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RESEARCH ARTICLE

INDIAN HERBS: A POSSIBLE PREVENTIVE MEASURE AND IMMUNITY BOOSTERS AGAINST CORONAVIRUS DISEASE (COVID-19)

Raminderjit Kaur, Shikha Choudhary, Sunil, Rahul and Neha Minocha
K. R. Mangalam University, Sohna Road, Gurugram-122103 Haryana, India.

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Abstract

In humans, coronaviruses are embraced in the span of viruses that affects the respiratory system and kidney; it shows symptoms like common cold, severe acute respiratory syndrome (SARS), fever, cough, diarrhoea etc. Transpire the infectious diseases associated with SARS became a crucial ultimatum to public health. COVID-19 proliferates quickly and is the principal reason of its wide spread in many countries. It is observed from many studies that COVID-19 predominately attacks the people with low immunity response against the virus. Immune response by acquired by COVID-19 basically have 2 phases i.e., during the incubation and non-severe phases and elimination of the virus and prohibition the development of disease to severe stages is only possible with a specific adaptive immunity. Hence, it's necessary to adopt the various strategies for boosting immune response against virus. This review focused in the use of the herbal products for strengthen the immunity of all aged groups against COVID-19. It is observed from various studies that many of the phytochemicals have the capability to inhibit lipid per-oxidation, decreases the oxidative stress, suppresses the activated T-cells (key mediators of antiviral immunity), stimulated phagocytosis of neutrophils, increases the concentration of various inflammatory mediators like cytokines, interleukin, tissue necrosis factor etc. Therefore, herbal drugs have the ability to boost immunity against antigen. In this review, we mainly discussed about the mechanism of increasing immunity by various herbal drugs like Green tea, Ashwaganda, Broccoli, Kutki, Jhandu and many more against the COVID-19.

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Introduction:-

Coronavirus is the crucial pathogen that predominately attacks the human respiratory system. Precursory outburst of coronavirus encompass the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV, these are previously distinguished as fatal negotiator that further be the reason for public health threat. It has been observed in the late December, the clump of patients was admitted in hospitals with a beginning recognition of pneumonia of an unknown etiology (1, 2). These patients were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China. Preliminary outlines divined the beginning of a prospective Corona virus outbreak given the judgment of a replicating number for 2019 Novel (New) Corona virus, which is classified as COVID-19 by WHO on Feb 11, 2020 (3). More than 100 years since the

outburst of 1918 influenza pandemic, we are now facing another pandemic. As the outburst of COVID-19 spreads in almost every continent, compelling us to reside with this virus for conceivably a long time. As now scientists and clinicians have grasped abundant of corona virus disease and pathogenesis (4), it has been observed that not all people exposed SARS-CoV-2 are necessarily infected. Moreover, the not all infected patients develop severe respiratory illness. From this observation, SARSCoV-2 infection can be roughly divided into three stages as below: (5)

Stage I: an asymptomatic incubation period with or without detectable virus.

Stage II: non-severe symptomatic period with the presence of virus.

Stage III: severe respiratory symptomatic stage with high viral load.

Individuals of stage I should become the carrier and are least manageable because at some extent, they spread the virus unknowingly, as in Germany the first asymptomatic transmission was reported (6). COVID-19 infects all age groups evenly, but the patients over 65 years are at high risk and there are chances to progression of disease in severe phase (7). One of the significant queries that why only some people develop severe disease, at the same time others doesn't. Understandably, the traditional perception based on overall immunity of infected patient cannot explain this broad spectrum disease presentation. Immunity is the condition of confrontation of an organism to overwhelm biotic and abiotic pathogens and their harmful effects that prevents the spread of the disease (8). There are basically 2 components of immunity i.e. specific and non-specific. The non-specific component deed as the obstacle or eliminator of vast array of pathogens irrespective of their antigenic composition. Additional components of immune system develop pathogen-specific immunity and adapt themselves to encounter the disease (9, 10). An immune system may contain innate and adaptive components. The innate system is composed of primordial bone marrow cells that are prearranged to recognise foreign substance and to fight against it (11). On the other hand, adaptive component include typical lymphatic cells that further helps in identifying self-substance and not to react. Moreover, innate immunity is also called as "Native Immunity" and it prevail by probity of an organism's configuration which is its genetic make-up, with lacking an extrinsic stimulation or primitive infection. However, it is categorised into two kinds, Non-specific which is a intensity of resistance to all infections and specific one that only resist a certain types of micro-organisms (12). At the same time, adaptive immunity can also be classified on the basis of inauguration of immunity i.e., "naturally acquired" that explains through chance contact with disease causing agent and "artificially acquired" which emerge through the vaccinations (13). Both of these immunities can further classified as "active immunity" which last for lifetime and "passive immunity" can be shortly lived, it can be adopted through the exposure (injection or infusion) of antibodies or activated T-cells from an immune host. The diagram below summarizes these divisions of immunity in Fig. 1. Activated immunity can further sub-divided on the basis of involvement of type of immune mediator; Humoral immunity is developed by release of antibodies however, cell mediated immunity includes T-lymphocytes alone. Humoral immunity is in activate phase when there is generation of its antibodies by the organism whereas transportation of antibodies between the individual classified it in passive phase. Likewise, cell-mediated immunity is active when the organisms' T-cells are stimulated and passive when T cells come from another organism (14).

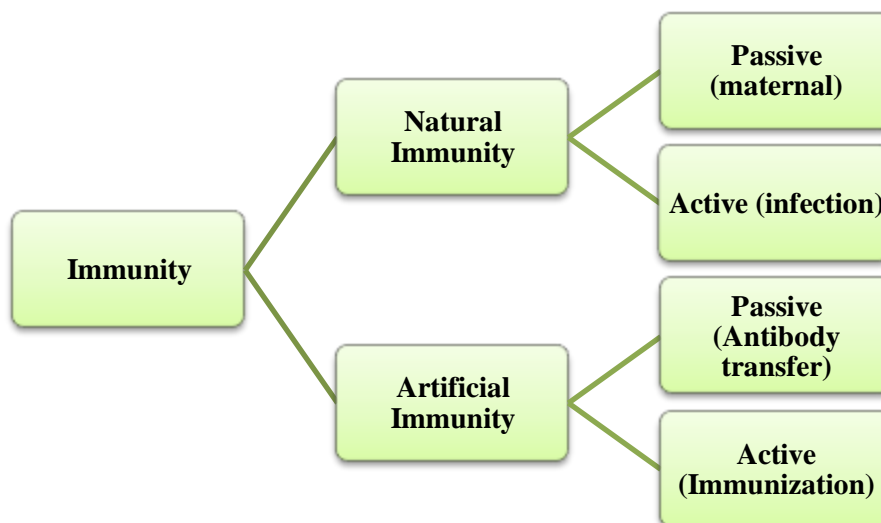


Fig. 1:- Summarization of division of immunity.

Signs and symptoms of COVID-19:

The appearing of symptoms of COVID-19 (Fig 2) infection could be after an incubation period. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days. The age of the patient and its immunity describes the range of period for the particular patient. The patients who are older than 70 years have less surviving rate with shorter period of days as compared to patients less than 70 years. The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia (15).

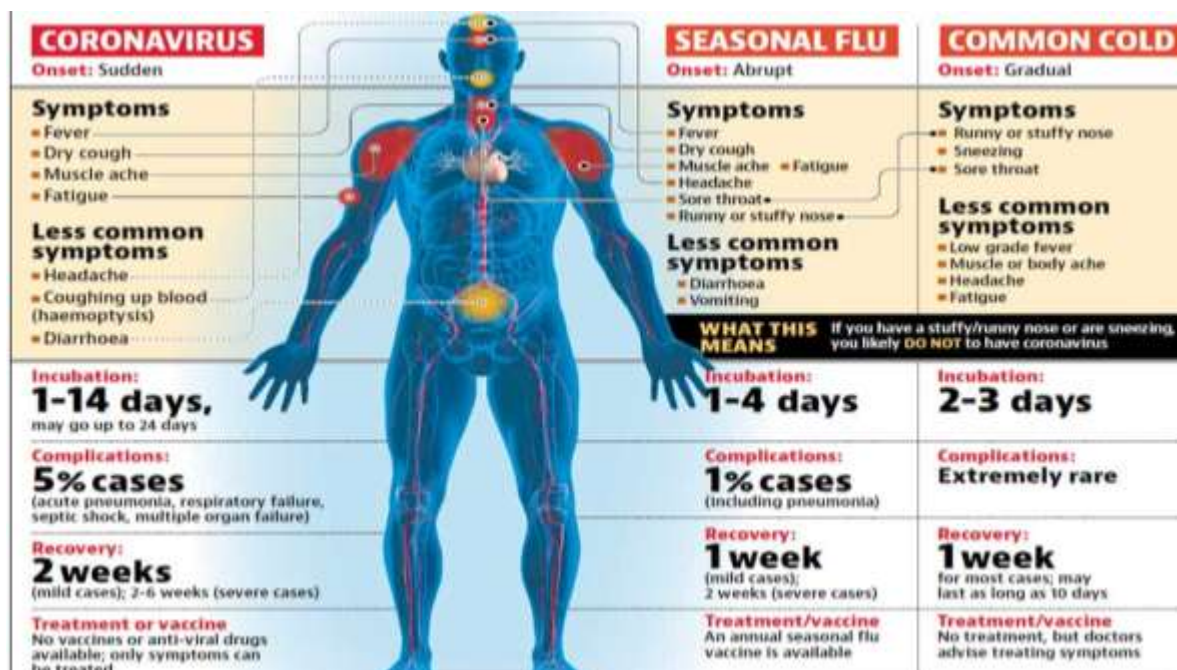


Fig 2:- Differentiate between the symptoms, incubation period and severity of COVID-19, Common flu and Seasonal flu. (16).

Incubation period of Corona Virus:

The incubation period (**time from exposure to the development of symptoms**) of the virus is estimated to be between 2 and 14 days based on the following sources (17)

1. The World Health Organization (18).
2. China's National Health Commission (NHC) had initially estimated an incubation period from 10 to 14 days (19)
3. The United States' CDC estimates the incubation period for COVID-19 to be between 2 and 14 days (20).
4. DXY.cn, a leading Chinese online community for physicians and health care professionals, is reporting an incubation period of "3 to 7 days, up to 14 days" (21).

Comparison between the incubation periods of various viruses causes SARS:

The incubation period is the time between infection and symptom onset and an important epidemiologic distribution; it is frequently involved in case definitions used to regulate appropriate quarantine periods (22). This period is extensively delineated because it is beneficial in infectious disease superintendence and control, in which the time of symptom onset may be the only indication of the time of infection. Severe acute respiratory syndrome (SARS) offers a dramatic example: by expeditiously dictate the maximum incubation period of SARS, public-health officials were able to set quarantine periods and cease a prospective pandemic without the assistance of a vaccine or treatment. The incubation period thus plays a crucial part in monitoring for healthcare-accompanying infections, and may help in detection (23). The incubation period of different viruses are reported in table 1.

VIRUS	INCUBATION PERIOD (typical case)
Noval coronavirus	2-14 days, or 0-24 days
SARS	2-7 days, as long as 10 days

MERS	5 days (range 2-14)
Swine Flu	1-4 days, as long as 7 days
Seasonal Flu	2 days (1-4 range)

Table 1:- Comparison between the incubation periods of various viruses.

Two-phase immune responses induced by COVID-19 infection:

It has been observed clinically that the immune response acquired by SARS-CoV-2 infection are of two phase i.e., during the incubation and non-severe phases, elimination of the virus and prohibition the development of disease to severe stages is only possible with a specific adaptive immunity. Therefore, we have to adopt the strategies to boost the immune response as it is the necessity of living during these phases. Our body generates specific anti-viral immunity with the development of endogen protective immune response which further depends upon the good general health and genetic background (e.g. HLA) of organism. Moreover, impairment of this protective immune response causes the invading of virus that further damages the affected tissues, especially the organs that have ACE2 receptors, e.g. lungs, intestine and kidneys. This massive destruction could be the reason for induction of inflammatory responses in the lungs that are arbitrated by the pro-inflammatory macrophages or granulocytes. Lung inflammation is one of the major etiologic reasons of life-threatening respiratory diseases at chronic stages. Therefore, efforts should be made to suppress the inflammation and to overcome the symptoms (24).

The role of Cytokine storm in lung damage:

The cytokine release syndrome (CRS) appears to influence the patients with serious diseases. As lymphocytopenia frequently observed in the patients with COVID-19, therefore CRS spawn by SARS-CoV-2 has to be arbitrating by leukocytes other than T cells and blocking IL-6 is efficacious in this condition (25). However, inhibiting the release of IL-1 and TNF-alpha may bring the beneficial results in patients with severe condition whilst many of the Chinese clinician claims the effectiveness of mesenchymal stromal/stem cells (MSCs) in severe cases with COVID-19 infection (26). One of the major challenges has been observed in the severely affected patients that T-cells are not rigorously invigorating by SARS-CoV-2 infection, hence, MSCs required to be stimulated by IFN γ to employ its anti-inflammatory action (Fig 2). Lung damage is the utmost stumbling block to recuperation in those severe patients. It has been seen from various preclinical studies that the animal models with bleomycin-induced lung injury, Vit B3 (niacin or nicotinamide) is the one of the potent treatments in halting the lung tissue damage (27).

The activation of cytokine plays a crucial role in the prevention of inflammatory response and clearance of pathogen. As alveolar macrophages are not able to inhibiting overwhelm of pathogen therefore, chemokines further activated neutrophils which causes phagocytosis due to which formation of reactive oxidative species occurred results in the necrosis of alveoli. (28)

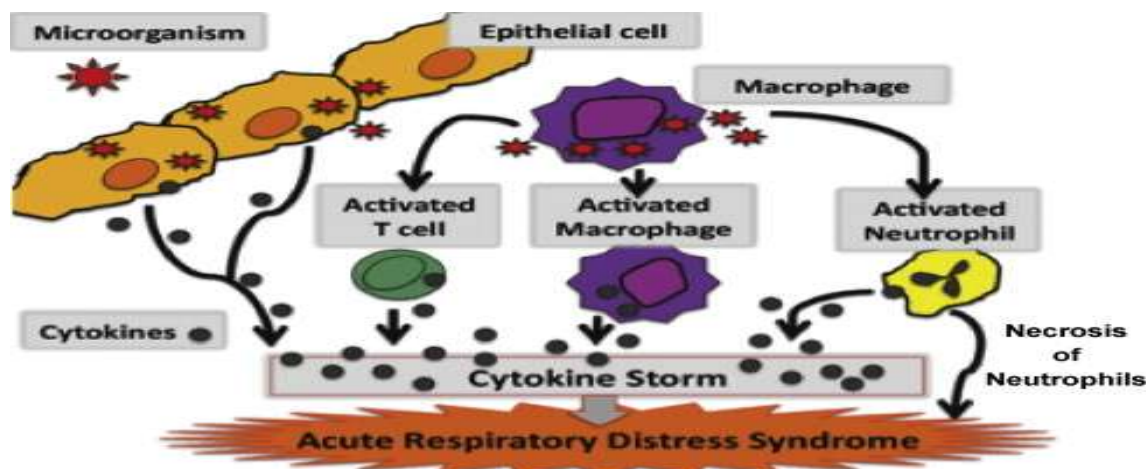


Fig 3:- Proposed mechanism for the cytokine storm and lung damage in COVID-19 patients. (28).

The pathophysiology of HLA haplotypes in SARS-CoV-2 infection:

The classical aspirant in suppression of genetic susceptibility in infectious diseases is the major-histocompatibility-complex antigen loci (HLA). It has been suggested by Immunologists that cell antigen receptors, on CD4+ or CD8+

T cells concede the conformational structure of the antigen-binding-groove together with the associated antigen peptides (29). Hence, distinct HLA haplotypes are accompanying with different diseases susceptibilities. Therefore, it is recognised that if HLA molecules will have increased binding identification to the SARS-CoV-2 virus peptides on the cell surface of antigen of host cell could be produce the beneficial effect (30). Undeniably, the susceptibility to various infectious diseases such as tuberculosis, leprosy, HIV, hepatitis B, and influenza is auxiliary with particular HLA haplotypes. Consequently, it is imperious to research whether particular HLA loci are accompanying with the expansion of anti-SARS-CoV-2 immunity and, if so, to recognize the alleles, either class I or II, that illustrate organization of protective immunity. Upon the recognition of dominant allele only simple kits will be used for the detection. This direction is crucial for (1) strategic clinical management; (2) evaluation of the efficacy of vaccination in different individuals in the general population; (3) assignment of clinical professional and managerial teams amid interactions with COVID-19 patients (31, 44)

Hyaluronan: a potential cause of fatalities:

Acute respiratory distress syndrome (ARDS) is associated with the activation of innate immunity against any virus which further lead to respiratory failure with the quick occurrence of inflammatory response in the lungs and that could give rise to necrosis of alveoli cells which proven fatal for patient. The symptoms of ARDS patients include short/rapid breathing, and cyanosis. The patients with emergency conditions are admitted in intensive care unit where they are treated with the mechanical supports such as extracorporeal membrane oxygenation (ECMO) and ventilators. It is observed in the CT scan that the lungs of these patients are filled with fluid in the form white patches called as “ground glass”. Although, it is proven with the reports of autopsies that lungs are filled with clear liquid jelly. Moreover, hyaluronan (HA) would be the pathological reason of ARDS. The COVID patients are associated with the high level of cytokines (IL-1, TNF) which further lead to the stimulation of HA-synthase-2 (HAS2) in CD31 endothelium, EpCAM lung alveolar epithelial cells, and fibroblasts, shown in Fig 3. Markedly, hyaluronan has the capacity to absorb water up to 1000 times its molecular weight. Hence, decreasing the level or blocking the release of hyaluronan will be the effective measure for helping COVID patients to breathe properly (32).

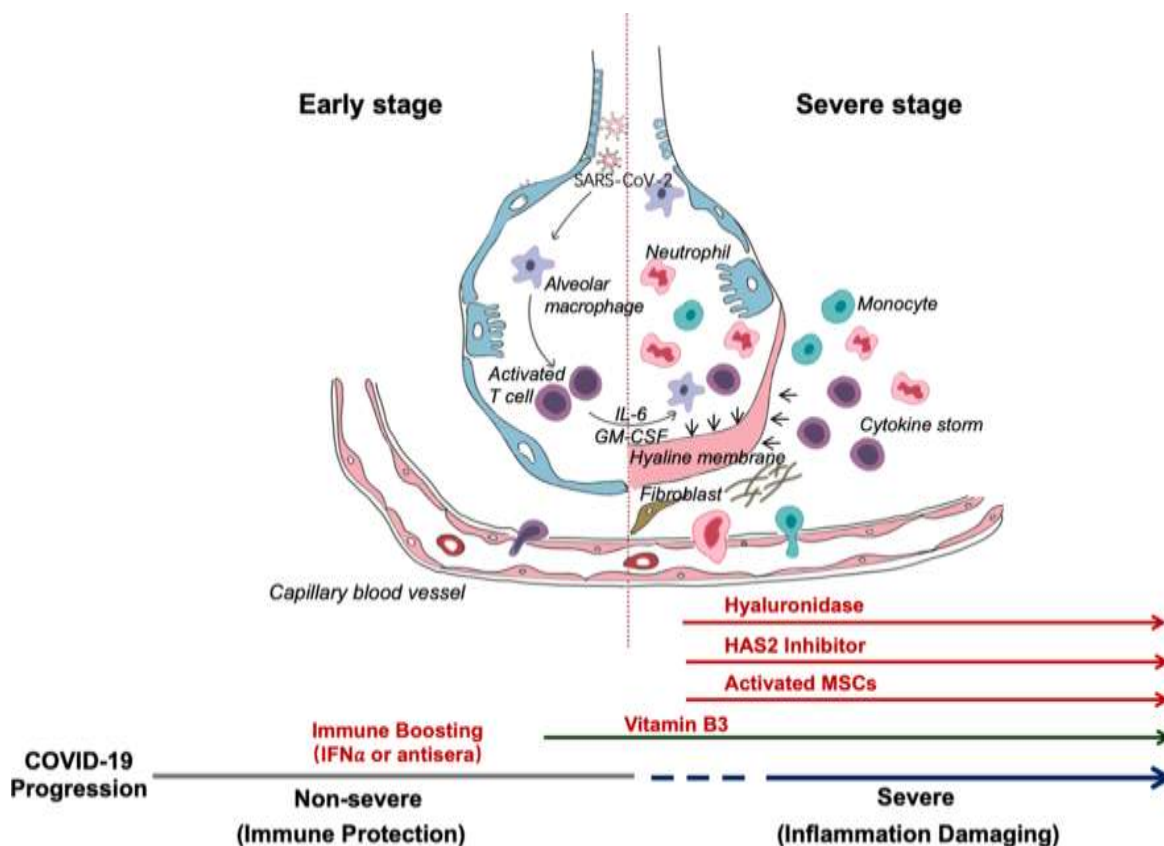


Fig. 4:- Schematic representation of the progression of COVID-19 infection and potential adjuvant interventions (33).

Potential Immune Evasion Mechanisms:

As the incubation period of COVID-19 is longer of 2-14 days as compared with influenza because Corona virus specifically remodel to evade immune detection bedew human immune responses. SARS-CoV and MERS-CoV both of these viruses are the members belongs to betacoronavirus genus therefore, immune evasion mechanism is quite similar with each other (Fig 4). The viral proteins include membrane (M) or non-structural (NS) proteins (eg. NS4a, NS4b, NS15) are the key molecules in host immune modulation. In concurrence with the previously mentioned research that the lower response of type I interferon could lead to poor outcomes i.e. death of the patient. For adaptive immune evasion, antigen extended via MHC class I and MHC class II was downregulated when the macrophages or dendritic cells were contaminated with MERS-CoV, which would conspicuously decline T cells activation (34)

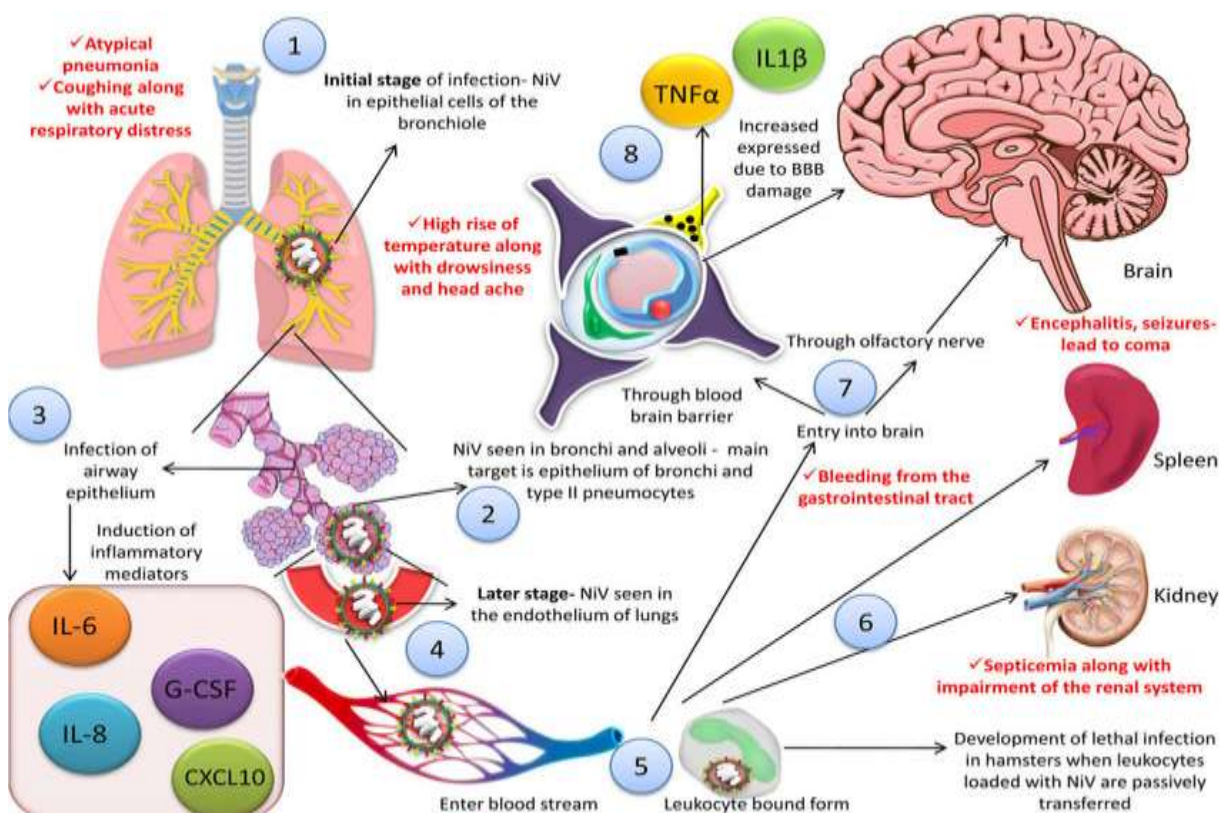


Fig 5:- Potential immune evasion mechanisms shared by SARS-CoV, MERS-CoV and SARS-CoV-2 (35).

Prophylactic vaccines: is it possible?

Many countries are endeavour towards the discovery of effective vaccine for SAR-CoV-2 with the rapid increase of its spread. Within the few weeks of outbreak, researchers have been accomplished to ignite SAR-CoV-2 vaccine development. They have gained knowledge from and MERS vaccines development path (36). The target antigen selection and vaccine platform are probably based on SARS-CoV and MERS-CoV vaccine studies, summarized in Table 2 (37). It has revealed from the clinical and pre-clinical studies that Full-length spike (S) or S1 which contains receptor binding domain (RDB) would be the effective vaccine antigen as it results in neutralizing antibodies that inhibited the host cell attachment and infection, described in Table 2. Curiously, nucleic acid-based vaccine, DNA vaccine, showed the most advance platform in response to appearing pathogens. However, during the outbreak of Zika virus DNA was the first applicant entered in the clinical trial (NCT02809443) (less than 1-year after the outbreak) for the development of vaccine against Zika virus. As per modern technological advancement, mRNA vaccine, another nucleic acid-based vaccine should be opted as troublesome vaccine technology, therefore efforts have been made to design the mRNA vaccine with better stability and protein translation efficiency thus it could persuade vigorous immune responses (38)

Vaccine platform	Immunogen
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Viral vector	Full-length Spike or S1, Vector used: ChAd or MVA
Subunit	Full-length Spike, S1, RDB, nucleocapsid formulated with various adjuvants and/or fused with Fc
Virus-like particles	RDB, S or Co-expressing of S1, M, and E Produced in baculovirus
Inactivated	Whole virus inactivated by Formaldehyde or gamma irradiation
Live-attenuated virus	Mutant MERS-CoV and SARS-CoV or recombination with other live attenuated virus
DNA	Full-length Spike, or S1im follow by electroporation

Table 2:- Selected antigens for development of vaccine have been tested for SARS-CoV and MERS-CoV.

Effect of vaccination on immune system:

Multiple procedures are arrogated in the formation of COVID vaccines that principally include target antigen is surface-exposed spike (S) glycoprotein or S protein for neutralizing antibodies. Various S-protein-based procedures have been strived for thriving COVID vaccines, e.g., use of full-length S protein or S1-receptor-binding domain (RBD) and expression in virus-like particles (VLP), DNA, or viral vectors (39). The S protein molecule contains two subunits, S1 and S2. The S1 subunit has an RBD that binds with its host cell receptor, angiotensin-converting enzyme 2 (ACE2), however the S2 subunit conciliate amalgamation between the virus and host cell membranes for liberating viral RNA into the cytoplasm for replication (40). Therefore, S-protein-based vaccines should more effectively used as it releases that further inhibiting viral receptor binding as well as un-coating of virus genome. It is observed that the C-terminal domain of the S1 subunit of porcine Deltacoronavirus contains the immune-dominant region, and the immune response to this region results in most potent neutralizing effect (41). Recombinant adenovirus-based vaccine expressing MERS-CoV S protein persuade systemic IgG, secretory IgA, and lung-resident memory T-cell responses when injected intra-nasally into and yield long-lasting neutralizing immunity to MERS spike pseudotyped virus, as a consequence it is proposing that the vaccine may confer protection against MERS-CoV (42).

Herbal drugs used to boost immunity:

In the wake of COVID-19 pandemic, there have been a lot of interests in ways to strengthen the immune system; therefore, it became more important to build up the first defence against the deadly virus. Immunity cannot be built up in a day, but it can be possible by eating a well-balanced diet and being physically and mentally active and maintaining good health. There are however, many phyto-chemicals extracted from the herbal drugs which are known to boost your immunity. As from the primitive period, herbs and spices were well known for their medicinal properties. According to the World Health Organisation, around 80% of the world's population uses herbal medicines for primary health care, particularly across Europe and South Asia. Studies revealed that many of these herbs not only have anti-inflammatory properties, but also help boosting the body's natural immunity. And unlike allopathic medicines like antibiotics, which can have serious side effects, most of these herbs and spices are relatively safe. Some of the herbal drugs have been discussed below:

1) Garlic:

Biological source: *Allium sativum*

Immunity boosting mechanism: It can scavenge free Radicals and act as successful anti-oxidant. It increases the production and release of Nitric Oxide (NO) that is further responsible for enhanced release of IFN-alpha in humans, beneficial against viral disease. In addition, it can enhance Natural Killer Cells and ultimately stimulate immune response (44).

2) Mushroom:

Biological source: *Agaricus bisporus*

Immunity boosting mechanism: These include augmenting the immune system through stimulating lymphocytes, NK cells and macrophages thus enhancing the cytokine production. (45)

3) Blueberries:

Biological source: *Ericaceae vaccinum*

Immunity boosting mechanism: Blueberries alleviate immunomodulation, lighten oxidative stress, and modulate the immune function of T-cells (46).

4) Andrographis:**Biological source: Andrographis paniculata**

Immunity boosting mechanism: It significantly increased the activities of anti-oxidant defence enzymes such as catalase, superoxide dismutase, glutathione-S-transferase and reduced glutathione content. The extract significantly inhibits lipid peroxidation by lowering the levels of thiobarbituric-acid-reactive substances in the liver and kidney of diabetic rats. A pre-treatment of andrographolide was reported to significantly attenuate the accumulation of the phorbol-12-myristate-13-acetate- (PMA-) induced formation of ROS and N-formyl-methionyl-leucyl-phenylalanine- (fMLP-) inducing adhesion of rat neutrophils (47).

5) Chinese Skullcap:**Biological source: Scutellaria baicalensis**

Immunity boosting mechanism: It significantly inhibited interleukin (IL)-4 productions, thus boosting the human immune system (48).

6) Cordyceps:**Biological source: Cordyceps militaris**

Immunity boosting mechanism: It induced the highest elevation of nitric oxide production and enhanced phagocytic activity. It also significantly induced the mRNA expression of TNF- α and IL-10 and the levels of phosphorylated MAPK (mitogen-activated protein kinase) (49).

7) Ginger:**Biological source: Zingiber officinale**

Immunity boosting mechanism: It suppresses cell proliferation and arrests cell cycle in G2/M phase. It also induces apoptosis, chromatin condensation (50, 51).

8) Broccoli:**Biological source: Brassica oleracea**

Immunity boosting mechanism: A chemical in broccoli switches on a set of antioxidant genes and enzymes in specific immune cells, which then combat the injurious effects of molecules known as free radicals that can damage cells and lead to disease. Free radicals are byproducts of normal body processes, such as the metabolic conversion of food into energy, and can also enter the body through small particles present in polluted air. (52)

9) Black tea:**Biological source: Camellia sinensis**

Immunity boosting mechanism: It influences activation of transcription factors such as NF- κ B or AP-1 that ultimately hinder the formation of nitric oxide expression gene. It boosts immunity by enhancing the disease-fighting ability of gamma delta T cells. It causes inhibition of redox sensitive transcription factors & pro-oxidant enzymes such as xanthine oxidase or nitric oxide synthase. However, their involvement in antioxidative enzyme induction as in glutathione-S-transferases is also well documented. (53)

10) Green tea:**Biological source: Camellia sinensis**

Immunity boosting mechanism: Green tea modulating production of immune-regulatory cytokines in stimulated dendritic cells and hence acts as suppressor of T cell activation by lowering the inflammatory reaction, reducing the lipid per-oxidation and formation of NO radicals, Thus acting as anti-oxidant (54).

11) Ashwagandha:**Biological source: Withania somnifera**

Immunity boosting mechanism: It increased release of various cytokines such as TNF α , IFN- γ , and/or IL-2. IFN- γ is a cytokine critical for both innate and adaptive immunity; IL-12 is primarily secreted by macrophages (55).

12) Amla:**Biological source: Emblica officinalis**

Immunity boosting mechanism: It is a rich source of antioxidants, including polyphenols, which confer its free radical scavenging potential (56).

13) Guduchi:**Biological source: *Tinospora cordifolia***

Immunity boosting mechanism: It increases the concentration of cytokines. Cytokines regulate the intensity and duration of immune responses by stimulating or inhibiting activation, proliferation and/or differentiation of various cells and by regulating the secretion of antibodies (57).

14) Brahmi:**Biological source: *Bacopa monnieri***

Immunity boosting mechanism: Brahmi, a traditionally reputed herbal drug, has been reported to exert antioxidant activity. There are many factors that produce free radical mediated oxidative stress. It also down regulated iNOS expression thereby inhibited nitric oxide generation (58-59).

15) Mandukaparni:**Biological source: *Centella asiatica***

Immunity boosting mechanism: It significantly increased proliferation and the production of IL-2 and TNF-alpha. It also inhibited mitogenesis and the production of IL-2 and TNF-alpha (60).

16) Draksha:**Biological source: *Vitis vinifera***

Immunity boosting mechanism: The redox sensitive transcription factor nuclear factor erythroid 2-related factor-2 (Nrf2) partly regulates the expression of genes encoding antioxidant enzymes. Nrf2 is bound in the cytoplasm to its inhibitor Keap1 (Kelch-like ECH-associated protein 1). When Nrf2 is activated by electrophiles, it is released from its cytosolic protein Keap1 and binds to the antioxidant response element of the DNA in the nucleus thereby regulating the transcription of target genes including γ -glutamylcysteine synthetase (γ GCS) and heme oxygenase-1 (HO-1) (61).

17) Haridra:**Biological source: *Curcuma longa***

Immunity boosting mechanism: It activates the superoxide dismutase enzyme against ROS that further catalyzes the dismutation (or partitioning) of the superoxide (O_2^-) radical into ordinary molecular oxygen (O_2) and hydrogen peroxide (H_2O_2) (62).

18) Jhandu:**Biological source: *Tagetes erecta***

Immunity boosting mechanism: It has radical scavenging activity and thus acts as anti-oxidant (63).

19) Kutki:**Biological source: *Picrorrhiza kurroa***

Immunity boosting mechanism: It stimulates the cell-mediated immunity significantly and also stimulated the humoral immunity by regulating the function of T-cells against antigen (64).

20) Vidarikand:**Biological source: *Pueraria tuberosa***

Immunity boosting mechanism: It inhibits the lipid peroxidation thus reduces the oxidative stress (65).

21) Purple Coneflower:**Biological source: *Echinacea***

Immunity boosting mechanism: It suppresses the ability of Jurkat T cells to produce IL-2 independently. It activates cellular immunity and stimulates phagocytosis of neutrophils (66-67).

22) Black Cumin:**Biological source: *Nigella sativa***

Immunity boosting mechanism: It directly influences immune system and improves helper T cells (T4) to suppressor T cells (T8) ratio (68, 69).

23) Liquorice:**Biological source: Glycyrrhiza glabra**

Immunity boosting mechanism: It elevates the level of malondialdehyde (MDA), superoxide dismutase (SOD), and catalase (CAT) (70).

24) Astragalus:**Biological source: Astragalus**

Immunity boosting mechanism: It causes stimulation of immune cells against stimulus-response action, elevates the tumor cell killing activity of cytotoxic T-lymphocyte (71).

Conclusion:-

Population with weak immunity is vulnerable for COVID-19, the world's pandemic disease. To strengthen and boosting the immunity natural products depict crucial role by enhancing the valuable bacteria in the body. Through the investigation it has noted that natural products like Draksha (*Vitis vinifera*) used in DNA synthesis and cell proliferation which synchronize innate and adaptive responses of immune system. Various herbal drugs i.e. Garlic (*Allium sativum*), Bleuberry (*Ericaceae Vaccinium*), Andrographis (*Andrographis paniculata*), Broccoli (*Brassica oleracea*), Tea (*Camellia sinensis*), Amla (*Embllica officinalis*), Brahmi (*Bacopa monnieri*), Haridra (*Curcuma longa*), Jhandu (*Tagetes erecta*), Vidarikand (*Pueraria tuberosa*) have anti-oxidant and immunomodulator activity thus enhancing the innate response of immune system. Similarly, herbal drugs like Liquorice (*Glycyrrhiza glabra*) which increases the level of malondialdehyde (MDA), superoxide dismutase (SOD), catalase and Purple coneflower (*Echinacea*) and Purple coneflower (*Echinacea*) suppressed the ability of activated T-cells to produce IL-2 that directly influence the immune response. Ginger (*Zingiber officinale*) is one of the herbal drugs that inhibit NF- κ B activation thus arrests cell cycle in G2/M phases. Cytokine regulates the intensity and duration of immune response stimulating or inhibiting activation, proliferation and/or differentiation of various cells and by regulating the secretion of antibodies, natural products like Ashwagandha (*Withania somnifera*), Guduchi (*Tinospora cordifolia*), Mandukaparni (*Centella asiatica*) have potential to elevate the cytokine levels.

References:-

1. Wu, F. Zhao, S. Yu, B. Chen, YM. Wang, W. Song, ZG. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, 19
2. Huang, C. Wang, Y. Li, X. Ren, L. Zhao, J. Hu, Y. (2019) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 395, 497–506
3. Yang, Y., Peng, F., Wang, R., Guan, K., Jiang, T., Xu, G., Sun, J., & Chang, C. (2020). The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *Journal of autoimmunity*, 109, 102434
4. Guan, WJ. Ni, ZY. Hu, Y. Liang, WH. (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine*
5. Wang, D. Hu, B. Hu, C. Zhu, F. Liu, X. Zhang, J. (2020) Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama*
6. Rothe, C. Schunk, M. Sothmann, P. Bretzel, G. Froeschl, G. Wallrauch, C. (2020) Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *The New England journal of medicine*. 382, 970-1
7. Wang, D. Hu, B. Hu, C. Zhu, F. Liu, X. Zhang, J. (2020) Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama*
8. Netea, M. G., Domínguez-Andrés, J., Barreiro, L. B., Chavakis, T., Divangahi, M., Fuchs, E., Joosten, L., van der Meer, J., Mhlanga, M. M., Mulder, W., Riksen, N. P., Schlitzer, A., Schultze, J. L., Stabel Benn, C., Sun, J. C., Xavier, R. J., & Latz, E. (2020). Defining trained immunity and its role in health and disease. *Nature reviews. Immunology*, 20(6), 375–388
9. Zemskov, VM. Pronko, KN. Zemskov, AM. Zemskova, VA. (2019) Contradictions of clinical immunology: Nonspecific and specific mechanisms in immunogenesis, *Clinical Practice*, 16(3)
10. Petrov, RV. Khaitov, RM. Chereshev, VA. (2017) The physiology of the immune system: cellular and molecular-biological mechanisms. *J. Bulletin RFBR*, 1(1), 96-119
11. Netea, M. G., Joosten, L. A., Latz, E., Mills, K. H., Natoli, G., Stunnenberg, H. G., O'Neill, L. A., & Xavier, R. J. (2016). Trained immunity: A program of innate immune memory in health and disease. *Science (New York, N.Y.)*, 352(6284), aff1098

12. Rachael, C. Thomas, K. (2005) Old Meets New: The Interaction between Innate and Adaptive Immunity. *J Invest Dermatol*, 125, 629–637
13. Fessler M. B. (2015). Regulation of Adaptive Immunity in Health and Disease by Cholesterol Metabolism. *Current allergy and asthma reports*, 15(8), 48
14. Ahmed, A. Saha, B. Patwardhan, A. (2009) The major players in adaptive immunity. *Resonance*, 14, 455-471
15. Holshue, ML. DeBolt, C. Lindquist, S. (2020) First case of 2019 novel coronavirus in the United States. *N Engl J Med*
16. <https://www.hindustantimes.com/india-news/the-7-strains-of-coronavirus-and-unknowns-of-covid-19/story-mmlppmKUOFgFzSr7YI9wDP.html>
17. Backer, JA. Klinkenberg, D. Wallinga, J. (2020). Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28 January 2020. *European communicable disease bulletin*, 25(5)
18. WHO) reported an incubation period for COVID-19 between 2 and 10 days (WHO. (2020) Corona disease (COVID-19) pandemic. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
19. Reuters. (2020, 22 Feb). Coronavirus incubation could be as long as 27 days, Chinese provincial government says. Retrieved from <https://www.reuters.com/article/us-china-health-incubation/coronavirus-incubation-could-be-as-long-as-27-days-chinese-provincial-government-says-idUSKCN20G06W>
20. Centre for disease control and prevention. (2020, 16 April). Clinical questions about COVID-19. Retrieved from <https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html>
21. Kaiyuan, S. Jenny, C. Cécile, V. (2020) Early epidemiological analysis of the coronavirus disease 2019 outbreak based on crowdsourced data: a population-level observational study. *Lancet Digital Health*, 2, 201–08
22. Virlogeux, V Fang, VJ. Park, M. Wu, JT. Cowling, BJ. (2016) Comparison of incubation period distribution of human infections with MERS-CoV in South Korea and Saudi Arabia. *Sci Rep*, 6(1)
23. Lessler, J. Reich, NG. Brookmeyer, R. Perl, TM. (2009). Incubation periods of acute respiratory viral infections: a systematic review. *The Lancet. Infectious diseases*, 9(5), 291–300
24. Xu, T., Jiang, X., Denton, D., & Kumar, S. (2020). Ecdysone controlled cell and tissue deletion. *Cell death and differentiation*, 27(1), 1–14
25. Dhama, K., Patel, S. K., Pathak, M., Yattoo, M. I., Tiwari, R., Malik, Y. S., Singh, R., Sah, R., Rabaan, A. A., Bonilla-Aldana, D. K., & Rodriguez-Morales, A. J. (2020). An update on SARS-CoV-2/COVID-19 with particular reference to its clinical pathology, pathogenesis, immunopathology and mitigation strategies. *Travel medicine and infectious disease*, 101755
26. Rogers, C. J., Harman, R. J., Bunnell, B. A., Schreiber, M. A., Xiang, C., Wang, F. S., Santidrian, A. F., & Minev, B. R. (2020). Rationale for the clinical use of adipose-derived mesenchymal stem cells for COVID-19 patients. *Journal of translational medicine*, 18(1), 203
27. Oldstone, M. B., & Rosen, H. (2014). Cytokine storm plays a direct role in the morbidity and mortality from influenza virus infection and is chemically treatable with a single sphingosine-1-phosphate agonist molecule. *Current topics in microbiology and immunology*, 378, 129–147
28. Bordon, J., Aliberti, S., Fernandez-Botran, R., Uriarte, S.M., Rane, M.J., Duvvuri, P., Peyarni, P., Ramirez, J.A. (2013) Understanding the roles of cytokines and neutrophil activity and neutrophil apoptosis in the protective versus deleterious inflammatory response in pneumonia. *International Journal of Infectious diseases*. 17 (2), e76-e83
29. Zhang, J., Xie, B., & Hashimoto, K. (2020). Current status of potential therapeutic candidates for the COVID-19 crisis. *Brain, behavior, and immunity*, S0889-1591(20)30589-4
30. Jamilloux, Y., Henry, T., Belot, A., Viel, S., Fauter, M., El Jammal, T., Walzer, T., François, B., & Sève, P. (2020). Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmunity reviews*, 19(7), 102567
31. Raoult, D., Zumla, A., Locatelli, F., Ippolito, G., & Kroemer, G. (2020). Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. *Cell stress*, 4(4), 66–75
32. Felsenstein, S., Herbert, J. A., McNamara, P. S., & Hedrich, C. M. (2020). COVID-19: Immunology and treatment options. *Clinical immunology (Orlando, Fla.)*, 215, 108448
33. Shi, Y., Wang, Y., Shao, C., Huang, J., Gan, J., Huang, X., Bucci, E., Piacentini, M., Ippolito, G., & Melino, G. (2020). COVID-19 infection: the perspectives on immune responses. *Cell death and differentiation*, 27(5), 1451–1454
34. Raoult, D., Zumla, A., Locatelli, F., Ippolito, G., & Kroemer, G. (2020). Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. *Cell stress*, 4(4), 66–75

35. Singh, Raj & Dhama, Kuldeep & Chakraborty, Sandip & Tiwari, Ruchi & Natesan, Senthilkumar & Khandia, Rekha & Munjal, Ashok & K, Vora & Latheef, Shyma & Karthik, Kumaragurubaran & Malik, Yashpal & Singh, Ravpreet & Chaicumpa, Wanpen & Mourya, Devendra. (2019). Nipah virus: epidemiology, pathology, immunobiology and advances in diagnosis, vaccine designing and control strategies – a comprehensive review. *The Veterinary quarterly*. 39. 26-55
36. Al-Amri, SS. Abbas, AT. & Siddiq, LA. (2017). Immunogenicity of Candidate MERS-CoV DNA Vaccines Based on the Spike Protein. *Sci Rep*,7:44875
37. Tebas, P. Roberts, CC. Muthumani, K. (2017). Safety and Immunogenicity of an Anti-Zika Virus DNA Vaccine - Preliminary Report. *N Engl J Med*, 16
38. Reichmuth, AM. Oberli, MA. Jaklenec, A. (2016). mRNA vaccine delivery using lipid nanoparticles. *Ther Deliv.*, 7(5):319-34
39. Graham, R. L., Donaldson, E. F., & Baric, R. S. (2013). A decade after SARS: strategies for controlling emerging coronaviruses. *Nature reviews. Microbiology*, 11(12), 836–848
40. Du, L., He, Y., Zhou, Y., Liu, S., Zheng, B. J., & Jiang, S. (2009). The spike protein of SARS-CoV--a target for vaccine and therapeutic development. *Nature reviews. Microbiology*, 7(3), 226–236
41. Chen, R., Fu, J., Hu, J., Li, C., Zhao, Y., Qu, H., Wen, X., Cao, S., Wen, Y., Wu, R., Zhao, Q., Yan, Q., Huang, Y., Ma, X., Han, X., & Huang, X. (2020). Identification of the immunodominant neutralizing regions in the spike glycoprotein of porcine deltacoronavirus. *Virus research*, 276, 197834
42. Kim, M. H., Kim, H. J., & Chang, J. (2019). Superior immune responses induced by intranasal immunization with recombinant adenovirus-based vaccine expressing full-length Spike protein of Middle East respiratory syndrome coronavirus. *PloS one*, 14(7), e0220196
43. Xu, T., Jiang, X., Denton, D., & Kumar, S. (2020). Ecdysone controlled cell and tissue deletion. *Cell death and differentiation*, 27(1), 1–14
44. Shang, A., Cao, S. Y., Xu, X. Y., Gan, R. Y., Tang, G. Y., Corke, H., Mavumengwana, V., & Li, H. B. (2019). Bioactive Compounds and Biological Functions of Garlic (*Allium sativum* L.). *Foods (Basel, Switzerland)*, 8(7), 246.
45. Hetland, G., Johnson, E., Lyberg, T., & Kvalheim, G. (2011). The Mushroom *Agaricus blazei* Murill Elicits Medicinal Effects on Tumor, Infection, Allergy, and Inflammation through Its Modulation of Innate Immunity and Amelioration of Th1/Th2 Imbalance and Inflammation. *Advances in pharmacological sciences*, 2011, 157015.
46. Zhu, Y., Bickford, P. C., Sanberg, P., Giunta, B., & Tan, J. (2008). Blueberry opposes beta-amyloid peptide-induced microglial activation via inhibition of p44/42 mitogen-activation protein kinase. *Rejuvenation research*, 11(5), 891–901.
47. Hu, X. Y., Wu, R. H., Logue, M., Blondel, C., Lai, L., Stuart, B., Flower, A., Fei, Y. T., Moore, M., Shepherd, J., Liu, J. P., & Lewith, G. (2017). *Andrographis paniculata* (Chuān Xīn Lián) for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis. *PloS one*, 12(8), e0181780.
48. Króliczewska, B., Graczyk, S., Króliczewski, J., Pliszcak-Król, A., Miśta, D., & Zawadzki, W. (2017). Investigation of the immune effects of *Scutellaria baicalensis* on blood leukocytes and selected organs of the chicken's lymphatic system. *Journal of animal science and biotechnology*, 8, 22.
49. Zhou, Xiaoxia & Luo, Liping & Dressel, Waikē & Shadibaer & Krumbiegel, Doreen & Schmidtke, Peter & Zepp, Fred & Meyer, Claudius. (2008). Cordycepin is an Immunoregulatory Active Ingredient of *Cordyceps sinensis*. *The American journal of Chinese medicine*. 36. 967-80..
50. Idris, N. A., Yasin, H. M., & Usman, A. (2019). Voltammetric and spectroscopic determination of polyphenols and antioxidants in ginger (*Zingiber officinale* Roscoe). *Heliyon*, 5(5), e01717.
51. Mohd Sahardi, N., & Makpol, S. (2019). Ginger (*Zingiber officinale* Roscoe) in the Prevention of Ageing and Degenerative Diseases: Review of Current Evidence. *Evidence-based complementary and alternative medicine : eCAM*, 2019, 5054395.
52. Subedi, L., Cho, K., Park, Y. U., Choi, H. J., & Kim, S. Y. (2019). Sulforaphane-Enriched Broccoli Sprouts Pretreated by Pulsed Electric Fields Reduces Neuroinflammation and Ameliorates Scopolamine-Induced Amnesia in Mouse Brain through Its Antioxidant Ability via Nrf2-HO-1 Activation. *Oxidative medicine and cellular longevity*, 2019, 3549274.
53. Subedi, L., Cho, K., Park, Y. U., Choi, H. J., & Kim, S. Y. (2019). Sulforaphane-Enriched Broccoli Sprouts Pretreated by Pulsed Electric Fields Reduces Neuroinflammation and Ameliorates Scopolamine-Induced Amnesia in Mouse Brain through Its Antioxidant Ability via Nrf2-HO-1 Activation. *Oxidative medicine and cellular longevity*, 2019, 3549274.

54. Prasanth, M. I., Sivamaruthi, B. S., Chaiyasut, C., & Tencomnao, T. (2019). A Review of the Role of Green Tea (*Camellia sinensis*) in Antiphotaging, Stress Resistance, Neuroprotection, and Autophagy. *Nutrients*, 11(2), 474.
55. Vetvicka, V., & Vetvickova, J. (2011). Immune enhancing effects of WB365, a novel combination of Ashwagandha (*Withania somnifera*) and Maitake (*Grifola frondosa*) extracts. *North American journal of medical sciences*, 3(7), 320–324.
56. Nashine, S., Kanodia, R., Nesburn, A. B., Soman, G., Kuppermann, B. D., & Kenney, M. C. (2019). Nutraceutical effects of *Embllicaofficinalis* in age-related macular degeneration. *Aging*, 11(4), 1177–1188.
57. Nair, P. K., Rodriguez, S., Ramachandran, R., Alamo, A., Melnick, S. J., Escalon, E., Garcia, P. I., Jr, Wnuk, S. F., & Ramachandran, C. (2004). Immune stimulating properties of a novel polysaccharide from the medicinal plant *Tinospora cordifolia*. *International immunopharmacology*, 4(13), 1645–1659.
58. Gupta, R., Singh, A., Srivastava, M., Singh, V., Gupta, M. M., & Pandey, R. (2017). Microbial modulation of bacoside A biosynthetic pathway and systemic defense mechanism in *Bacopa monnieri* under Meloidogyne incognita stress. *Scientific reports*, 7, 41867.
59. Mathur, D., Goyal, K., Koul, V., & Anand, A. (2016). The Molecular Links of Re-Emerging Therapy: A Review of Evidence of Brahmi (*Bacopa monniera*). *Frontiers in pharmacology*, 7, 44.
60. Gray, N. E., Alcazar Magana, A., Lak, P., Wright, K. M., Quinn, J., Stevens, J. F., Maier, C. S., & Soumyanath, A. (2018). *Centella asiatica* - Phytochemistry and mechanisms of neuroprotection and cognitive enhancement. *Phytochemistry reviews : proceedings of the Phytochemical Society of Europe*, 17(1), 161–194.
61. Esatbeyoglu, T., Ewald, P., Yasui, Y., Yokokawa, H., Wagner, A. E., Matsugo, S., Winterhalter, P., & Rimbach, G. (2016). Chemical Characterization, Free Radical Scavenging, and Cellular Antioxidant and Anti-Inflammatory Properties of a Stilbenoid-Rich Root Extract of *Vitis vinifera*. *Oxidative medicine and cellular longevity*, 2016, 8591286.
62. Lee, H. Y., Kim, S. W., Lee, G. H., Choi, M. K., Chung, H. W., Lee, Y. C., Kim, H. R., Kwon, H. J., & Chae, H. J. (2017). Curcumin and Curcuma longa L. extract ameliorate lipid accumulation through the regulation of the endoplasmic reticulum redox and ER stress. *Scientific reports*, 7(1), 6513.
63. Moliner, C., Barros, L., Dias, M. I., López, V., Langa, E., Ferreira, I., & Gómez-Rincón, C. (2018). Edible Flowers of *Tagetes erecta* L. as Functional Ingredients: Phenolic Composition, Antioxidant and Protective Effects on *Caenorhabditis elegans*. *Nutrients*, 10(12), 2002.
64. Hussain, A., Shadma, W., Maksood, A., & Ansari, S. H. (2013). Protective effects of *Picrorhiza kurroa* on cyclophosphamide-induced immunosuppression in mice. *Pharmacognosy research*, 5(1), 30–35.
65. Pawar, N., Gandhi, K., Purohit, A., Arora, S., & Singh, R. R. (2014). Effect of added herb extracts on oxidative stability of ghee (butter oil) during accelerated oxidation condition. *Journal of food science and technology*, 51(10), 2727–2733.
66. Karsch-Völkl, M., Barrett, B., Kiefer, D., Bauer, R., Ardjomand-Woelkart, K., & Linde, K. (2014). Echinacea for preventing and treating the common cold. *The Cochrane database of systematic reviews*, 2(2), CD000530.
67. Fonseca, F. N., Papanicolaou, G., Lin, H., Lau, C. B., Kennelly, E. J., Cassileth, B. R., & Cunningham-Rundles, S. (2014). *Echinacea purpurea* (L.) Moench modulates human T-cell cytokine response. *International immunopharmacology*, 19(1), 94–102.
68. Yimer, E. M., Tuem, K. B., Karim, A., Ur-Rehman, N., & Anwar, F. (2019). *Nigella sativa* L. (Black Cumin): A Promising Natural Remedy for Wide Range of Illnesses. *Evidence-based complementary and alternative medicine : eCAM*, 2019, 1528635.
69. Gholamnezhad, Z., Shakeri, F., Saadat, S., Ghorani, V., & Boskabady, M. H. (2019). Clinical and experimental effects of *Nigella sativa* and its constituents on respiratory and allergic disorders. *Avicenna journal of phytomedicine*, 9(3), 195–212.
70. Chowdhury, B., Bhattamisra, S. K., & Das, M. C. (2013). Anti-convulsant action and amelioration of oxidative stress by *Glycyrrhiza glabra* root extract in pentylenetetrazole- induced seizure in albino rats. *Indian journal of pharmacology*, 45(1), 40–43.
71. Adesso, S., Russo, R., Quaroni, A., Autore, G., & Marzocco, S. (2018). *Astragalus membranaceus* Extract Attenuates Inflammation and Oxidative Stress in Intestinal Epithelial Cells via NF-κB Activation and Nrf2 Response. *International journal of molecular sciences*, 19(3), 800.