

Review on Immunological Perspectives and Therapeutic Management Strategies for COVID-19

Rushikesh K. Kakde¹, Nitin R. Kale² and Dr. Gajanan Sanap³

¹Student, Late Bhagirathi Yashwantrao Pathrikar College of Pharmacy, Pathri, Phulambri, Chhatrapati Sambhajnagar, Maharashtra, INDIA.

²Assistant Professor, Bachelor of Pharmacy, Late Bhagirathi Yashwantrao Pathrikar College of Pharmacy, Pathri, Phulambri, Chhatrapati Sambhajnagar, Maharashtra, INDIA.

³Principal, Late Bhagirathi Yashwantrao Pathrikar College of Pharmacy, Pathri, Phulambri, Chhatrapati Sambhajnagar, Maharashtra, INDIA.

¹Corresponding Author: rushikeshkakde143@gmail.com

ORCID

<https://orcid.org/0009-0007-5418-2910>



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ABSTRACT

The global spread of COVID-19 due to SARS-CoV-2 has posed unique challenges to public health. This review was carried out from the perspective of immunological and pathological changes affecting epidemiological features of the disease during progression and therapy. COVID-19 primarily affects the respiratory system but may also affect cardiovascular and neurological systems, manifesting various symptoms from fever and cough to such severe complications as acute respiratory distress syndrome (ARDS) and organ failure. Patterns in immune responses involving decreases in peripheral T cells and natural killer cells have been recognized as being part of a potential biomarker and therapeutic target. Finally, it discusses the dynamic of the transmission of SARS-CoV-2, including droplet mode spread and possible fecal-oral pathway. The virus's structural and pathological attributes are emphasized, complemented by a historical overview that chronicles its transformation from a non-threatening variant to a worldwide hazard. Various management approaches, encompassing traditional Indian medicinal practices and immune-enhancing measures such as zinc, iron, magnesium, vitamins, and herbal treatments, are assessed regarding their effectiveness in bolstering immunity and facilitating recovery. Additionally, lifestyle habits such as physical activity, sufficient rest, and proper hydration contribute to the maintenance of immune health. This extended review presents analyses of SARS-CoV-2 mechanisms of immune alteration and a unified approach toward the understanding and combat of COVID-19.

Keywords- COVID-19, SARS-CoV-2, Immunity booster, Herbs, Ayurvedic treatment.

I. INTRODUCTION

An emergency situation has been declared worldwide due to the current outbreak of coronavirus disease 2019 (COVID-19), which has caused major disruptions due to its quick spread and high mortality rate. There has been a fast increase in the number of persons who are infected with severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2), which is the agent that causes COVID-19. Patients infected with COVID-19 have the potential to develop pneumonia [1], acute respiratory distress syndrome (ARDS) symptoms that are severe, as well as failure of numerous organs [2]. Immune patterns are closely connected with the progression of disease in individuals who are infected with viruses, according to an increasing body of research. In patients

who have severe acute respiratory syndrome (SARS), a distinguishing feature is a reduction in the subsets of peripheral T cells [3]. The amount of peripheral T cells can be used as an accurate diagnostic test for SARS because it is seen that patients who have recovered experience a rapid restoration of peripheral T cell subsets. During the course of SARS, the immune system was found to be damaged, which was mentioned in another study [4]. This phenomenon was also documented. When compared with healthy donors, the number of natural killer (NK) cells was shown to be lower in patients who had Ebola, according to another study [5]. After the commencement of symptoms of Ebola virus disease, proinflammatory cytokines were shown to be high, but low cytokine levels were observed in individuals who had recovered from the disease [6]. Immune characteristics are now being identified as potential biomarkers for disease development as well as prospective treatment targets for COVID-19. This recognition comes as a result of the unraveling of the link between immune responses and COVID-19 through research[7]. Furthermore, we explore the putative mechanisms of SARS-CoV-2-induced immune alterations, their effect on disease outcomes, and their implications for prospective COVID-19 treatments. In this review, we provide a summary of the immunological characteristics of COVID-19 and include a discussion of these mechanisms [8].

Structure of COVID-19

Coronaviruses are medium-sized, spherical or pleomorphic enclosed, non-segmented (single-stranded) positive-sense RNA viruses connected with a nucleoprotein within a capsid composed of matrix protein of the Nidovirales order. The envelope features spike-like projections on its surface, composed of glycoprotein, which imparts a distinctive crown-like appearance to the virus [9].

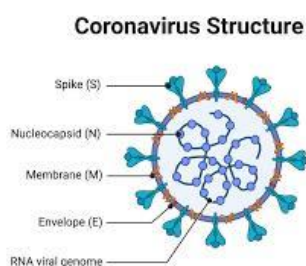


Fig.1. Structure of SARS-COV-2

Epidemiology

On 31 December 2019, the Wuhan Municipal Health Commission revealed that 27 pneumonia patients were linked to a South China seafood market, marking the initial identification of COVID-19[10]. Subsequently, the number of COVID-19 patients surged dramatically during the Chinese New Year. As of 16 May 2020, COVID-19 had impacted over 200 countries and regions, with the total number of confirmed cases reaching 4,425,485 worldwide [11]. Following the emergence of COVID-19,

researchers commenced forecasting the incubation period of SARS-CoV-2. Data gathered in January 2020 indicate that the incubation period for COVID-19 patients varies from 2 to 14 days, with an average of approximately 5 days (95% credible interval: 4.2–6.0) based on the optimal lognormal distribution model. Consequently, specialists advised that suspected patients be confined for a minimum of 14 days [12]. The mode of transmission of SARS-CoV-2 is a crucial aspect of epidemiological study. Human-to-human transmission of COVID-19 predominantly occurs by respiratory droplets; however, the potential ocular transmission of SARS-CoV-2 remains uncertain[13,14]. Numerous studies indicate that the primary complaint of many COVID-19 patients involved digestive symptoms, with nucleic acids of SARS-CoV-2 detected in fecal samples or anal swabs, suggesting the potential for an oral–fecal transmission route[15-17]. Additionally, mother-to-child transmission represents a possible pathway for COVID-19.[18,19] Fortunately, the infection rates among children are comparatively low, and the majority of hospitalized children exhibit only moderate symptoms while being sick, resulting in minimal harm to them [20-22].

II. HISTORY AND ORIGIN

The initial case of the coronavirus was reported as a cold in 1960. A Canadian research from 2001 discovered roughly 500 people with flu-like symptoms. Seventeen to eighteen cases were verified as infected with the coronavirus strain via polymerase chain reaction. Until 2002, Corona was regarded as a benign, non-fatal virus. In 2003, multiple reports documented the transmission of the coronavirus to numerous nations, including the United States, Hong Kong, Singapore, Thailand, Vietnam, and Taiwan. Numerous cases of severe acute respiratory syndrome caused by the coronavirus, resulting in over 1,000 fatalities, were recorded in 2003. This was a disastrous year for microbiologists. When microbiologists began to concentrate on understanding these issues. Following an extensive investigation, they elucidated the pathogenesis of the disease, identifying it as a coronavirus. However, a total of 8,096 patients have been identified as infected with the coronavirus. In 2004, the World Health Organization and the Centers for Disease Control and Prevention announced a "state of emergency." A separate study report from Hong Kong revealed 50 patients with severe acute respiratory syndrome, of whom 30 were identified as infected with the coronavirus. In 2012, Saudi Arabian sources documented several infected patients and fatalities. COVID-19 was initially discovered and isolated from a pneumonia patient in Wuhan, China [23].

III. SYMPTOMS

Symptoms of COVID-19 infection emerge after an incubation period of around 5.2 days [24]. The period

from the onset of COVID-19 symptoms to mortality ranged from 6 to 41 days, with a median of 14 days. The duration is dependent on the patient's age and the status of their immune system. The duration was diminished in patients aged over 70 years relative to those under 70. The primary early symptoms of COVID-19 are fever, cough, and fatigue, with supplementary symptoms such as sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia [25]. The chest CT scan revealed clinical signs of pneumonia, along with anomalous features such as RNAemia, acute respiratory distress syndrome, acute cardiac injury, and ground-glass opacities, which were associated with mortality [26]. Numerous peripheral ground-glass opacities were observed in the subpleural regions of both lungs, possibly eliciting systemic and localized immune responses that led to increased inflammation [27].

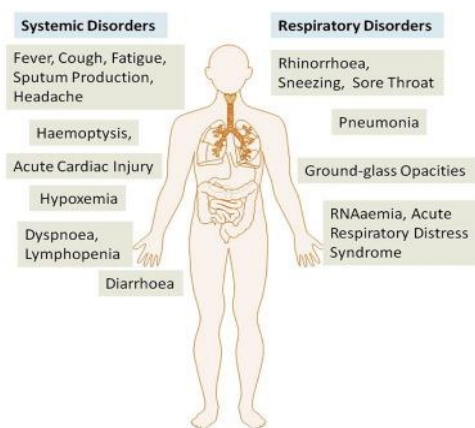


Fig. 2. Schematic representation of the covid-19 symptoms.

IV. MODE OF SPREADING

Individuals can contract the infection by close contact with an infected person exhibiting symptoms such as coughing and sneezing. The coronavirus was primarily transmitted through airborne zoonotic droplets. The virus replicated in the ciliated epithelium, resulting in cellular damage and infection at the site of infection. A 2019 study indicates that Angiotensin converting enzyme 2 (ACE2) is a membrane exopeptidase that serves as a receptor for the entry of coronavirus into human cells [28,29].

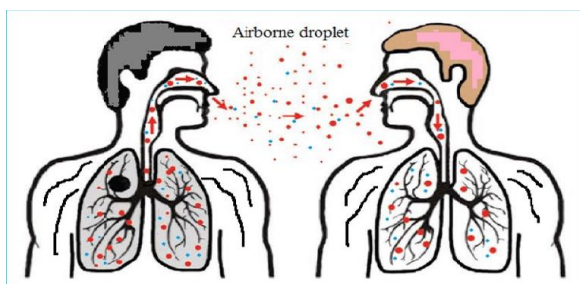


Fig 3. Transmission of corona virus via airborne droplets.

V. KEY FEATURES AND ENTRY MECHANISM OF HUMAN CORONAVIRUSES

All coronaviruses possess distinct genes in the downstream areas of ORF1 that encode proteins essential for viral replication, nucleocapsid assembly, and spike protein production [30]. The glycoprotein spikes on the outside of coronaviruses facilitate the attachment and ingress of the virus into host cells. The receptor-binding domain (RBD) is loosely associated with the virus, allowing it to infect several hosts [31,32]. Other coronaviruses primarily identify aminopeptidases or carbohydrates as essential receptors for entry into human cells, but SARS-CoV and MERS-CoV target exopeptidases. The entry route of a coronavirus relies on cellular proteases, including human airway trypsin-like protease (HAT), cathepsins, and transmembrane protease serine 2 (TMPRSS2), which cleave the spike protein and facilitate further penetration alterations [33,34]. MERS-coronavirus utilizes dipeptidyl peptidase 4 (DPP4), whereas HCoV-NL63 and SARS-coronavirus necessitate angiotensin-converting enzyme 2 (ACE2) as a principal receptor.

SARS-CoV-2 exhibits the characteristic structure of coronaviruses, featuring a spike protein and other polyproteins, nucleoproteins, and membrane proteins, including RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and auxiliary proteins [35,36]. The spike protein of SARS-CoV-2 possesses a three-dimensional structure in the receptor binding domain to sustain van der Waals forces [37]. The 394 glutamine residue in the receptor-binding domain of SARS-CoV-2 is acknowledged by the essential lysine 31 residue on the human ACE2 receptor [38]. The complete pathway of SARS-CoV-2 pathogenicity, encompassing attachment to replication, is thoroughly illustrated in (fig: 4).

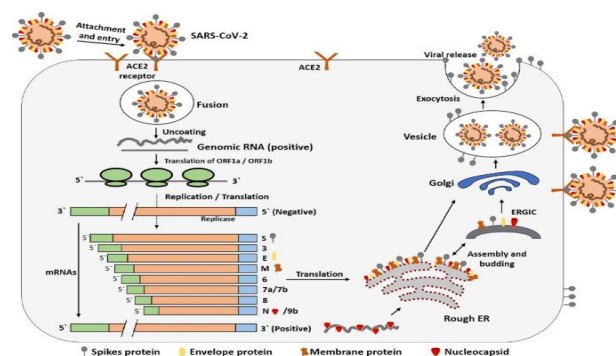


Fig 4. The life cycle of SARS-CoV-2 in host cells commences when the S protein attaches to the cellular receptor ACE2.

Following receptor contact, the conformational alteration in the S protein promotes viral envelope fusion with the cell membrane via the endosomal route. SARS-

CoV-2 subsequently injects RNA into the host cell. The genomic RNA is translated into viral replicase polyproteins pp1a and pp1ab, which are subsequently broken into smaller products by viral proteases. The polymerase generates a sequence of subgenomic mRNAs through discontinuous transcription, which are subsequently translated into corresponding viral proteins. Viral proteins and genomic RNA are then organized into virions within the endoplasmic reticulum and Golgi apparatus, then transported via vesicles and expelled from the cell. ACE2 refers to angiotensin-converting enzyme 2; ER denotes endoplasmic reticulum; ERGIC signifies the ER–Golgi intermediate compartment.

Pathology: COVID-19 is a disease that can affect many organ systems. The subsequent paragraphs detail the primary pathological changes observed in the most frequently impacted organ systems, with a specific focus on immunopathology [39].

Respiratory system: SARS-CoV-2 predominantly targets the respiratory system, infiltrating upper and lower respiratory epithelial cells, resulting in influenza-like symptoms, including fever, cough, and dyspnea [40]. The subsequent immune response is inhibited in certain individuals, resulting in unchecked viral multiplication that promotes advancement to a pulmonary phase characterized by pneumonia. In advanced disease, immune response hyperactivation leads to extensive hyperinflammation and the onset of severe conditions, including ARDS. Histological analyses revealed diverse patterns of diffuse alveolar damage (DAD) accompanied by interstitial T-cell infiltration [41].

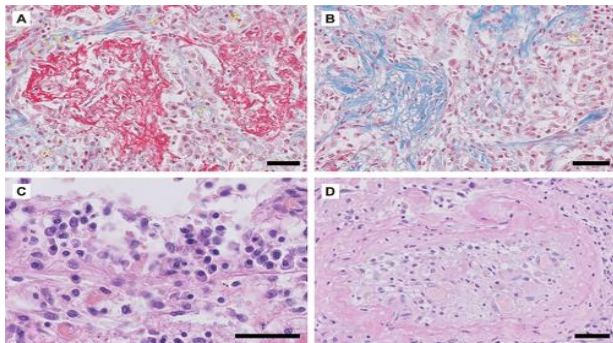


Fig.5. Exemplary instances of lung pathology associated with COVID-19. Panels A, B, and D present photomicrographs of the lung tissue from a 55-year-old male who succumbed to COVID-19 4–5 weeks following his admission to the intensive care unit (ICU) at the University Medical Center Groningen. Panel C pertains to a 63-year-old male who succumbed 2.5 weeks following his admission to the ICU. Alveolar gaps are infiltrated with fibrin, which is stained red. Organizing pneumonia is characterized by fibrosis depicted in blue; fibroblast growth is evident on the right side. Lymphoplasmacytic invasion. Occluded artery (thrombosis) with recanalization. (A, B) Martius scarlet blue; (C, D) Hematoxylin and Eosin. Scale bar = 50 μ m.

Cardiovascular system: Myocardial damage, indicated by elevated blood troponin levels, has been often documented in COVID-19 [42]. Pre-existing cardiovascular illness correlates with a poor prognosis, while COVID-19 can precipitate cardiovascular problems, including abrupt heart failure, arrhythmias, acute coronary syndrome, and myocarditis [43–45]. The latter has elicited significant worry, with numerous case reports documenting COVID-19-related myocarditis and research indicating persistent cardiac inflammation following recovery from COVID-19 [46–48]. Myocarditis may arise from the direct cardiotoxic consequences of SARS-CoV-2 infection or from indirect effects, such as cytokine-mediated cardiotoxicity or the elicitation of an autoimmune response targeting cardiac components [49]. Consistent with ACE2 expression in several cell types within the human heart, SARS-CoV-2 has been identified in multiple cells of myocardial tissue, including interstitial inflammatory cells, cardiomyocytes, and capillary endothelial cells. These data suggest that SARS-CoV-2 may directly penetrate the heart through the bloodstream, aligning with the observation of cardiac endotheliitis, or indirectly through immune cell migration. An autopsy research revealed that the detection of SARS-CoV-2 in myocardial tissue was not linked to a cardiac inflammatory response indicative of myocarditis. COVID-19-associated myocarditis may instead arise from secondary responses to the disease [50–52].

Nervous system: Neurological signs are commonly reported in COVID-19 individuals, encompassing anosmia, dysgeusia, headache, and cognitive impairment, as well as severe illnesses such as ischemic stroke and encephalopathy/encephalitis [53,54]. Cognitive abnormalities have been observed even post-recovery, likely associated with the occurrence of delirium in numerous instances [55]. The neurological manifestations may arise from the direct cytopathic consequences of SARS-CoV-2 infection or from additional illness variables, such as hypoxia-induced damage, drug-related alterations, and detrimental immunological responses [56,57]. SARS-CoV-2 has been identified in cerebrospinal fluid (CSF) and post-mortem brain tissues from COVID-19 patients, suggesting its neurotropic potential [58,59]. The virus can infiltrate the central nervous system (CNS) by the haematogenous route, which [60] includes immune cell transmigration or breaching of the blood–brain barrier, as well as through the neuronal pathway. The presence of viral particles in the olfactory bulb, along with the frequent manifestation of anosmia, suggests the olfactory pathway as a likely route for neuroinvasion by SARS-CoV-2 [61–64].

Gastrointestinal system :- Gastrointestinal (GI) manifestations of COVID-19, such as anorexia, diarrhea, and abdominal pain, are prevalent and correlate with increased disease severity [65,66]. A multitude of evidence indicates the gastrointestinal system as a plausible locus for active SARS-CoV-2 infection and replication. ACE2 was identified as being very prevalent

on the brush boundary of absorptive enterocytes in both the small and large intestine, facilitating SARS-CoV-2 infection and serving as a potential pathway for faecal-oral transfer. Moreover, single-cell transcriptomics demonstrated significant co-expression of ACE2 and TMPRSS2 in absorptive enterocytes throughout the whole gastrointestinal tract [67]. Additional evidence of viral gastrointestinal infection is indicated by the extended detection of SARS-CoV-2 RNA in the fecal samples of infected individuals [68]. In certain instances, RNA positivity remained in fecal samples despite its absence in respiratory tract samples, potentially attributable to the makeup and activity of the gut microbiota, which exhibits significant inter-individual variability and diverse host immune responses [69].

VI. THERAPEUTICS AND MANAGEMENT

Traditional medicine in India to treat covid19: Similarly, in India, traditional medicine is employed with contemporary treatments and immunizations for the management of COVID-19. Traditional Indian medicine is regarded as one of the oldest components that play a crucial part in the global healthcare system. These traditional practices encompass Siddha, Unani, Ayurveda, yoga, naturopathy, and homeopathy, and are effectively employed for the treatment of various infections. These conventional methods utilize animal products, botanical sources, and minerals for the treatment of various ailments [70]. Approximately 25,000 herbal formulations and extracts have been utilized in traditional medicine throughout South Asia. Recently, a decoction of clove (*Syzygium aromaticum*) and ginger (*Zingiber officinale* Roscoe) has been recommended for both healthy individuals and COVID-19 patients. This is due to its promotion of humoral and cell-mediated immune responses while mitigating airway hypersensitivity. Similarly, the active constituent in *Curcuma longa* Linn., curcumin, is reported to suppress the release of cytokines, including interleukin-1, interleukin-6, tumor necrosis factor- α , and other pro-inflammatory cytokines. It is recommended to be consumed with milk. The inhibition of cytokine release is considered a primary focus of research for influenza and various other pathogens. Likewise, it has been utilized in the context of COVID-19, where cytokine storm plays a crucial role in disease advancement [71].

Ayurvedic medicine to treat COVID-19 : Ayurveda is an old global therapeutic system believed to effectively address numerous illnesses without unwanted consequences. Ayurveda is equipped with several therapeutic methods for complex detrimental conditions [72]. Ayurveda healthcare specialists have recognized many bacteria and the diseases they induce. Ayurveda and Siddha originated in India and are extensively utilized to treat various ailments. The identification, isolation, and characterisation of bioactive phytochemicals in medicinal

herbs may assist in combating various infections. Consequently, repurposing old medicinal herbs may offer a new approach to fighting diverse viral infections [73].

Ayurvedic kadha : Ayurvedic medicine and its extracts have been utilized in the prophylaxis and management of viral infections. Kadha exemplifies the primordial form of medicine created by amalgamating botanical remedies and spices. It is an extract derived from less succulent or desiccated components, including herbs and spices from diverse Indian botanical substances. Preparing Kadha for oral ingestion is a significant Ayurvedic practice that enhances the pharmacological efficacy of active constituents in herbal medicines. The Indian government advocated the use of Kadha during the COVID-19 epidemic to enhance immune response and facilitate recovery [74]. The phytochemical components derived from Ayurvedic Kadha exhibit a strong binding affinity for many viral and host targets. A fact suggesting their antiviral efficacy by modulating viral replication within host cells. Recently, the Ministry of AYUSH (Ayurvedic, Yoga, Naturopathy, Unani, Siddha, and Homeopathy) in India endorsed the consumption of Kadha as an immune booster and for alleviating discomfort during the COVID-19 pandemic [75].

Immunity: The immune system possesses distinct defensive capabilities against infections. Bacteria that penetrate elicit two fundamentally distinct types of reactions. Innate immunity is inherent, with reactions resembling the encountered infectious agent, whereas acquired immunity is adaptive, exhibiting a robust response upon repeated exposure to a specific pathogen. Phagocytic cells, cells that secrete inflammatory mediators, and natural killer cells are components of innate immune responses [76]. Immunity is a complex and redundant mechanism that requires all nutrients for optimal functioning. The immune response is categorized into three phases: reaction, regulation, and resolution. The nutritional requirements are elevated during the reaction because to the necessity for mediator cell growth and production [77].

Immunity booster: The immune system is tasked with combating foreign invaders, such as pathogenic bacteria and viruses, as well as eliminating cells that become malignant within the body. Inadequate nutrition leads to heightened infections, prolonged recovery from injuries and infections, and more vulnerability to symptoms and problems arising from immune system failure. Research indicates that immune function frequently diminishes with age, and current studies propose that this decline is associated with nutrition, which may be mitigated or even halted through the maintenance of a balanced diet. Specific meals may aid in enhancing the immune system and in the prevention of colds and influenza. This is an overview of five essential nutrients required for optimal immune system function and the foods in which they can be found. The immune system preserves homeostasis by combating viruses and bacteria that can induce inflammation, sickness, and disease. Nutritional deficits

can compromise immune function, elevating both the likelihood and severity of infections [78].

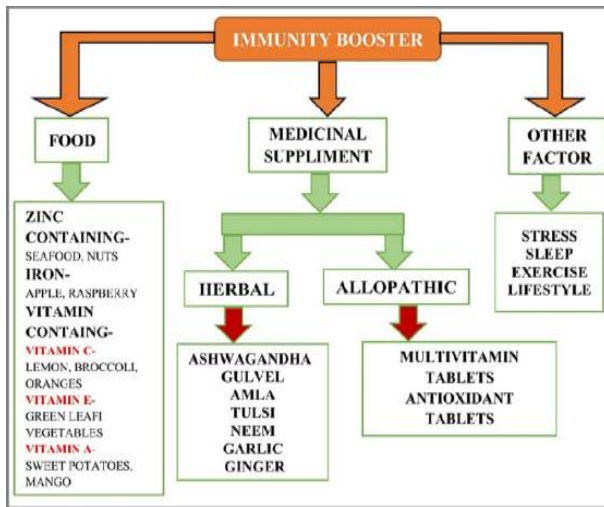


Fig.6. The various types of immunity booster.

Boosting immunity refers to the eating of specific foods that confer supplementary advantages to the body. To enhance immunity, it is essential to consume appropriate meals in the correct quantities, as seen in Fig. 6. [79].

Supplements and Immunity nutrition boosting foods for COVID-19: Although the aforementioned strategies will certainly assist, there is an urgent necessity for a rapid enhancement of your immune system to maintain its optimal functionality. If you are apprehensive about obtaining adequate nutrients from your diet, ask your physician regarding a supplementation plan to enhance your immune system. Below are few prevalent vitamins and superfoods that may provide assistance. There is evidence of several micronutrient deficits. Deficiencies in zinc, iron, and vitamins A, C, and E modify immunological responses [80].

Zinc containing: Zinc is a mineral frequently used into supplements and healthcare goods, such as lozenges, designed to enhance immune function. Zinc is essential for the growth and communication of immune cells and plays a significant role in the inflammatory response.

Iron containing: Iron is crucial for immunological function. A diet deficient in iron can lead to anemia and compromise the immune system. Iron-rich foods encompass meat, chicken, fish, shellfish, legumes, nuts, seeds, cruciferous vegetables, and dried fruit. Integrating iron-rich meals with vitamin C can enhance absorption significantly. It is important to note that excessively elevated iron levels in the bloodstream can be detrimental and may inhibit immunological function. Consequently, it is advisable to consume iron supplements alone in the presence of an iron deficit [81].

Magnesium containing: Magnesium is a crucial electrolyte that enhances the efficacy of the immune system's natural killer cells and lymphocytes. Adenosine triphosphate (ATP) is a vital energy source for our cells;

without it, cellular activity is impaired. Magnesium aids hemoglobin in our blood, which is responsible for transporting oxygen from the lungs to the entire body, thereby assisting in the context of a COVID-19 infection, as the virus targets the respiratory system. Foods abundant in magnesium include dark chocolate, black beans, avocados, and healthy grains [82].

VII. VITAMINS

Vitamin C: Vitamin C elevates serum antibody levels and facilitates the differentiation of lymphocytes, so assisting the body in identifying the requisite form of protection. One can effortlessly obtain 200 mg of vitamin C from a variety of foods, including oranges, grapefruit, kiwi, strawberries, Brussels sprouts, red and green peppers, broccoli, cooked cabbage, and cauliflower. Vitamin C serves as a potent antioxidant, safeguarding against damage caused by oxidative stress resulting from the accumulation of reactive molecules termed free radicals .

Vitamin E: Vitamin E is essential for preserving the general health of aged individuals, particularly their immune function. Vitamin E is a potent antioxidant that safeguards against several illnesses, germs, and viruses. Soaked almonds, peanut butter, sunflower seeds, and hazelnuts should be ingested to obtain the daily requirement of vitamin E [83].

Vitamin A: Beta carotene is turned into vitamin A, which is vital for a robust immune system. It functions by aiding antibodies in their response to poisons and exogenous chemicals. Excellent sources of beta carotene comprise sweet potatoes, carrots, mangoes, apricots, spinach, kale, broccoli, squash, and cantaloupe. It fosters growth and development while safeguarding epithelial and mucosal integrity [84].

VIII. HERBS

Contemporary studies on natural treatments indicate that several herbs exert multifaceted effects on immune function, influencing multiple sites within the comprehensive cascade of immunological responses and serving as potent immune stimulants. The World Health Organization reports that over 80% of the global population use herbal medications to enhance their immunity. And sustain primary health. This review article provides a comprehensive overview of many natural herbs [85].

Ashwaganda: Family: Solanaceae. Common nomenclature: Ashwagandha, Indian ginseng, Indian Winter Cherry. Biological function: It serves as an antioxidant. Upon oral dosing, Ashwagandha churna demonstrated a notable enhancement in neutrophil adherence and a delayed-type hypersensitivity (DTH) reaction. Ashwagandha churna substantially enhanced cellular immunity. Ashwagandha offers various additional advantages for both the body and the brain. For

instance, it can enhance cognitive performance, reduce blood sugar and cortisol levels, and assist in alleviating symptoms of anxiety and sadness. The entire plant of Ashwagandha (*W. somnifera*) is depicted in Fig. 7.



Fig.7.The whole plant of Ashwaganda (*W. somnifera*)

Application: A team of medical researchers in Portland has discovered that consuming whole cow's milk with Ashwagandha, a herb utilized for over 5,000 years in Ayurvedic therapy, might enhance the body's white blood cell count, hence improving immunity a universal health tonic and a remedy for various health issues. It functions as a sedative, diuretic, anti-inflammatory, immunological stimulant, energy enhancer, endurance booster, adaptogen, and anti-stress agent [86].

Tulsi (*Ocimum tenuiflorum*) : Tulsi is highly effective in addressing bacterial and fungal infections, as well as immunological conditions like as allergies and asthma. Haritha explains that Tulsi is abundant in Vitamin C and Zinc, functioning as a natural immunity enhancer. The leaves of Tulsi (*Ocimum tenuiflorum*) are depicted in Fig. 8.

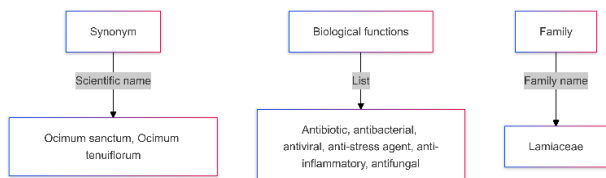


Fig.8. The leaves of Tulsi (*Ocimumtenuiflorum*)

The Tulsi plant, when kept inside, can provide protection against specific infections and disorders, including colds, coughs, and viral infections. The potent bactericidal and germicidal properties are not the sole reason Tulsi is an excellent herb for enhancing immunity [87].

Neem (*azadirachta indica*): Purified neem extracts contained immunomodulators that activate terminating

cells and macrophages. The leaves of Neem (*Azadirachta indica*) are depicted in Fig. 10.

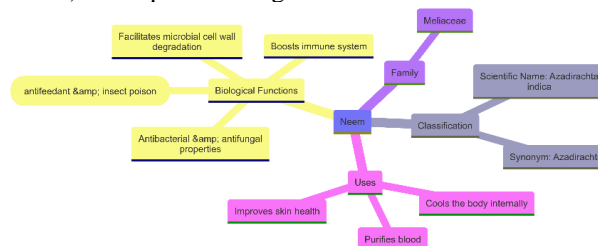


Fig 9. Overview of the Neem plant [88].



Fig.10:The Leaves of Neem *Azadirachta*indica .

Ginger (*zingiber officinale*)

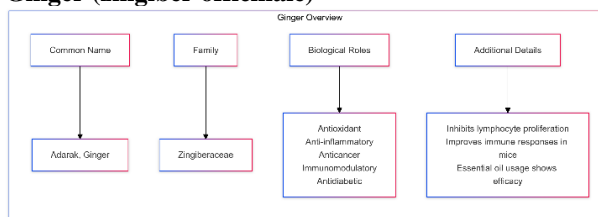


Fig no11. Overview of GINGER plant [89]



Fig.12.The Root Parts of Ginger (*Z. officinale*)

Use: Ginger can help improve immune health due to its antioxidant and anti-inflammatory effects. In fact, starting your morning with a glass of ginger tea or ginger kashayam may ward off illness and boost the immune system [90].

Turmeric (*curcuma longa*)

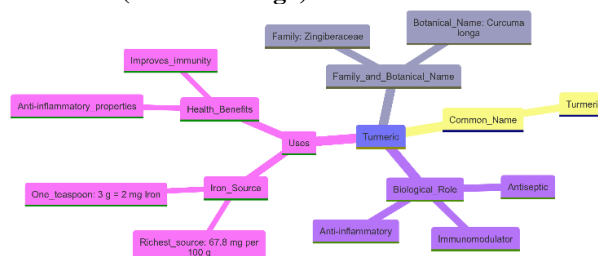


Fig.13. Overview of turmeric plant



Fig.14. The root parts of Turmeric (*curcuma longa*).
Amla (*Emblca Officinalis*)

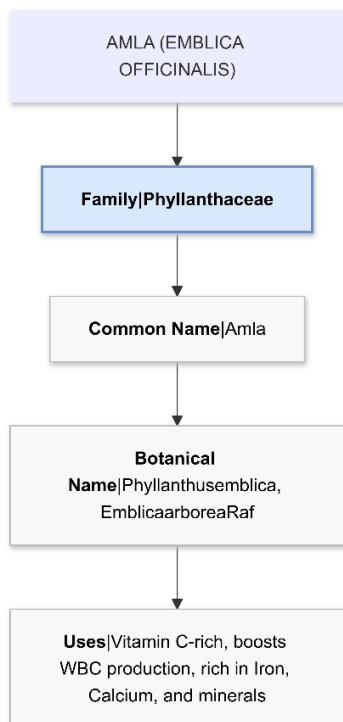


Fig.15.Overview of the amla (*emblca officinalis*).[92].



Fig.16.The fruit part of Amla (*E. officinalis*).

IX. OTHER WAYS TO BOOST THE IMMUNE SYSTEM

Exercise: Consistent physical activity is a fundamental component of a healthy lifestyle. It enhances cardiovascular health, reduces blood pressure, aids in

weight management, and provides protection against several diseases. Does it contribute to the natural enhancement and maintenance of a healthy immune system? Similar to a nutritious diet, physical activity can enhance overall health and thus support a robust immune system.

Don't Compromise on Sleep: Optimal sleep duration of 7 to 8 hours is essential for enhancing immune function; insufficient sleep results in fatigue and diminishes cognitive performance. Insufficient sleep hinders the body's ability to rest, hence compromising several physiological functions that directly affect immunity. Insufficient sleep negatively impacts the efficacy of the flu vaccine.

Stay hydrated: Consume 8 to 10 glasses of water daily to maintain hydration. Hydration aids in eliminating toxins from the body and reduces the likelihood of influenza. Additional options comprise citrus fruit drinks and coconut water to combat the heat.

Improve your diet: The diet you consume significantly influences your general health and immunity. Adopt a low-carbohydrate diet to effectively manage elevated blood sugar and hypertension. A low-carbohydrate diet will mitigate diabetes progression and emphasize a protein-rich regimen to maintain optimal health. Regularly consume vegetables and fruits abundant in beta-carotene, ascorbic acid, and other vital vitamins. Foods such as mushrooms, tomatoes, bell peppers, and green vegetables like broccoli and spinach are effective in enhancing the body's resilience against illnesses [93].

X. CONCLUSION

The COVID-19 pandemic highlights significant impacts of viral infection both on human health and global systems. The virus, SARS-CoV-2 responsible for COVID-19, has been widely studied with the goal to elucidate the structure, epidemiology, pathology, and effects that come along with it on immune responses. Its transmission dynamics are mainly respiratory droplets but can extend to other routes such as fecal-oral, so there is a need for aggressive public health measures and continued research to prevent and control outbreaks. The fact that COVID-19 may interfere with multiorgan systems, especially the respiratory, cardiovascular, and nervous systems, stresses the necessity for multidisciplinary treatment approaches and care. This immune dysregulation, with altered T-cell populations and enhanced levels of pro-inflammatory cytokines, underscores the possibility of using immune markers as both diagnostic instruments and therapeutic objectives.

Conventional and integrative medical practices like Ayurveda and use of herbal remedies have the potential to strengthen immune response and help regain health. The emphasis on dietary habits and lifestyle adjustments, including the sustenance of a nutritious diet abundant in vital vitamins and minerals, consistent physical activity, sufficient rest, and proper hydration,

corresponds with the overarching objective of enhancing immune resilience. In summary, although considerable progress has been achieved in the comprehension and management of COVID-19, the pandemic underscores the necessity of international cooperation in research, prevention, and therapeutic approaches. It has thereby integrated conventional knowledge with contemporary scientific practices to bring together a comprehensive approach in combating present and future health emergencies.

REFERENCES

- [1] Zhu, N. et al. A Novel Coronavirus from patients with Pneumonia in China, 2019. *N. Engl. J. Med.*
- [2] Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.
- [3] Chen, N. et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.
- [4] Wang, D. et al. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus-infected Pneumonia in Wuhan, China.
- [5] Li, T. et al. Significant changes of peripheral T lymphocyte subsets in patients with severe acute respiratory syndrome. *J. Infect.*
- [6] Cui, W. et al. Expression of lymphocytes and lymphocyte subsets in patients with severe acute respiratory syndrome.
- [7] Cimini, E. et al. Different features of Vdelta2 T and NK cells in fatal and non-fatal human Ebola infections.
- [8] Reynard, S. et al. Immune parameters and outcomes during Ebola virus diseases
- [9] Fehr A.R., Perlman S., "Coronaviruses: An overview of their replication and pathogenesis", *Methods in Molecular Biology* 2005
- [10] Wuhan Municipal Health Commission. Information about the current situation of pneumonia in Wuhan, 2019.
- [11] WHO. Coronavirus disease 2019 (COVID-19) Situation Report – 117, 2020
- [12] Linton NM, Kobayashi T, Yang Y, et al.. Incubation period and other epidemiological characteristics of 2019 novel coronavirus infections with right truncation: a statistical analysis of publicly available case data. *J Clin Med.* 2020;9:538.
- [13] Chan JF, Yuan S, Kok KH et al.. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet.* 2020;395:514–23.
- [14] Wu P, Duan F, Luo C, et al.. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol.* 2020. doi:10.1001/jamaophthalmol.2020.1291.
- [15] Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible?. *Lancet Gastroenterol Hepatol.* 2020;5:335–7. doi:10.1016/s2468-1253(20)30048-0.
- [16] Xu Y, Li X, Zhu B, et al.. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med.* 2020;26:502–5. doi:10.1038/s41591-020-0817-4.
- [17] Wang W, Xu Y, Gao R, et al.. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA.* 2020. doi:10.1001/jama.2020.3786.
- [18] Dong L, Tian J, He S, et al.. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. *JAMA.* 2020. doi:10.1001/jama.2020.4621.
- [19] Chen H, Guo J, Wang C, et al.. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet.* 2020;395:809–15. doi:10.1016/S0140-6736(20)30360-3.
- [20] Wei M, Yuan J, Liu Y, et al.. Novel coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA.* 2020. doi:10.1001/jama.2020.2131.
- [21] Zeng H, Xu C, Fan J, et al.. Antibodies in infants born to mothers with COVID-19 pneumonia. *JAMA.* 2020. doi:10.1001/jama.2020.4861.
- [22] Liu W, Zhang Q, Chen J, et al.. Detection of Covid-19 in children in early January 2020 in Wuhan, China. *N Engl J Med.* 2020;382:1370–1. doi:10.1056/NEJMc2003717.
- [23] Dharmendra Kumar, Rishabha Malviya, Pramod Kumar Sharma, Corona Virus: A Review of COVID-19
- [24] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, et al. Early transmission dynamics in wuhan, China, of novel coronavirus-infected pneumonia *N. Engl. J. Med.* (2020),
- [25] W. Wang, J. Tang, F. Wei Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China.
- [26] L.L. Ren, Y.M. Wang, Z.Q. Wu, Z.C. Xiang, L. Guo, T. Xu, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study *Chinese Med J* (2020)
- [27] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.

- [28] W.G. Carlos, C.S. Dela Cruz, B. Cao, S. Pasnick, S. Jamil Novel wuhan (2019-nCoV) coronavirus Am. J. Respir. Crit. Care Med., 201 (4) (2020).
- [29] CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia Radiology (2020),
- [30] S. van Boheemen, M. Graaf, C. Lauber, T.M. Bestebroer, V.S. Raj, A.M. Zaki, et al. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans.
- [31] V.S. Raj, H. Mou, S.L. Smits, D.H. Dekkers, M.A. Müller, R. Dijkman, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC.
- [32] S. Perlman, J. Netland Coronaviruses post-SARS: update on replication and pathogenesis.
- [33] I. Glowacka, S. Bertram, M.A. Müller, P. Allen, E. Soilleux, S. Pfefferle, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response.
- [34] S. Bertram, I. Glowacka, M.A. Müller, H. Lavelander, K. Gnirss, I. Nehlmeier, et al. Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease.
- [35] F. Wu, S. Zhao, B. Yu, Y.-M. Chen, W. Wang, Z.-G. Song, et al. A new coronavirus associated with human respiratory disease in China.
- [36] P. Zhou, X. Yang, X. Wang, B. Hu, L. Zhang, W. Zhang, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin.
- [37] X. Xu, P. Chen, J. Wang, J. Feng, H. Zhou, X. Li, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission.
- [38] Y. Wan, J. Shang, R. Graham, R.S. Baric, F. Li Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS j virol (2020)
- [39] Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020; 26: 681–687.
- [40] Bourgonje AR, Abdulle AE, Timens W, et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol 2020; 251: 228–248.
- [41] Dos Santos WG. Natural history of COVID-19 and current knowledge on treatment therapeutic options. Biomed Pharmacother 2020
- [42] Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020; 5: 802–810.
- [43] Inciardi RM, Adamo M, Lupi L, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. Eur Heart J 2020; 41: 1821–1829.
- [44] Hu H, Ma F, Wei X, et al. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. Eur Heart J 2021; 42: 206.
- [45] Kesici S, Aykan HH, Orhan D, et al. Fulminant COVID-19-related myocarditis in an infant. Eur Heart J 2020; 41: 3021.
- [46] Dolhnikoff M, Ferreira Ferranti J, de Almeida Monteiro RA, et al. SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. Lancet Child Adolesc Health 2020; 4: 790–794.
- [47] Rajpal S, Tong MS, Borchers J, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. JAMA Cardiol 2020; 6: 116–118.
- [48] Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020; 5: 1265–1273.
- [49] Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nat Rev Cardiol 2021; 18 169–193.
- [50] Nicin L, Abplanalp WT, Mellentin H, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. Eur Heart J 2020; 41: 1804–1806.
- [51] Lindner D, Fitzek A, Bräuninger H, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol 2020; 5: 1281–1285.
- [52] Tavazzi G, Pellegrini C, Maurelli M, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail 2020; 22: 911–915.
- [53] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77: 683–690.
- [54] Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain 2020; 143: 3104–3120.
- [55] Hampshire A, Trender W, Chamberlain SR, et al. Cognitive deficits in people who have recovered from COVID-19 relative to controls: an N=84,285 online study. medRxiv 2020.
- [56] Solomon IH, Normandin E, Bhattacharyya S, et

- al. Neuropathological features of Covid-19. *N Engl J Med* 2020; 383: 989–992.
- [57] Kantonen J, Mahzabin S, Mäyränpää MI, et al. Neuropathologic features of four autopsied COVID-19 patients. *Brain Pathol* 2020; 30: 1012–1016.
- [58] Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* 2020; 94: 55–58.
- [59] Huang YH, Jiang D, Huang JT. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain Behav Immun* 2020; 87: 149.
- [60] Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med* 2020; 383: 590–592.
- [61] Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J Med Virol* 2020; 92: 699–702.
- [62] Matschke J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol* 2020; 19: 919–929.
- [63] Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. *Cell* 2020; 183: 16–27.e1.
- [64] Morbini P, Benazzo M, Verga L, et al. Ultrastructural evidence of direct viral damage to the olfactory complex in patients testing positive for SARS-CoV-2. *JAMA Otolaryngol Head Neck Surg* 2020; 146: 972–973.
- [65] Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut* 2020; 69: 1002–1009.
- [66] Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. *Gastroenterology* 2020; 159: 81–95.
- [67] Zhang H, Kang Z, Gong H, et al. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. *Gut* 2020; 69: 1010–1018.
- [68] Wu Y, Guo C, Tang L, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020; 5: 434–435.
- [69] Yang L, Tu L. Implications of gastrointestinal manifestations of COVID-19. *Lancet Gastroenterol Hepatol* 2020; 5: 629–630.
- [70] Guo Y-R, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak—an update on the status. *Mil Med Res.* 2020;7(1):1–10.
- [71] Zeng F, et al. Association of inflammatory markers with the severity of COVID-19: a meta-analysis. *Int J Infect Dis.* 2020;96:467–74.
- [72] Goothy SSK, et al. Ayurveda’s holistic lifestyle approach for the management of coronavirus disease (COVID-19): Possible role of tulsi. *Int J Res Pharm Sci.* 2020.
- [73] Janiaud P, et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. *JAMA.* 2021;325(12):1185–95.
- [74] Maurya, DK, Sharma D. Evaluation of traditional ayurvedic kadha for prevention and management of the novel coronavirus (SARS-CoV-2) using in silico approach. *J Biomol Struct Dyn.* 2022;40(9):3949–64.
- [75] Hirsch JS, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int.* 2020;98(1):209–18.
- [76] Delves PJ, Roitt IM. The immune system. First of two parts. *N Engl J Med* 2000;343(1):37-49.
- [77] Percival SS. Nutrition and immunity: balancing diet and immune function. *Nutrition Today* 2011;46(1):12-7.
- [78] Wessels I, Maywald M, Rink L. Zinc as a Gatekeeper of Immune Function. 2017, *Nutrients*; 9(12), 1286-1298.
- [79] Spritzler F. Ten Magnesium-Rich Foods that are Super Healthy. <https://www.healthline.com/nutrition/10-foods-high-in-magnesium#section7> (Accessed August 22, 2018).
- [80] Anywara G, Kakudidia E, Byamukamab R, Mukonzoc J, Schubertd A, Oryem-Origaa H. Indigenous traditional knowledge of medicinal plants used by herbalists in treating opportunistic infections among people living with HIV/AIDS in Uganda. *J Ethnopharmacol.* 2020; 246: 1-13.
- [81] Chauhan RS. Efficacy of herbal immune plus in enhancing humoral and cell mediated immunity dogs. *Livest Int.* 2001; 5: 12-18.
- [82] . Kuttan G. Use of *Withania somnifera* as an adjuvant during radiation therapy. *Indian J Exp Biol.* 1996; 34: 854-856.
- [83] Upadhyay SN, Dhawan S, Garg S, Talwar GP. Immunomodulatory effect of neem (*Azadirachta indica*) oil. *Int J Immunopharmacol.* 1992; 14: 1187- 1193.
- [84] Vasudevan SK. Augmentation of murine natural killer cell and antibody dependent cellular cytotoxicity activities by *Phyllanthus emblica*, a new immunomodulator. *J Ethnopharmacol.* 1994; 44: 55- 60.

- [85] Gupta MS, Shivaprasad HN, Kharya MD. Immunomodulatory Activity of the Ayurvedic Formulation "Ashwagandha Churna". *Pharm Biol*, 2006; 44(4): 263-265.
- [86] Somasundaram S, Sadique J, Subramoniam A. Influence of extraintestinal inflammation on the in vitro absorption of ¹⁴C-glucose and the effects of anti-inflammatory drugs in the jejunum of rats. *Clin Exp Pharmacol Physiol*, 1983; 10: 147-152.
- [87] Mahady GB, Gyllenhal C, Fong HH, Farnsworth NR. Ginsengs: a review of safety and efficacy. *Nutr Clin Care*, 2000; 3: 90-101.
- [88] Tarver T. The Review of Natural Products. *J Consum Health Internet*, 2014; 18(3): 291-292.
- [89] Seely D, Dugoua JJ, Perri D. Safety and efficacy of Panax ginseng during pregnancy and lactation. *J Clin Pharmacol*, 2008; 15: 87-94.
- [90] Scaglione F, Ferrara F, Dugnani S, Falchi M, Santoro G, Fraschini F. Immunomodulatory effects of two extracts of Panax ginseng C.A. Meyer. *Drugs Exp Clin Res*, 1990; 16(10): 537-542.
- [91] Schroeder HW, Cavacini L. Structure and function of immunoglobulins. *J Allergy Clin Immunol*, 2010; 125(2): 41-52.
- [92] Lindsay B. The immune system. *Essays Biochem*, 2016; 60(3): 275-301.
- [93] Ryu HS, Kim HS. Effect of Zingiber officinale Roscoe extracts on mice immune cell activation. *Korean J Nutr*, 2004; 37(1): 23-30.