumab), and anti-inflammatory interleukin (IL-10) are proposed to have a therapeutic role in the reduction of severity and mortality of COVID-19 [18,19]. As increased risk of thromboembolic phenomena is also found to be associated with COVID-19, prophylactic antithrombotic medications are advised during this stage [20].

3. Ayurveda Purview:

4.1. Disease Concept:

It seems that most early cases had a history of contact with the original market for seafood, but the disease has now advanced to be transmitted through human to human contact [1]. Thus this disease can be considered as Communicable- both contagious and infectious diseases. In Ayurveda, epidemics are discussed under the term of *Janapadodhwamsa* (C.S.Vi. 3/5-6) by Charaka and *Maraka* by Sushruta (S.S.Soo. 6/17) [21,22]. The symptoms like fever, cough, breathing difficulty, headache, and vomiting resemble with clinical features of SARS (S.S.Soo. 6/19) [22]. Dalhana in his commentary has mentioned that symptoms like anosmia, cough, catarrh will occur after the entry of contaminated air through the nasal opening which is similar to typical clinical features of COVID-19 (S.S.Soo. 6/19) [22]. Furthermore, this disease can be classified as *Adidaivika Bala Pravritta Vyadhi* (ABPV), *Sansargaja*, *Upsargaja*, and *Aupasargic Roga*. ABPV are those diseases arising due to causes that cannot be controlled by human intelligence. *Upasargaja Vyadhi* are those fever-like diseases that manifest due to close contact with diseased persons (S.S.Soo. 24/7 Dalhana) whereas *Sansargaja Vyadhi* resides with people who are cursed by almighty god i.e. due to influence of invisible forces/ forces behind human control (S.S.Soo. 24/7 Dalhana) [22]. *Aupasargic Vyadhi* is defined in two different ways by Sushruta; one as a disease which spreads from one person to another person (S.S.Ni. 5/33-34) and another as “.....*Upadravasangyah*” i.e. complications or associated diseases that manifest after primary disease (S.S.Soo. 35/18) [22]. Sushruta mentions the diseases like *Jwara*, *Kustha* (skin diseases), *Shosha* (tuberculosis), *Netrabhisyadi* (conjunctivitis), and other *Aupasargika roga* (alike communicable diseases) can be spread through *Prasanga* (intimate relationship), *Gatra Sansparsha* (direct contact), *Nishwasa* (breathing or airborne), *Sahabhajana* (eating together), *Sahashayana* (sleeping together), sharing and using of others’ clothes, ornaments, ointments, etc. (S.S.Ni. 5/33-34) [22].

Agantuja Vyadhi (~diseases of exogenous origin) occurs due to physical/ external factors like *Bhuta*, *Visha*, *Vayu*, *Agni*, and *Prahara* (trauma), etc. without any involvement of *Vataadi Dosha* initially; however, in later stage dosha are involved in the disease process (C.S.Soo11/45) [21]. Cakrapanidatta clarifies that *Bhuta* means *Visakṛimi* or a virulent organism (C.S.Sa.1/121; *Krimi* may be *Sahaja* (natural) or *Vaikarika* (pathogenic) organisms that may be visible (macroscopic) or invisible to the naked eye (microscopic) (C.S.Vi. 7/9,11) [21].

Thus, it is difficult to correlate this disease with specific Ayurveda terminology but, while interpreting the disease on the basis of *Samprapti* by considering the causative agent and the clinical features like fever (*Jwara*), cough (*Kasa*), anorexia (*Aruchi*), fatigue (*Tandra*), generalized body ache or myalgia (*Angamarda*) and Tiredness; it can be contemplated as an *Agantuka Vyadhi* which later on due to the involvement of dosha develops to *Nija Vyadhi* as *Kapha-Vatolvana Hina Pitta Sannipataja Jwara* (Severe *Vata* and *Kapha* with mild *Pitta*) (C.S.Soo. 11/45; C.S.Chi. 3/92) [21]. While talking about the pathogenesis of fever in Ayurveda, Charaka mentioned that when *Vataadi* dosha either singly or in *Sansrista* (two dosha) or in *Sannipataja* (all three dosha) got aggravated then it enters *Amashaya* and mixed with *Rasa Dhatu* causing obstruction of *Rasavaha* and *Swedavaha Srotas* resulting in the destruction of *Agni*; *Agni* then spreads out from its *Sthana* to whole over the body causing the febrile condition (C.S.Ni.1/20, 23, 26; C.S.Chi.3/129-132) [21].

4.2. Immunity concept in Ayurveda:

Strength, health, lifespan, and vital breath are dependent on the condition of *Agni* (C.S.Soo. 27/342) [21]. Charaka has mentioned the term *Vyadhikshamatwa* and states that during certain conditions, or due to certain factors, even unwholesome (unhealthy) food does not produce disease immediately; all unwholesome diet are not equally harmful, all dosha are not equally powerful, all persons are not capable of resisting diseases (C.S.Soo. 28/7) [21]. This suggests that the body's immune system plays a crucial role in disease development. The equilibrium state of *Dhatu* is called *Swasthya* (C.S.Soo 9/4) [21]. The person who is desirous to be healthy should adopt healthy practices related to diet, conduct, and activities (C.S.Soo. 7/60) [21]. Thus, Immunity can be considered in Ayurveda as *Vyadhikshamatwa* and *Oja*; which depends on the condition of *Agni*, *Dosha*, and *Dhatu*.

There are three factors *Aahara*, *Swapna*, and *Brahmacharya* (diet, sound sleep, and celibacy) that support the life with which the body will be endowed with strength, complexion, and development till life span (C.S.Soo. 11/35) [21]. *Bala* (~ Strength / Immunity) is of three types- congenital, time affected, and acquired. Congenital is that which is developed naturally in the body and mind; time affected is due to seasonal variation and age factor and acquired one is produced by the proper application of diet and exercise (C.S.Soo. 11/36) [21]. Thus not only diet but also performing yoga or exercises with proper methods by giving rest in between exercises as *Rasayana* therapy will increase acquired strength. (C.S.Soo.11/36 Chakrapanidatta) [21]. *Oja* is also called *Bala*; is the essence of all *Sapta Dhatu*, being located in *Hridaya*, combines with *Rasa* and circulates through the *Dhamani* and performs

Tarpana or *Prinanam* of the whole body (S.S.Soo. 15/19; C.S.17/74 Chakrapanidatta) [22,21]. The equilibrium state of *Kapha* promotes strength, that's why normal *Kapha* is called *Oja*. (C.S.Soo. 17/117 Chakrapanidatta) [21]. Normal pure blood promotes strength, complexion, health, and lifespan (C.S.Soo. 24/4) [21]. While dealing with *Sannipataja Jwara*, Susruta in *Uttarsthana* mentioned *Abhinyasa Jwara*, also called as *Hataujasa Jwara*, indicating the loss or deranged condition of *Oja* (S.S.Utt. 39/39-44) [22].

The word “*Rasayana* (*Rasa+ayana*)” refers to nutrition and its transportation in the body for attaining excellent Rasadi *Dhatus*; which leads to gain longevity, freedom from disorders, optimum strength of physique and sense organs (C.S.Chi. 1:1/4-8) [21]. *Rasayana* promotes nutrition by explicitly enriching the nutritional value of *Rasa* by enhancing *Agni*, i.e. digestion, metabolism, and absorption (by *Srotashodhana*). Consequently, any medication that improves *Rasa*'s consistency would enhance the health of all body tissues.

4. Role of Ayurveda and Traditional Medicine:

Every society has its own medical system, which is deeply rooted in its culture and guided by its philosophy of life. Being culturally and linguistically diverse countries, there developed several types of traditional medicines (TM) based on practices, skill, traditional knowledge based on beliefs, theories, and experiences indigenous to different cultures. Ayurveda, Traditional Chinese medicine (TCM), Ancient Egyptian medicine, Sowa Rigpa, etc. system of medicine remain the most ancient yet living traditions in South East Asia, Western Pacific, Eastern Mediterranean, Africa region. Up to 80 percent of the population in some Asian and African countries depend on TM for primary health care (PHC) needs [23]. Still, there is a high trend of using many herbs in religious and cultural works, therapeutically for common ailments and as spices for foods according to occasion specific and seasonal regimes. Ayurveda and TM have made a significant contribution to the prevention and alleviation of various communicable and non-communicable diseases for thousands of years. A long history of using many herbal remedies and experiences passed from generation to generation has resulted in people relying on herbal remedies and some simple home remedies for common diseases can be used even by illiterate citizens. The self-care, an integral part of PHC, with home remedies using various herbs is the most common treatment for India, Nepal, Bhutan, and China for different flu, common cold, fever, GI disorders, etc. Prevention of smallpox in China has been an epoch-making effort in the period of mankind's preventive care. One observational study found that the prevalence between the total number of COVID-19 cases per million population and the grams of spice supply per capita per day is clearly

interrelated. Most nations with lower spice intake per capita reported more COVID-19 cases per million population and vice versa [24]. Nevertheless, with the invention of drugs, many herbal remedies used historically have become modern medicines. Few notable examples include morphine, digoxin, artemisinin and colchicine. As many herbs are found to have immunomodulatory role and possess antiviral activity, many people are being optimistic over the traditional system of Medicine. Ayurveda and TCM have descriptions of immunomodulation along with anti-viral treatments, even targeted to the coronavirus family [25,2].

The key factor for COVID-19 to occur and evolve is the interaction between the virus and an individual's immune system [26]. As medicinal plants enhance NK cell activity, inhibit activated transcription factor 2 (ATF-2), down-regulate Th17-related cytokines including transcription factor RORc, IL-17A and Th2-related cytokines including IL-5, IL-13, and IL-6, inhibit GATA3, IL-4, IL-6, IL-1 β , ROR γ t, IL-17A, TNF- α expression and increase the secretions of IL-10, INF- γ , etc., it shows that natural products have potent immune-modulatory and immune-boosting effects that may be helpful during the infection course by increasing innate immune response to infections [27,28].

5. *Ayush Kwath*:

Considering the importance of immunity boosting measures in the wake of COVID-19 outbreak, the Ministry of AYUSH, Government of India with the interest of health promotion of the masses, recommends “*Ayush Kwath*” or ‘*Ayush Kudineer*’ or ‘*Ayush Joshanda*’ which comprises of four medicinal herbs (**Table 1**) [29,30]. The herbs like holy basil, cinnamon, ginger, black pepper are highly available, accessible and widely used in the kitchen and are convenient to educate and train about its use to community health workers, community and even to all public that they can have cost-effective treatment with herbal home remedies. This will help to promote immunity and to lower the gatherings at hospitals and pharmacies in this pandemic. This type of public health measure would eventually promote 'health for all' with the theme 'our health in our own hands' making responsible to each and every people by active involvement in their own health instead of relying on mass distribution of some medicine. As people leave their homes to earn a living, this herbal decoction will ensure broad access to health care. The WHO SEARO adopted a resolution to revitalize PHC through health systems strengthening to achieve health for all with the emphasis on health promotion and disease prevention [31]. This *Kwath* is not just a mechanical mixture invented for the COVID-19 pandemic, but it is a revival of health tradition.

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Method of preparation and use:

Take all the ingredients in dry form as per standards laid down in Ayurvedic Pharmacopoeia and make coarse powder. Make sachets or tea bags each of 3 grams of powder or 500 mg. tablet of aqueous extract, to be consumed like tea or hot drink by dissolving in 150 ml of boiled water, once or twice daily. *Gud* (Jaggery) / *Draksha* (Resins) and/or Lemon Juice can be added while consuming the formulation.

5.1. *Tulsi*:

Many in-vitro, animal and human experimental scientific studies showed that; due to presence of eugenol, phenolic compounds, linoleic acid, etc. compounds *Tulsi* has antimicrobial (including antibacterial, antiviral, antimalarial), anti-diarrheal, anti-oxidant, anti-inflammatory, hepato-protective, cardio-protective, reno-protective, analgesic, antipyretic, immune-modulatory properties and is thus recommended as a treatment for a range of diseases including features like cough, fever, asthma, anxiety, diarrhea, gastric, cardiac and genitourinary disorders [32,33,34,35,36]. Due to its anti-inflammatory and antioxidant properties, it protects against toxic chemical-induced injury, enhance the antioxidant enzymes and protect cellular organelles and membranes by clearing damaged free radicals [37].

The compounds such as ursolic acid, carnosol, rosmarinic acid, cirsilineol, apigenin, eugenol, and cirsimaritin present in *O. sanctum* increase haemoglobin concentration, enhance SRBC agglutinin titers, decrease cyclo-oxygenase (CoX)-2 and lipoxygenase (LOX)-5 enzymes activity, suppress NF- κ B classical pathway, up regulation of IL-2, IFN- γ and TNF- α , down regulation of IL-1 β and produce of SRBC antigen-specific antibodies, which represent a major defense mechanism to assess T-cell-dependent antibody responses i.e. *Tulsi* by enhancing immune response boost the defense mechanism against the infection [38,39,40]. Several studies have shown that *Tulsi* (aqueous and methanol extract of leaf and seed oil) besides improving vital capacity also is an immune-modulator and regulator as it enhances immune response by increasing T-helper and NK cells; phagocytic activity and index with the rise in lymphocyte count, neutrophil count and antibody titer [41,42].

In an acute toxicity study, it did not produce any hazardous symptoms or CNS and ANS toxicities or death and did not show any change in water and food consumption, body weight, and hematological and biochemical profiles [43].

5.2. *Dalchini*:

It is a potent immune system booster and is used in various ailments like flu, indigestion, edema, cough, etc. [44,45]. Cinnamon bark contains cinnamaldehyde, benzaldehyde, cuminaldehyde and terpenes [46]. In one study, cinnamon at high dose (100 mg/kg) showed immune-stimulant activity as it significantly increased the phagocytic index, serum immunoglobulin levels and antibody titer and decreased the percentage reductions in neutrophil count. Cinnamon low dose (10 mg/kg) increased serum immunoglobulin levels only. This showed that high dose increases both cell mediated and humoral immunity whereas low dose showed effect only on humoral immunity [47]. The studies also suggest that cinnamaldehyde can act as a strong regulator of monocyte/macrophage-mediated immune responses by inhibition of PI3K, PDK1 and NF- κ B activation of signaling components. In addition to this, by the activation of CD29 and CD43, it blocked cell migration cell-cell adhesion induced but not cell-fibronectin adhesion and it was able to suppress both the production of nitric oxide (NO) and up regulation of surface levels of co-stimulatory molecules (CD69 and CD80) and pattern recognition receptors (TLR2 and CR3) [48].

Cinnamon bark decrease systemic levels of IFN- γ without altering the levels of IL-4 or IL-2, inhibit anti-CD3 Ab-stimulated IFN- γ and IL-4 at the mRNA and secreted protein levels, enhance IL-2 protein secretion at the cellular level which helps to decrease cell death, inhibit IL-2mRNA expression, inhibit anti-CD3-induced p38, JNK, ERK1/2, and STAT4 activation, but not I κ B α degradation or STAT6 and ultimately alter the inflammatory responses in T cells. This shows the immune-modulatory effect of cinnamon on cytokine secretion and the involvement of intracellular signaling molecules in activated T cells. It also causes a reduction in the sub-G1 phase, accompanied by an increased ratio of apoptotic cells to necrotic cells [49]. The constituents like cinnamaldehyde, cinnamophilin etc are found to be a thromboxane A2 receptor antagonist, anticoagulative, anti-atherosclerotic and thus prevents unnecessary clumping of platelets and atherosclerotic CVD [50].

In a systematic review of its adverse events, relatively few self-limiting adverse effects were reported like allergic reactions and gastrointestinal disorders on clinical trials, case reports and case series. The evidence available show that cinnamon is safe for use as spice in daily diets or as a medication [51]. However, its use for therapeutic reasons, in high doses or for prolonged periods, can cause some adverse effects and should be observed clinically.

5.3. *Sunthi*

An alcohol extract increases the immunological status of mice with increased phagocytosis by macrophages whereas crude extract was also shown to increase humoral and cell-mediated immune responses [52]. The bioactive compounds of ginger such as nevirapine, β -sitosterol, 6-gingerdiol, germacrene, methyl-6-shogaol, 6-gingerol, α -linalool, 6-shogaol, gingerdion, zingiberene, etc., are known to inhibit viral replication; among these the most potent inhibitors of reverse transcriptase (RT) enzyme is β -sitosterol, which is predicted to be used as non-nucleoside reverse transcriptase (NNRTIs) HIV-1 inhibitors [53,54]. It is reported that Ginger contains TNF- α which is also known as an anti-influenza cytokine [55]. The rhizome of Ginger and its main components like gingerols, shogaols, etc inhibit prostaglandin and leukotriene biosynthesis, inhibit cyclooxygenase and lipoxygenase activities, inhibits the synthesis of pro-inflammatory cytokines such as IL-1, TNF- α , and IL-8 without any significant effect in IL-6 levels; inhibit the excessive production of NO, PGE (2), TNF- α , and IL-1 β , reduce the elevated expression of NF κ B and TNF- α , down-regulate inflammatory iNOS and COX-2 gene expression, inhibit thromboxane synthetase, raise levels of prostacyclin without a concomitant rise in PGE 2 or PGE 2 alpha, inhibit platelet aggregation, decrease age-related oxidative stress markers and enhance fibrinolysis [56,57,58,59,60,61]. The concentration of IgM and eosinophil count in non-smokers was significantly increased in a comparative study of the effect of ginger extract among male smokers and non-smokers, whereas the concentration of hemoglobin and lymphocyte count in smokers was strongly increased. This indicates that in non-smokers, ginger results in a stronger antibody response or humoral immunity than in smokers [62].

According to Ayurveda, it is contraindicated to be used in a few diseases: *Kushtha*, *Pandu*, *Mutrakriccha*, *Raktapitta*; and in *Grishma* (summer) and *Sharada* (autumn) *Ritu*. There are few minor adverse effects recorded that did not need care, such as mild gastrointestinal symptoms, sleepiness, mild diarrhea during prior few days of treatment. It is also explained that ginger has the ability to induce heartburn and as a gastric irritant with doses above 6 gram [63]. During pregnancy, ginger did not pose a major risk for side effects or adverse events [64].

5.4. *Marich*

It has been also found to increase bioavailability, thus enhance the therapeutic efficacy of many drugs, vaccines and nutrients and have immune-modulatory, anti-oxidant, antiplatelets, antihypertensive, anti-asthmatic, antipyretic, analgesic, anti-carcinogenic, anti-

inflammatory, anti-diarrheal, antispasmodic, anxiolytic, antidepressants, hepatoprotective, anti-ulcer, anti-thyroids, anti-apoptotic, anti-metastatic, antimutagenic, antibacterial, antifungal and anti-amoebic properties [65,66,67,68]. The extract and its constituents like piperine, regulate the balance of the cytokines production of Th1, Th2, Th17, and Treg cells, reduce the accumulation of inflammatory cells, inhibit the expressions of GATA3, IL-4, IL-6, IL-1 β , ROR γ t, IL-17A and TNF- α , increase INF- γ and IL-10 secretions in BALF (Broncho-alveolar lavage fluid) and increase macrophage activation and T and B cell proliferation [69,66].

Beside this, *Marich* possess cytotoxic activity, suppresses the levels of total IgE, anti-OVA IgE, anti-OVA IgG1 and histamine release in serum, ameliorates fibrosis and infiltration of inflammatory cells, inhibits the allergic responses, inhibits Th2/Th17 responses and mast cells activation, inhibits NF- κ B, c-Fos, cAMP response element-binding (CREB) and activated transcription factor 2 (ATF-2); suppresses PMA-induced MMP-9 expression, inhibits PKC α /extracellular signal-regulated kinase (ERK) 1/2 and reduces NF- κ B/AP-1 activation. In addition, piperine also inhibits the P-glycoprotein (P-gp) and CYP3A4 functions [70,71,72]. *Piper nigrum* is found to have dose dependent antifertility effects on mice [73].

6. Discussion:

According to Ayurveda, therapeutics is of two types: 1. *Swasthasyorjaskara*- which promotes strength (immunity) in the healthy and 2. *Roganut*- which alleviates disorders. Both of these groups perform both of these functions but *Rasayana* and *Vajikarana* are mostly used for promotive treatment (C.S.Chi. 1:1/4-8) [21]. *Ayush Kwath* has both immune promoting and disease alleviating properties which can be achieved by various treatment modalities like *Rasayana*, *Satwawajaya*, *Yuktivyapashraya*, *Vyadhi Viparitarthakari chikitsa*, etc.

The *Katu* and *Tikta Rasa*, *Usna Virya* and *Deepana*, *Pachana*, *Yakriduttejaka* properties of *Ayush Kwath* help to improve *Agni* and *Srotosodhana* (improves microcirculation and tissue perforation); thus promotes proper digestion, metabolism, and absorption and acts as *Rasayana* for the development of preceding *Dhatu* and finally form *Oja*. *Oja* itself acts as immunity to prevent disease. Immunity is dependent on the condition of *Agni*. *Ayush Kwath* with its *Agni* promoting and *Kaphashamaka* properties balance *Kapha*; and with *Raktashodhaka*, *Hridhya*, *Krimighna* properties purify the blood. It is already mentioned that natural *Kapha* and pure blood promote *Oja* and *Bala* respectively. *Krimighna* is the *Prabhava* (special action) of *Tulsi* and *Sunthi* which directly acts against pathogens. The properties like *Jwaraghna* (esp. *Vatashlaishmika*, *Vishama*), *Kasahara*, *Swasahara*, *Kshayanashaka*,

Shoolaprashamana, *Swothahara*, *Kaphaghna*, *Hridayaottejaka*, *Yakridutejaka* have direct role to alleviate various clinical signs, symptoms and complications.

As this disease is considered as *Kapha-Vatolvana Hina Pitta Sannipataja Jwara*, the *Kapha Vata Shamaka* properties of *Ayush Kwath* can play a significant role in balancing the vitiated doshas. After six days of *Jwara*, *Charaka* suggests the decoction of *Pachana* drugs in the case of *Amdosha* and *Shamaniya* drugs in *Niramadosha* (C.S.Chi. 3/160) [21]. This shows that *Yuktivyapashraya* and *Vyadhiviparita* chikitsa can be done even after the involvement of *Dosha* in later stages. *Ayush Kwath* has potential psycho-neuro-immune mechanisms via evidence of a reduction in depression, anxiety, and stress in controlled trials and shows meaning response as it is a specific remedy for cough and respiratory problems; this shows the role of *Satvawajaya Chikitsa* in its management [74].

Immunity plays a key role in the pathogenesis of COVID-19 both during the early non-severe stage and during the severe stage of the disease. The early-stage strong immune response may prevent the propagation and spread of viruses inside the body thus reducing the severity of cases and early termination of infection. While during later stage, strong cell-mediated immunity of the body against the virus itself can be a factor responsible for grave consequences due to cytokine storm. The target during the early stage should be to reduce viral propagation, while at a later stage should be to reduce the inflammatory response of the immune system. Medicinal herbs with immune booster property can be an option during the early non-severe stage while herbs with anti-inflammatory and anti-thrombotic properties can be an option during a later or severe stage. Cytokine storm that is believed as a major factor responsible for complications and death of COVID-19 patients has been found to be reduced with anti-inflammatory drugs like steroids and IL-6 receptor antagonists, Anti-inflammatory interleukins (IL-10) in modern medicine [75]. The role of medicinal herbs with anti-inflammatory property on the cytokine storm is still lacking in research. Like anti-inflammatory interleukins and IL-6 receptor antagonist (Tocilizumab); IL 10 that are proposed in modern medicine to have a therapeutic role in the reduction of severity and mortality of COVID-19. Cinnamon bark that is found to decrease INF- γ and IL-4, Its anti-atherosclerotic, anti-coagulative and anti-platelet activity can be a topic of research to reduce inflammatory and thrombotic complications in COVID-19 patients. *Sunthi* due to its inhibitory effects on pro-inflammatory cytokines and *Marich* with its property of reducing the accumulation of inflammatory cells with controlled cytokine production balance can be an option to reduce cytokine storm in COVID-19 patients and need to be researched with the therapeutic trial.

Each herbal constituent of *Ayush Kwath* is found to have some role in increasing the immune response. On correlating immune-pathogenesis of COVID-19 with immune-modulatory effects of herbs, *Ayush Kwath* can be an option before infection and during the non-severe stage to enhance immune response, prevent the propagation of COVID-19 virus to lower airways and thus help in early recovery with mild symptoms. Pharmacodynamics and pharmacokinetics of this polyherbal formulation (PHF) is not yet studied, but it is believed that the pharmacological agents or the active principles of PHF may exert potentiating, synergistic, agonistic antagonistic actions resulting maximum therapeutic efficacy with minimal side effects [76,77].

The dose of each herb is mentioned in API (The Ayurvedic Pharmacopoeia of India) as 2-3 gm. powder of *Tulsi* leaves, 1-3 gm. powder of cinnamon bark, 250 mg - 1 gm. powder form of black pepper, and 1-2 gm. powder of ginger [78].

According to Ayurveda, on the basis of predominance of dosha, every person has their own different constituent, and every season and the place have their identical role over the person's *Prakriti*. According to Ayurveda, *Tikshna* properties can stimulate the urinary system thus increasing urine, and can cause sweating [30]. As these drugs have *Laghu* and *Tikshna* properties, they can cause *Srotoshodhana*, thus can increase urination and defecation in higher doses. Due to *Usna Virya*, it can cause *Pitta Vriddhi Lakshan* like hyperacidity, hot or burning sensation, excessive sweating, fatigue, loss of taste and sleep disturbances. Ginger is contraindicated in the summer and autumn season. It is mentioned that *Chandraprabhavati*, which contains *Sunthi*, *Marich* and *Dalchini*, clears fluid and *Kapha* from *Mutravaha Srotas* and *Ambuvaha Srotas*; this excess of fluid can cause cystitis, burning, and painful urination. There may be too high content of sugar and albumin in the urine [79]. These drugs seemed to increase *Pitta*, tend to have some adverse effects such as headache, sleepiness, mild diarrhea, etc. Also, there may be hypo or hyper immune sensitivity of this formulation or occurrence of chemical incompatibility due to many chemical constituents [80]. Though the maximum use of each herbs traditionally for a long time ensures that these herbs are safe but it is essential to determine dosage of PHF for adults and pediatrics in the form of bodyweight or dosage per kg and according to severity of disease, the person's *Prakriti* and his/her residing climate and region. Thus, this formulation must be evaluated using scientific methods to understand bioactive compounds responsible, their mechanism of action, and ways to regulate the activity of these compounds on COVID-19 related immunological factors. Toxicological studies and clinical trials must be done before its extensive usage.

7. Conclusion:

With various Ayurveda concepts and biomolecular studies, these Ayurveda herbs are seen to have rich sources to fight against the immuno-pathogenesis process of viral diseases, but to date, no study has been found about its effectiveness against COVID-19. *Ayush Kwath* due to its antiviral, immune-modulatory, antioxidant, anti-inflammatory, anti-platelet, anti-atherosclerotic, hepato-protective, reno-protective properties; seems to be effective in regulating immunity for the prevention and reduction of viral disease complications. As there is lack of enough evidence to support its specific role against coronavirus, there is a requirement to validate the effectiveness of these formulations with extensive biotechnological, pharmacological, and clinical research.

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9. Transparency Declaration

The authors declare that there is no conflict of interest regarding the publication of this article.

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Table 1: Contents and Properties of Ayush Kwath

S N	Name	Scientific Name	Parts used	Main Chemical Constituents	Rasa	Virya	Ayurvedic Dosha karma	Sansthanika Karma	Prop orti on	Remarks
1.	Tulsi	Ocimum sanctum Linn.	Leav es	Volatile oil (Phenol, Aldehyde), Eugenol, Ascorbic acid, Linoleic acid, Carotene	<i>Katu, Tikta</i>	<i>Ushna</i>	<i>Kapha- vatashamaka Pittabardhaka</i>	<i>Vedanahara, Deepana, Pachana, Anulomana, Krimighna, Hridhya, Raktashodhaka, Kasahara, Swasahara, Kshayanashaka, Mutrala, Vishaghna, Jwaraghna esp. useful in Vatashlaishmika, Vishama and Jirna Jwara</i>	4 part s	Prabhava (Special action): <i>Krimighna</i>
2.	Dalchini	Cinnamomum zeylanicum Breyn	Stem Bark	Cinnamaldehy de, cuminaldehyd e Eugenol	<i>Katu, Tikta, Madhu ra</i>	<i>Ushna</i>	<i>Kapha- vatashamaka Pitta vardhaka</i>	<i>Deepana, Pachana, Vajikarana., Vataanulomana, Yakridutejaka, Grahi, Hriyottejaka, Ojovardhaka, Raktashodhaka, Shelshmahara, Yakshmanashaka, Mutrajanana,</i>	2 part s	
3.	Sunthi	Zingiber officinale Rosc.	Rhizo me	Zingiberene, Zingiberol	<i>Katu</i>	<i>Ushna</i>	<i>Kapha- vatashamaka</i>	<i>Deepana, Pachana, Vrishya, Shoolaprashamana, Raktashodhaka, Hridhyottejaka, Shothahara, Kaphaghna, Swasahara, Jwaraghna, Aampachana</i>	2 part s	Prabhava: <i>Krimighna</i> Contraindica tions: <i>Pandu, Kushtha, Mutrakriccha, raktapitta, Grishma and Sharada Ritu</i>
4.	Marich	Piper nigrum Linn.	Fruit	Piperine, Piperidine, Piprettine and Chavicine	<i>Katu</i>	<i>Ushna</i>	<i>Kaphashamak a</i>	<i>Deepana, Pachana, Yakriduttejaka, Vatanulomana, Krimighna, Hridhyottejaka, Kaphaghna, Kaphamissaraka, Jwaraghna, esp. Vishamjwara pratibandhaka.</i>	1 part	