



ORIGINAL ARTICLE

# Physical Activity and Natural Products and Minerals in the SARS-CoV-2 Pandemic: An Update

<sup>1</sup>Ayoub Saeidi, <sup>2</sup>Seyed Morteza Tayebi, <sup>3</sup>Oam To-aj\*, <sup>4</sup>Nilofar Karimi, <sup>5</sup>Sahar Kamankesh, <sup>6</sup>Saber Niazi, <sup>7</sup>Abedin Khosravi, <sup>8</sup>Mitra Khademosharie, <sup>9</sup>Mohammad Soltani, <sup>10</sup>Kelly E. Johnson, <sup>11</sup>Harunor Rashid, <sup>12</sup>Ismail Laher, <sup>13</sup>Anthony C. Hackney, <sup>14</sup>Hassane Zouhal\*

<sup>1</sup>Damghan Branch, Islamic Azad University, Damghan, Iran. <sup>2</sup>Allameh Tabataba'i University, Tehran, Iran. <sup>3</sup>Bangkok Thonburi University, Bangkok, Thailand. <sup>4</sup>University of Mazandaran, Babolsar, Iran. <sup>5</sup>Razi University, Kermanshah, Iran. <sup>6</sup>Kharazmi University, Tehran, Iran. <sup>7</sup>Payame Noor University, Tehran, Iran. <sup>8</sup>Kowsar University, Bojnord, Iran. <sup>9</sup>Shahid Beheshti University, Tehran, Iran. <sup>10</sup>Coastal Carolina University, Conway SC, USA. <sup>11</sup>National Centre for Immunisation Research & Surveillance of Vaccine Preventable Diseases (NCIRS), Westmead, Australia. <sup>12</sup>University of British Columbia, Vancouver, Canada. <sup>13</sup>University of North Carolina, Chapel Hill, NC, USA. <sup>14</sup>University of Rennes 2, Rennes, France.

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## ABSTRACT

Coronavirus-disease 19 (COVID-19) has rapidly become a global public health issue, and there is a desperate need for strategies of prevention, reduction, and treatment to halt the epidemic. The coronavirus affects the immune system, and individuals with a compromised immune system, such as those with diabetes, hypertension, obesity, are more susceptible to this virus. Lifestyle-related variables such as physical activity and nutritional supplements can decrease inflammatory markers, increase anti-inflammatory and antioxidant status, and improve the immune system. Lifestyle-related variables play preventive roles against various infectious diseases including COVID-19. This review highlights the effects of physical activity and nutrients supplements on the immune system and their possible benefits in combating the harms caused by infection with the COVID-19 virus.

**KEYWORDS:** *Coronavirus, Covid-19, Immune Response, Immune System, Lung Tissue, Inflammation, Anti-Inflammatory, Cellular Effects, Hormonal Effects, Antioxidant, Nutrition, Nutrients Supplements, Curcumin, Black Cumin, Adiantum Capillus-Veneris, Thyme, Ginger, Cinnamon, Zinc, Vitamin C, Garlic, Beeswax, Honey, Selenium, Lemon, Magnesium, Physical Activity, Sport, Exercise, Training.*

\*. Corresponding Authors:

1. **Oam To-aj**, PhD. E-Mail: Oam.deto@gmail.com

2. **Hassane Zouhal**, Professor. E-Mail: hassane.zouhal@univ-rennes2.fr

## INTRODUCTION

The word coronavirus is derived from the Greek word “*korone*”, meaning something curved, and the Latin word “*corona*”, meaning garland or crown. The term refers to the appearance of virions (the infectious form of the virus) seen under an electron microscope, which has a large, onion-like margin and is reminiscent of a picture of a royal crown or solar crown, so that the coronavirus is sometimes also referred to as the crown virus (1). Different coronaviruses have been identified in dogs, rabbits, mice, chickens, turkeys, cows, cats, horses, and humans, and can cause a variety of serious illnesses including gastrointestinal and respiratory diseases (1). A series of symptoms of pneumonia with clinical signs very similar to viral pneumonia appeared in Wuhan (China) in December 2019, which soon spread worldwide including several cases of pneumonia of unknown etiology (2, 3). In the early stages of the disease, severe acute symptoms of respiratory infection occurred, with some patients rapidly developing acute respiratory distress syndrome (ARDS) (4). A new coronavirus was then identified by the Chinese Center for Disease Control and Prevention (CDC) from a swab of a patient's throat, and subsequently named by the WHO as the 2019-nCoV, COVID-19 (4). The disease then quickly spread to 27 other countries (5).

Coronaviruses (CoVs) are single, non-fragmented, enveloped single-stranded viral genomes ranging in size from 26 to 32 kilobases, and represent the largest known RNA virus genome (6). Virion has a nucleocapsid composed of genomic RNA protein and phosphorylated nucleoprotein (N) protein, which is located within the phospholipid layers and is covered by two different types of spike proteins (6). Spike glycoprotein (S) is found in all CoVs, while hemagglutinin esterase (HE) is found only in some CoVs (6). Membrane protein (M) (a type III transmembrane glycoprotein) and envelope (E) proteins are among the S proteins in the virus envelope (6). The subfamily Coronavirus is genetically and serologically divided into four genera:  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ . Coronavirus  $\beta$ - can be further classified into four virus classes, A-D (6). There are about 30 kinds of CoVs that infect humans, mammals, chickens and other animals (6). Human CoV infection is caused by corona viruses  $\alpha$  and  $\beta$  (6).

Seven coronaviruses transmitted from animals to humans have been identified by their host range and genome sequence (7). Among them, HCoV-229E and HCoV-OC43 were identified in the mid-1960s as causing common colds (7). Other corona viruses are HCoV-NL63 and HCoV-HKU1, which were discovered in 2004 and 2005 (7). Severe acute respiratory syndrome coronavirus (SARS-CoV) killed about 800 people in 2002-2003, causing acute and severe respiratory distress syndrome (1, 8). A newer strain of the virus, Middle East Respiratory Syndrome coronavirus (MERS-CoV) was first discovered in 2012 in a 60-year-old man in Saudi Arabia (9) and a second case in a 49-year-old man in Qatar (9); both cases were fatal (10). Another new corona causing Severe Acute Respiratory Syndrome (SARS-CoV-2) was later identified in 2019 (2). Similar to SARS-CoV and MERS-CoV, the 2019-nCoV encodes non-structural proteins (such as quimotrypsin-3-like protease, quaternary papain, helicase and RNA dependent RNA polymerase), structural proteins (such as spike glycoprotein) and side protein (6, 11). These four non-structural proteins are key enzymes in the virus life cycle, and the spike glycoprotein is essential for cell-virus receptor interactions for viral invasion (11).

Preliminary analyzes of SARS-CoV-2 genomic sequences indicates that the catalytic sites are protected from the four SARS-CoV-2 enzymes that can be antiviral targets, and have a high level of sequence similarity to SARS-CoV and MERS-CoV enzymes (12). In addition, structural analysis of the protein suggests that important pockets of drug binding in virus enzymes are probably similar in all corona viruses such as COVID-19, SARS and MERS-CoV (12). The 2019-nCoV virus has a 96% similarity with the bat coronavirus, making the bat a widely suspected source of transmission, but the origin of the 2019-nCoV still needs further investigation (13). Common symptoms of infection with the Covid-19 virus include fever and cough. Muscle pain, sputum production, and sore throat are less common, and in most cases lead to milder symptoms severe cases may present with shortness of breath. People infected with the virus can be asymptomatic or present with flu-like symptoms (14). Diarrhea and upper respiratory symptoms such as sneezing, runny nose or sore throat are less common (14, 15). Viral

transmission can occur through respiratory droplets as often occurs during coughing and sneezing or direct or indirect contact (15, 16). According to the World Health Organization, the duration of symptoms is usually between 2 and 14 days, with an average of 5 days (16). Preliminary data suggests that transition of the disease to severe illness is within 1 week (16), with the onset of symptoms being 2-8 weeks in fatal cases (16). The standard method of diagnosis is through reverse polymerase chain reaction (RT-PCR) of a throat swab. Infection also can be detected by a combination of symptoms, risk factors, and CT scans of the chest that show the characteristics of pneumonia (14). Mortality is estimated as between 1 and 5 percent in infected people but can vary according to age and other health conditions (14). There are a larger number of males in a study of 99 cases of 2019-nCoV infections (14)(14), similar to findings in of infections with As MERS-CoV and SARS-CoV (14). Reduced susceptibility of women to viral infections can be attributed to protection against the X chromosome and sex hormones, which play an important role in innate immunity (17). About half of the patients infected with 2019-nCoV were reported to have serious complications related to cardiovascular, brain and diabetes, and 2019-nCoV due to poor immune function. It is more likely to infect older men (14).

The immune system protects the body against bacteria and viruses that can harm the body and lead to illness and infections (18). There are several factors which affect the function of immune system: age, gender, diet, pre-existing medical illness and physical activity (PA) level (19, 20). The global spread of COVID-19 means the need for people to protect themselves by maintaining their health, with PA and diet being two factors that can boost the immune system and provide protection against viral infections (19, 20). The clinical characteristics of people infected with the COVID-19 virus indicates increases in inflammatory cytokines (“cytokine storm”) and decrease in anti-inflammatory markers through cellular changes may weaken the immune system and is leading to invade of this virus to the sensitive parts of the body, especially in the lungs (6). This review highlights the effects of PA and nutritional supplements on the immune system and their possible benefits in relieving the harms of viral infections for example, with the COVID-19 virus.

## IMMUNE RESPONSE TO CORONAVIRUS

A viral infection leads to an activation of the host immune system, and when immune defenses are overwhelmed, there is lung tissue damage and decreased lung capacity (21). Chemotactic agents are critical for immune responses to viral infections due to their regulatory effects on the spread and location of leukocytes in the pulmonary system (21). Accordingly, spectral changes in chemotactic factors may lead to highly maladaptive immune responses. Immune deficiency or a change in direction in the immune system can increase virus proliferation and cause tissue damage, while hyperactive immune responses can induce immune-related pathological conditions (21). The host's innate immune system detects viral infections using pattern recognition receptors (PRR) to detect pathogen-related molecular patterns (PAMPs) (21). PRRs mainly includes toll - like (TLR) receptors, RIG - I - like (RLR) receptors, NOD - like receptors (NLR), and C-type pseudo-lectin receptors (CLmin), and also molecules in the cytoplasm such as cGAS, IFI16, STING, and DAI (21). On the other hand, adaptive immune systems (T cells, CD4 + T cells and CD8 + T cells) plays a significant role against the virus (22).

***Cytokine storm in Covid-19 infections.*** White blood CD4 cells, also known as T helper cells or simply as T cells, produce specific B-cells that produce virus-specific antibodies, while CD8 + T cells are cytotoxic and can eradicate virus-infected cells (23). The CD8 + T comprise about 80% of the inflammatory cells that penetrate the lungs of COVID-19 patients, and have an important role in clearing CoVs in infected cells (23). The innate immune response and adaptive immune responses in CoV infection are such that the CoV then infect macrophages , which can subsequently provide the CoV antigen to T cells (6). This process activates and differentiates T cells, including the production of cytokines associated with various subtypes of T cells (i.e. Th17), followed by the widespread release of cytokines to enhance the immune response (6). Continued production of these mediators negatively affects the activation of natural killer (NK) and CD8+-T cells due to viral persistence (6). However, CD8+T cells produce mediators able to clear COVID-19 viral particles (6). On the other hand, the binding of CoV to DPP4R on the host cell via S protein leads to the emergence of

genomic RNA in the cytoplasm, allowing CoV replication to occur partially as a result of dsRNA (6). The stimulation of TLR-3 stimulated by dsRNA signals IRFs and NF- $\kappa$ B activation to produce IFNs and cytokines (6). Production of 1 type IFNs is important to increase the release of antivirus proteins to protect non-infectious cells (6). CoV side proteins can also interfere with TLR-3 signaling and add to the effects of dsRNA in increasing CoV proliferation, so preventing TLR-3 activation and preventing a robust immune response (6). TLR-4 can detect protein S and lead to the activation of pre-inflammatory cytokines via the MyD88-dependent signaling pathway, and increase the production of immune mediators (6). The secretion of large amounts of chemokines and cytokines (IL-1, IL-6, IL-8, IL-21, TNF- $\beta$ , and MCP-1) in infected cells is enhanced in response to CoV infection (6). These chemokines and cytokines, in turn, adsorb lymphocytes and leukocytes at the site of infection (6).

### **EFFECT OF CORONAVIRUS IN THE LUNGS**

Lung damage caused by a virus initiates an immune, tissue damage and an accumulation of waste products (24). The extent of viral damage is related to the phase gap between the virus's reproductive curve and the compromised immune response delay, while lesion-related damage is attributed to an imbalance in the destruction of virus, cellular, and metabolic products (24). Treatment strategies should be aimed to slow viral reproduction, accelerate the immune response, and improve circulation in the lungs (24). Accordingly, treatment strategies should neutralize direct lung infection, strengthen and promote immune responses, dilute the viral concentration in lung tissue, maintain the balance of waste products, protect the heart and kidneys, and control other infections (24). Allergic reactions and other inflammatory responses should be managed, and monitoring of diet, emotional factors, lifestyle, and environmental factors, will also help to reduce lung damage (24).

Lungs are damaged by the rapid increase in resistance due to the retention of white blood cells in the lung tissue. White blood cell retention initially causes a viral infection but is exacerbated by low-temperature injuries. The lungs are initially damaged by fluid leakage, which is accelerated by the rapid release of blood into the alveolar spaces.

It is estimated that a retention of white blood cells in the lungs by 0.1% can lead to failure in 5 to 10 days (25). Suggesting importance of maintaining the microcirculation and the function of body organs during the disease, especially after the spread of the virus in the lungs (25).

The lungs are affected the most by COVID-19 because the virus has access to host cells through the enzyme angiotensin-converting enzyme 2 (ACE2), which is abundant in alveolar type II lung cells (5, 26). Cleavage of surface specific glycoproteins (initially called spike proteins) by transmembrane protease serine 2 (TMPRSS2) allows the entry and spread of SARS-CoV-2 virus through interaction with ACE2 receptors, leading to severe lung damage (27, 28). Tissue damage is proportional to the density of ACE2, suggesting that decreased ACE2 activity may be protective, e.g. by inhibiting TMPRSS2 (27, 28). TMPRSS2 promotes the spread of the virus in the airways of rat models after coronavirus infection (5). Alveolar disease leads to respiratory failure and death (29). ACE2 can also allow the COVID-19 virus to invade the heart and cause acute heart damage, further increasing the vulnerability of people with existing cardiovascular conditions (29).

The COVID-19 virus particles spread through the respiratory mucosa, infecting other cells and activating cytokines in the body, altering peripheral white blood cells and immune cells such as lymphocytes (14). The absolute number of lymphocytes in most infected patients is decreased, suggesting that COVID-19s acts primarily on lymphocytes, especially T lymphocytes, much as is the case for SARS-CoV (14). Some patients rapidly develop acute respiratory distress syndrome (ARDS), and later develop to multiple organ failure (14). Intravenous administration of immunoglobulin and treatment with steroids (methylprednisolone 1-2 mg / kg / day) is recommended for highly infected patients who develop ARDS (14).

A first step in combating disease is to prevent exposure to the COVID-19 virus, and in the absence of effective treatment strategies, a second step is to use health optimization methods through changes in lifestyle such as exercise and improved nutrition (25).

### **EFFECTS OF PHYSICAL ACTIVITY ON THE IMMUNE SYSTEM**

Some studies have investigated the effects of PA on the immune system, but with conflicting

results (30-32). The response of the immune system to PA is related to the intensity, duration and the type of PA (30, 31, 33-35). According to the results of epidemiological studies on the effects of PA on the function of the immune system, there is a J-shaped curve describing the

relationship between exercise intensity and risk of infection, where moderate PA can enhance immune function, while high intensity PA can impair immune function while exhaustive exercise can be detrimental and increase the risk to infections (33, 36) (Fig 1).

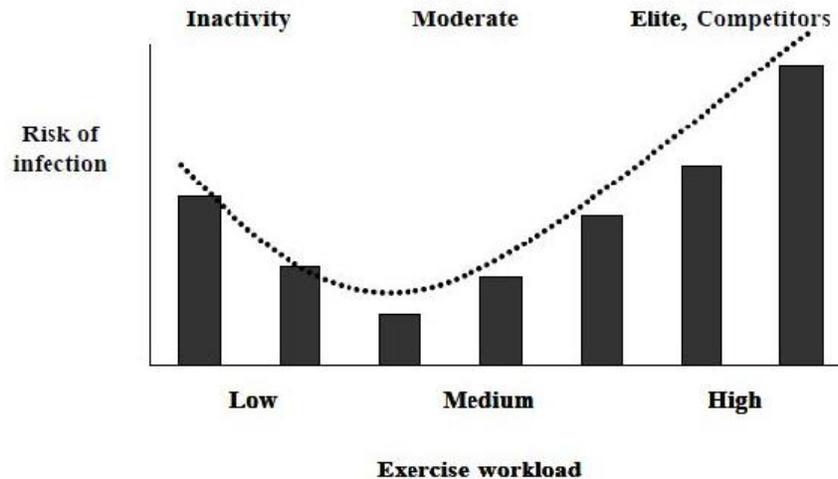


Figure 1. The risk of infection in relation to PA workload (33).

Appropriate levels and types of exercise increase anti-inflammatory (31, 32, 36, 37) and antioxidant biomarkers (37-40) and improves the immune defenses against viral infections (30, 33, 35, 39, 41). Psychological stress on the other hand is linked to inflammation and oxidative stress, both of which are associated with immune dysfunction (30, 42-44)

**Anti-Inflammatory Effects of Physical Activity.** Patients with a weakened immune system are likely to have a severe disease if infected with the SARS-CoV-2 with high levels of inflammatory biomarkers such as tumor necrosis factor (TNF), interleukin-6 (IL-6) and C-reactive protein (CRP) (18, 45, 46). The anti-inflammatory effects of PA can be achieved through a reduction of visceral fat mass (47, 48), as indicated by increases in anti-inflammatory biomarkers (31, 32) and reduced expression of Toll-like receptors (TLRs) on monocytes and macrophages (49). Adipose tissue increases the production of pro-inflammatory adipokines and decreases anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (IL-1ra) (31, 50).

A study of 1293 middle-aged patients reported that cardiorespiratory fitness was inversely associated with CRP, IL-6, and IL-18, and

directly associated with the anti-inflammatory cytokine IL-10; these effects are partly explained by a reduction in abdominal obesity and a decrease in the metabolic syndrome risk profile (48). Another study demonstrated that 8 weeks of combined aerobic and resistance training improved body composition (weight, body mass index (BMI), body fat%), inflammatory (IL-6, CRP and TNF- $\alpha$ ) and immune markers (leukocyte, natural killer (NK) cells) in obese adult men (47). Moreover, changes in lifestyle such as diet and PA in obese women decreased leptin, CRP and IL-6 and increased interleukin levels, and accompanied by decreases in BMI, waist-to-hip ratio, and fasting insulin concentrations (51).

There is a short-term transient increase in serum CRP after strenuous PA, a response that is largely mediated by IL-6. Based on the open window theory, immune system during this period has a weakened ability to combat bacteria and viruses for a period lasting from a few hours up to a day (33, 52).

Other causes of inflammation and increases in inflammatory markers during PA are mechanical changes and dehydration in the airways, and environmental factors such as air pollution and allergens can exacerbate inflammation and

further weaken the immune defenses (33, 53). Consuming fluids to reduce dehydration is one of the strategies to reduce the complications of COVID-19 (14).

Activation of TLR signaling increases the expression and secretion of pro-inflammatory cytokines; TLR mediates systemic inflammation and provides a link between a sedentary lifestyle, inflammation and disease. Regular PA downregulates TLR expression and reduces inflammatory responses and the risk of chronic inflammatory diseases (31, 49). As indicated in studies, after PA, appearance of IL-10 and IL-1ra in the circulation will be increased which contributes to mediating the anti-inflammatory effects of PA (54). IL-10 inhibits the production of cytokines and chemokines and plays an important role on the inflammatory reaction involving macrophage/monocyte activation (31, 54).

**Cellular Effects of Physical Activity.** A large number of immune cell infiltration occurs in patients with COVID-19. Most cellular responses to PA are related to changes in the total number and composition of circulatory leukocytes; these responses are different in the various stages before, during and a few hours after PA cessation (34). The dominant immune cell changes with PA are neutrophils and lymphocytes, with a smaller contribution of monocytes. The total leukocytes count during PA is related to the intensity and duration of the PA, the fitness level and age of the individual (39). A bout of intensive PA elevates blood neutrophil count and decreases natural killer cell (NK) activity, followed by a rapid reduction in lymphocytes (30, 34). Increases in circulating numbers of pro-inflammatory monocytes then occur in response to TLR (30, 34). Based on the open window theory, these transient changes may remain for several hours to days (30, 34), but is followed by thorough compensatory intracellular and extracellular changes (30, 31).

Increases in leukocytes by exercise can reduce immune burden (55). Raised levels of IL-6 due to excessive PA increases the secretion of adrenocorticotrophic hormone (ACTH), which stimulates cortisol release; cortisol has anti-inflammatory effects (54, 55). Acute increases in IL-6 stimulates the release of IL-1ra from monocytes and macrophages (54). Regular PA increases levels of circulating regulatory T cells (TReg cells) decreases inflammatory

(CD14<sup>low</sup>CD16<sup>+</sup>) monocytes and the expression of TLR4 in macrophages, ultimately boosting immunity against viruses and infections (31).

A study in young mice reports that high-intensity PA increases CD4<sup>+</sup> CD25<sup>+</sup> TReg cell numbers and decreases IFN- $\gamma$  expression and T-lymphocyte proliferation, changes that were associated with reduced pro-inflammatory markers and increased anti-inflammatory cytokine expression (35). In contrast, another study in elderly individuals demonstrated that 6 months of moderate PA improved expression of CD4<sup>+</sup> on T-helper (Th) cells and the balance of Th1/Th2 and decreased the risk of infections and autoimmune diseases (41) (35, 41). On the other hand, a study by Wolach et al (2000) reported decreased function of neutrophils in female judo athletes compared to sedentary women after prolonged endurance PA, while cross-sectional studies show boosted NK cell activity in athletes compared with non-athletes in both younger and older groups (56). These findings indicate that the cellular responses to PA are largely related to the individuals' level of fitness, the intensity and duration of the PA, and also the age of the individual.

An organized PA and healthy nutritional status preserves the anti-inflammatory phenotype of adipose tissue by resizing adipocytes and increasing M2-type macrophages and CD4<sup>+</sup> TReg cells (31). Acute and chronic PA produces anti-inflammatory cytokines such as IL-10 and IL-1ra by modulating the distribution of Th2 cells, Th1 cells, Th17 cells, monocytes, macrophages, dendritic cells (DCs), B cells, CD8<sup>+</sup> T cells and CD4<sup>+</sup> T cells (31, 35, 39).

Several studies report that the effects of PA are related to changes in immunoglobulins (Ig), specifically IgA (30, 31, 57). IgA is activated by pathogens that invade the upper respiratory tract (57). A study by Klentrou et al (2002) reported that moderate PA increases resting salivary IgA concentrations in people with regular PA (58). PA modulates activity of the renin-angiotensin system (RAS), with some experimental studies reporting that PA can stimulate the ACE2-Ang-(1-7)-Mas receptor axis in parallel with the inhibition of the ACE-Ang II-AT1 receptor pathway (59). A study by Magalhães et al (2020) indicates that both moderate and high-intensity aerobic PA increases ACE2 levels, but with greater increases after moderate-intensity aerobic PA (60). Another study by Prata et al (2017)

showed for the first time that exercise training activation of ACE2 can potentially reduce pulmonary fibrosis (61).

**Hormonal Effects of Physical Activity.** PA causes a rapid release of catecholamines increases and a stimulation of the hypothalamic-pituitary adrenal (HPA) axis and sympathetic -adrenal medullary (SAM) axis, leading to the release of cortisol within a few hours (31, 39). These hormonal responses are related to the intensity and duration of PA (62). Furthermore the release of catecholamines and glucocorticoids by PA change the production of cytokines which can affect the distribution of leukocyte subtypes (39, 62).

**Mental Health Effects of Physical Activity.** The physical and social effects of COVID-19 lead to various psychological dysfunctions that can ultimately weaken the immune system (63). Regular PA reduces stress and anxiety (42). Increases in cytokine levels induced by anxiety and stress can also suppress the immune system (42), decreases in plasma ACTH and corticosterone levels which is rated to the type of PA (acute or chronic). (42, 64). Levels of monoamine neurotransmitters involved in anxiety, such as dopamine (DA), noradrenaline (NE), and serotonin (5-HT), can be modulated by PA (42, 64, 65). Brain-derived neurotrophic factor (BDNF) is a neurotrophin associated with both anxiety and depression (64). Voluntary PA for 20 days increased the levels of BDNF mRNA in the hippocampus and caudal neocortex (65).

**Antioxidant Effects of Physical Activity.** Oxidative stress in host cells is an important factor in the infectivity of human coronavirus (46, 66, 67). Oxidative stress activates phagocytes and causes the release pro-oxidant cytokines such as TNF, IL-1 and IL-6, leading to the suppression of the immune system (66, 68). Infection of mice with influenza A is associated with decreased total lung glutathione concentrations and antioxidant markers such as vitamin E (37).

PA decreases oxidative stress by improving antioxidant defenses consisting of enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, and non-enzymatic antioxidants including glutathione (37). Longitudinal studies suggest that PA induced reduction of oxidative stress depends on the mode, intensity and frequency of PA (37, 68).

Strenuous acute PA increases oxidative metabolism and induces oxidative stress, while

long-term moderate PA augments antioxidant enzyme activity, leading to a greater mitochondrial capacity to scavenge free radicals and reduce free radical levels (30, 40). PA increases glutathione peroxidase (GPX) levels and decreases levels of creatine kinase (CK) and lactate dehydrogenase (LDH) after 1 month regular PA and sedentary group. CK and LDH enzymes are released into plasma as the result of the destruction of the cell membrane by oxidative stress or tissue necrosis (69).

Patients with COVID-19 have higher levels of LDH and CRP (45). A recent study reports that PA improves promote immune function in young males and females by regulating catecholamine concentrations, anti-inflammation and antioxidant biomarkers, LDH activity (70). The World Health Organization (WHO) has recommended exercise to combat the effects of COVID-19 (16) by stimulating the immune system and improving mental health (31, 42).

## EFFECTS OF NATURAL PRODUCTS ON THE IMMUNE SYSTEM

The cytokine storm that occurs in COVID-19 is an inflammatory response mediated by CRP, IL-1 $\beta$ , IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GM-CSF, IFN- $\gamma$ , TNF- $\alpha$ , IP-10, MCP1, M1P1A, M1P1 $\beta$  (6). We describe effects of some medicinal plants and supplements on inflammatory and oxidative stress, particularly as it related to COVID19.

**Curcumin.** Curcumin is a yellow material found in the plant *Cormonalga* that possesses anti-oxidant, anti-infective and anti-apoptotic effects (71). The recommended dose of curcumin is 150 to 6000 mg per day, although the European Food Safety Authority (EFSA) suggests doses of up to 3 mg per kilogram of body weight per day (72). McFarlane and colleagues compared the effects of three doses of curcumin (200, 400, and 1000 mg) on serum inflammatory cytokines and concluded that the optimal dose is 400 mg per day (73).

Curcumin interacts with neutrophils, macrophages, monocytes, natural lethal cells (NK), dendritic cells (DC), and B and T cells and affects innate and adaptive immunity (74). The inhibitory effects of curcumin on the proliferation of immune cells is dose- and time-dependent (73, 74). Curcumin also prevents the activation, differentiation and production of cytokines by

suppressing immune responses in T cells (71) and regulates genes for c-MYC, BCL-XL, and NFkB (73-75). Curcumin reduces the inflammation of the lungs caused by the flu virus by inhibiting the NF-kB pathway, reducing the activation and polarization of macrophages (75) and altering the proliferation and oxidative function of macrophages by inhibiting the TLR4 pathway. Curcumin increases IgA levels and suppresses its degradation, leading to increased immune function in animals consuming a high fat diet (76) and also increases Th1 production CD4 + and CD8 + counts (77).

The possible that the beneficial effects of curcumin supplementation in the inflammatory process may be due to the inhibition of NF-κB, signal converter and Janus kinase transcription activator (JAK / STAT) and mitogen activated kinase protein (MAPKs) signaling pathways and inhibition of TNF-α, IL-1, -2, -6, -8, -10 production (78). Curcumin suppresses leukocyte infiltration, activation, and maturation, and also the production of inflammatory mediators (TNF-α, CRP, IL-8, and IL-6) and nitric oxide synthase activity (78).

Curcumin modulates the expression of chemokines such as IL-6, IL-10, IFNc, and MCP-1 which participate in ARDS in lung tissue Curcumin also reduces TGFβ II receptors and inhibits the expression of smooth muscle actin and tenascin-C (indicators of myofibroblast activation) (79, 80). This data strongly supports the important role of curcumin in modulating inflammation and differentiation of myofibroblasts in the pathogenesis of ARDS caused by viruses in a preclinical models (79, 80).

Nasal administration of curcumin reduces allergic airway inflammation and inhibits structural integrity in mice with allergic asthma by modulating cytokine levels (IFN-1, 5, IL-4, and TNF-α) and phospholipase A2 to inhibit the release of PGD2 (71, 81). In addition, curcumin suppresses ERK 42/44, P38 MAPK and JNK 54/56 activation in mice with advanced asthma (71, 81). Cytokines such as IL-10 inhibit the synthesis of inflammatory cytokines such as CRP, IL-6, and TNF-α (73, 82). Higher levels of IL-10 and IL1RA have been reported in curcumin-treated groups (73, 82).

Curcumin inhibits lipid peroxidation, and protect cell membranes from oxidative damage; . this inhibition of lipid peroxidation results from curcumin binding to iron and also by increasing

the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx), (77). Curcumin reduces chronic stress-induced oxidative damage in the brain, lungs, liver and kidneys (83).The effects of curcumin on the immune system suggests that it may have potential use in supporting treatment strategies for COVID-19.

**Black Cumin.** Black seed (or also knows as black cumin, kalonji) is derived from *Nigella Sativa* the plant family Ranunculaceae (84). The seeds of this plant contain amino acids, proteins, carbohydrates and volatile oils (0.5 to a maximum of 1.5%) and non-volatile or fixed oils (30%). Black cumin has antibacterial, antifungal, anti-schistosomiasis, antioxidant, anti-diabetic, anti-cancer, anti-inflammatory and analgesic properties, and interact with the immune, cardiovascular, gastrointestinal, hepatic and renal systems (85).

Administration of black cumin oil and black cumin polyphenols produces analgesic and anti-inflammatory effects in mice (86), likely due to inhibition of the cyclooxygenase and 5-lipoxygenase pathways (87). Black cumin has beneficial effects on the respiratory tract and lung parenchyma (88) as shown by improvements of respiratory disorders such as asthma and bronchospasm, possibly due to inhibition of histamine release (89). Numerous studies have examined the anti-inflammatory and anti-asthma effects of black seed (90, 91), as shown by the ability of black seed extracts to reduce lung remodeling, preventing endothelin 1 release and improve metaloproteinase matrix 3 (MMP3) and growth factors generation (92).

It is possible that consuming black cumin could be improve symptoms of Covid-19. The protective effect of *Nigella sativa* extract on lung inflammation and oxidative stress was recently demonstrated in a study in rats treated with lipopolysaccharide (LPS) , where it also limited tissue damage (93). LPS increases counts of WBC, eosinophils, neutrophils, basophils, and monocytes, and of oxidative stress markers in bronchoalveolar fluid and serum, and levels of TGF-β1, IFN-γ, PGE2, and IL-levels (93).

**Adiantum Capillus-Veneris.** *Adiantum capillus-veneris* is perennial herbaceous plant of the ferns family, with a rhizome (underground root stem) brown, narrow and knotted, and narrow and thin roots (94). This plant has three-part leaflets and the leaves very narrow branched

to brown or dark purple. One of its main characteristics is the Haggins, which are seen in the tip of the leaflets as prominent, green or brown spots (94). The chemical compounds in this plant include Mucilages, sugar, coffee acid, gallic acid and a bitter substance called Capillarine (94). New studies show that there are substances called Triterpene oxide, Flavonoids, Astragalins and Tannin in this plant, as well as biologically active substances such as Triterpenoids, Olean, Phenylpropanoids, Carotenoids and Alicyclics (94).

In a study of plant composition in northern Iran based on phytochemical tests, it was found that this plant contains tannins, flavonoids, terpenoids and unsaturated sterols (95). Separation of active ingredients was based on the presence of terpenoids and unsaturated sterols. For this purpose, chromatographic method was used on the column. With this method, three compounds were separated from the plant, the structure of which was identified using the results obtained from the mass spectra of infrared (IR) and (PMR) mass and elemental decomposition. These compounds include: 1) Isobaureol with a closed formula (C<sub>30</sub>H<sub>50</sub>O) and a molecular mass of 426. 2) a derivative of isoburonol with an epoxy structure with a closed formula (C<sub>29</sub>H<sub>48</sub>O) and a molecular mass of 412. 3) D methyl terephthalate. With closed formula (C<sub>10</sub>H<sub>10</sub>O<sub>4</sub>) and molecular mass 194 (95, 96). The extract of this plant is used as an herbal medicine and emollient to soothe and strengthen the breast. *Adiantum capillus-veneris* has a long history in pharmaceutical use and its main ingredients have been used in cough syrup called capillaire in the nineteenth century (97, 98). Oxidative stress refers to a condition in which the biological system's ability to detoxify or repair the destructive effects of a variety of oxygen free radicals is insufficient, leading to oxidative damage to cells, tissues or organs of the body, and macromolecules such as DNA, Carbohydrates and protein. Cellular antioxidants significantly delay or inhibit the oxidation of macromolecules (97, 98). The extract of *Adiantum capillus-veneris* leaves provides membrane passage in laboratory conditions and neutralizes free radicals (98). Free radicals cause damage to lipid peroxidation in the DNA and membranes of living organisms, leading to various diseases. Antioxidants neutralize the effects of free radicals in various ways and may

prevent various diseases in the body (98). Inoculation (perineal period) of peripheral blood lymphocytes with H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide) for 2 hours dramatically increases lipid peroxidation and reduces glutathione levels and antioxidant enzymes (94). But the extract of *Adiantum capillus-veneris* leaves effectively prevents lipid peroxidation and significantly increases the antioxidant enzyme activity and glutathione content. Toxic compounds with free radicals are usually combined with glutathione and removed from the body (94). In 2009, Kumar studied the effects of *Adiantum capillus-veneris* antioxidants on human lymphocytes in the laboratory (98). This study surveyed the potential antioxidant effects of this plant on hydrogen peroxide due to oxidative stress that causes damage to peripheral blood lymphocytes (98). Environmental blood lymphocyte incubation with 100 mM of hydrogen peroxide for 2 hours significantly increased lipid peroxidation and reduced glutathione levels and antioxidant enzymes (SOD, CAT, GPX). *Adiantum capillus-veneris* leaves extract was able to significantly prevent lipid peroxidation and improve the activity of antioxidant enzymes and glutathione content. Free radicals caused by lipid peroxidation cause damage to cell membranes and DNA (98). In order to investigate the anti-inflammatory effect of ethanolic extract *Adiantum capillus-veneris* L, a study conducted by Qianing Young et al. (2013) showed that NF- $\kappa$ B signaling in stimulated cells may help to the underlying mechanism of observed anti-inflammatory potential (97). Most importantly, since *Adiantum capillus-veneris* plant extracts suppress inflammation in CD-1 mice caused by LPS (lipopolysaccharide) without liver and heart toxicity, *Adiantum capillus veneris* is a promising drug for the treatment of inflammatory diseases (97). In another study by Yadegari et al., the effect of chronic hypoxia and *Adiantum capillus-veneris* supplements on protein response of P53, TNF- $\alpha$  and exercise-related respiratory changes were investigated and was shown that 3 weeks of exposure to hypoxia, after 6 weeks of exercise, increased P53 and TNF- $\alpha$  and decreased respiratory rate. After 3 weeks of taking Ac-v extract during exposure to hypoxia, the levels of P53 and TNF- $\alpha$  decreased and the level of respiration increased (95).

According to the results of studies, *Adiantum capillus veneris* by inhibiting free radicals and anti-inflammatory effects, leads to the

improvement of the body's immune system, and through this, the body can be protected against various virus and infectious diseases such as COVID-19.

**Thyme.** Thyme is a herbaceous plant with the scientific name of *thymus vulgaris* and is green and fragrant (99). This plant is the most well-known medicinal plant that has high antioxidant properties and there are various species that have been considered by researchers. Anti-inflammatory, antibacterial, antiseptic, antispasmodic, antioxidant, anti-cough and performance enhancer Immune system is one of the remarkable properties of this medicinal plant (100). The medicinal parts of this plant include its branches and dried leaves (aerial parts), which contain various compounds, the most important of which are thymol and carvacrol (101). The medicinal parts of this plant include its branches and dried leaves (aerial parts), which contain various compounds, the most important of which are thymol and carvacrol. Naturally, thymol is the main component in thyme and carvacrol is also a sub-component (101). The biological and therapeutic effects of this extract are mainly attributed to these compounds (101). This plant has a positive therapeutic status in the German Pharmaceutical Commission and ranks first in the Commission of the World Health Organization (101). Thyme extract has been used in traditional medicine to treat several respiratory ailments such as asthma and bronchitis (102) and to treat other injuries caused by the properties of this plant such as antiseptic, antispasmodic, antifungal, antioxidant and antivirus (103, 104). Thyme oils have also been described as a potent bactericide against positive (GARM p) and negative (GARM n) bacteria as well as a bronchospasmodic (105). However, little research has been done on the anti-inflammatory activity of thyme. For example, thyme oil has been reported to produce NO in mice J774A.1 (106). The biological activity of medicinal plants depends on their composition. The most important compounds are thyme, carvacrol and thymol (107, 108). Timol has several biological activities, including anti-inflammatory effects (109), strengthening the immune system (110), antioxidant effects (111), antibacterial, antifungal (112), and free radical improvement (113). Carvacrol also has antimicrobial, antifungal, antioxidant antiseptic and anti-cancer activities (114-117). The therapeutic effect of thyme and oregano oils that

containing thymol and carvacrol as their main compounds in colitis mice has been observed with decreased levels of pre-inflammatory cytokines IL-1 $\beta$ , IL-6 and TNF- $\alpha$ . However, the mediating mechanisms of these repressive effects are unclear (104). Bornol, another ingredient in thyme, has been described as an anti-inflammatory because its dietary supplements significantly reduce the concentration of pre-inflammatory cytokines IL-1 $\beta$ , CRP and IL-6 in mice (118).

Three different species of thyme (*Thymus vulgaris*, *Thymus zygis* and *Thymus hyemalis*) were identified by GC-MS. The main constituents of thyme include thymol, 1,8-cineole, carvacrol, and bidol (119). Treatment of activated cells with thyme was resulted to overall reduction depending on Dose in the release of pre-inflammatory cytokines, TNF $\alpha$ , IL-1 $\beta$ , and IL-6, and a group was treated with some diclofenac (5 micrograms per million liters) (120, 121). In general, thyme extract has a better anti-inflammatory effect at lower concentrations, reducing pre-inflammatory cytokines (TNF- $\alpha$  and IL-1 $\beta$ ) more than diclofenac, and increasing IL-10 anti-inflammatory factor that was not associated with Diclofenac treatment (122).

After 24 hours of incubation, the treated activated cells with each of the thyme sections showed a significant decrease in TNF- $\alpha$  emission compared to the untreated cells. Both *Thymus zygis* and *Thymus vulgaris* had similar effects on TNF- $\alpha$  secretion. For concentrations of 15  $\mu\text{g} / \text{ml}$  and above, the TNF- $\alpha$  decrease was such that the cytokine level was much lower than the inactive baseline level. For *thymus hymalis*, TNF- $\alpha$  secretion was less than the inactive control group for injectable concentrations of 25  $\mu\text{g} / \text{ml}$ . Despite a sharp decrease in TNF- $\alpha$  secretion in 24-hour treatments, treatment with injections *Thymus zggis* and *vulgaris* for 48 hours showed a decrease in TNF- $\alpha$ . For this section, only a concentration of 25  $\mu\text{g} / \text{ml}$  has significantly reduced the TNF- $\alpha$  level, equal to the inactive base level (106, 109).

Thyme had antagonistic effects on the anti-inflammatory cytokine IL-10. 24-hour treatment with each of the sections increased the dose-dependent IL-10 secretion. Higher injection concentrations cause more IL-10 secretion. *Thymus zygis* and *Thymus vulgaris* were more effective than *Thymus hyemalis*. In the case of *Thymus hyemalis*, the increase in IL-10 secretion was less

and was significant only when 15 micrograms per milliliter or higher concentrations were injected. Also, TNF- $\alpha$  did not change with extract. Only *Thymus hyemalis* S2 significantly reduced cytokine gene expression (106, 109).

Cytokines play an important role in the inflammatory response involved in atherosclerosis and other chronic inflammatory diseases (CIBD) such as covid19. Among these cases, interleukin IL-1b, IL-6, IL-10, and tumor necrosis factor ( $\alpha$ ) (TNF- $\alpha$ ) are expressed in atherosclerotic lesions by endothelial cells, macrophages, and smooth muscle cells (123, 124).

Some of them are involved in protogenic processes, such as the re-regulation of adhesion molecules on endothelial cells, and have also been shown to have anti-autogenic roles, such as reducing the differentiation of monocytes in macrophages. Both IL-1 and IL-6 enhance the inflammatory process. Imbalance in the expression of cytokines is involved in the development of many diseases, including CIBDs (125). Cytokines have pathological and beneficial effects on their target cells and are produced by many cell types (126).

Thyme appears to cause expression pre-inflammatory cytokine TNF- $\alpha$ , IL-6 and IL-1 $\beta$ , and anti-inflammatory cytokine IL-10. The amount of pre-inflammatory cytokines decreased with consuming *Thymus vulgaris*, *Thymus zygis*, or *Thymus hyemalis* (after 24 or 48 hours of incubation). These results were consistent with the results of cytokine gene expression in 24 hours of incubation (127). Due to the independent effect of thyme on immune, infectious and disease-related symptoms, this plant can be considered effective in these functions.

**Ginger.** Ginger is the root of fresh or dried *Zingiber officinale*. Ranjil powder and is used to treat flu and appetite, or as an anti-inflammatory agent in the treatment of migraine headaches (128). Ginger compounds include carbohydrates, free fatty acids, amino acids, protein, phytosterols, vitamins, such as niacin, vitamin C components (folic acid, inositol, choline and pentonic acid), vitamins B3 and B6, and essential nutrients Such as calcium, magnesium, phosphorus and potassium (129, 130). This spice is used as an antioxidant and to reduce the pain caused by osteoarthritis. 6- Shogawaol (1-4-hydroxy-3-methoxy-4-desen-1) is one of the important compounds in ginger. It has been reported that this plant has antipyretic and

analgesic effects, as well as inhibitory effects on lipoxygenase activity, which has anti-inflammatory properties in ginger powder (131). Ginger extract has antioxidant properties and neutralizes superoxide anion and hydroxyl radicals. The main antioxidants in ginger include gingerol, shogawaol, zingerun, and a number of phenolic ketone derivatives that have been shown in the laboratory to have many pharmacological and physiological activities such as anti-inflammatory, analgesic, anticarcinogenic, and cardiotoxic effects. Ginger also decrease serum glutamate oxaloacetate transaminase (GOT) levels and glutamate pyruvate transaminase (GPT) (132). Ginger reduces lipid peroxidation and free radicals by reducing malondialdehyde (MDA) and increasing plasma antioxidant capacity. Malondialdehyde is the most important sign of lipid peroxidation (133). Various researchers have confirmed the antioxidant properties of ginger and the elimination of superoxide anion and hydroxyl radicals. Therefore, the anti-inflammatory effect of ginger may be due to a decrease in the formation of prostaglandins and leukotrienes (133). Ginger has also been shown to inhibit the metabolism of arachidonic acid, which has anti-inflammatory properties. One of the mechanisms of inflammation is metabolized oxygenase and prostaglandin E2 and leukotriene B4, which are the two mediators of inflammation. Ginger contains chemicals that have anti-inflammatory potential, and these effects may be due to the effects of gingerols, shogavols, di-aryl heptanoids, and dialdehyde diprenes, which inhibit inflammatory prostaglandins (134). Sudipa Tripathi et al. Observed that ginger extract stimulate IL-12, TNF- $\alpha$ , IL-1 $\beta$  (inflammatory cytokines) and RANTES, MCP-1 in LPS macrophages. Ginger extract also regulated the expression of B7.1, B7.2 and MHC class II molecules (135). In addition, ginger extract had a negative effect on antigen performance in macrophages and saw a significant reduction in T cell proliferation in response to threshold, when ginger-treated macrophages were used as APCs. Significant reductions in IFN- $\gamma$  and IL-2 production were also observed by T cells in response to the simulation threshold (135). In herbal medicine, this herbal supplement has been used to treat influenza and viral and infectious diseases due to its anti-inflammatory and antioxidant properties.

**Cinnamon.** Cinnamon is the dried and peeled pieces of cinnamomum tree bark, which is used as a spice and medicine. Cinnamon contains amidone, mucilage, tannin, a pigment, calcium oxalate, sugar, cinnamomine and resin (136). The main component of cinnamon essential oil is cinnamaldehyde and 5-18% eugenol. Cinnamaldehyde essence has been reported to have an antispasmodic effect on cinnamon. Pharmacological and toxicological research does not pose a risk to human consumption of cinnamon. Cinnamon has the healing properties of carminato, antimicrobial, antioxidant, antiviral and antispasmodic antidiabetic anti-flatulence, antiperspirant, warming and stimulates the uterus (137). There have also been reports of liver cell swelling, increased stomach thickness, and nephritis following long-term use of cinnamon, which has been attributed to its essence (138). The main constituents of cinnamon are 80-95% cinnamon aldehyde, which is the taste of cinnamon due to this substance, 5% cyanoyl acetate, 4% agnol, 3% cariopylen, 2% linalool, 0.7% alpha alpha triplene, 0.7% Coumarin, 0.6% and 8-cineole and 0.4% terpene-4L. Cinnamaldehyde is the main ingredient in cinnamon essence (139). The antioxidant properties of cinnamon extract have been proven during research. aldehyde, gammaegenol, 4-terpineol, terpinene, and camfen are among the phenolic and non-phenolic compounds of cinnamon that have antioxidant properties (140). Also, some of the phenolic and non-phenolic and non-volatile compounds of cinnamon shells that have antioxidant properties include cinacacilli, beta-cystrol, epicatechin, creatinine, syringic acid, cinnamic acid, coumarin and vanillic acid (140). In a recent study by Robert Ossie et al., The addition of cinnamon supplementation significantly inhibited the maturation of DC dendritic cells and inhibited the proliferation of specific T cells, such as the production of Th1 and Th2 cytokines (141). The release of sulfidololcuterin and CD63 expression by basophils was also significantly reduced after the addition of ethanolic cinnamon extract (CE). Treatment of OBA-sensitive mice (OVA) with CE resulted in a significant shift from OVA-specific IgE to IgG2a production and severe inhibition of specific OVA proliferation (141). In addition, inflammation of the airways as well as anaphylaxis is reduced after the challenge of intrauterine or systemic in mice treated with CE.

In general, the anti-inflammatory effect of cinnamon may be used to treat allergic inflammation (141).

**Zinc.** Zinc is an important nutrient for maintaining hemostasis in the immune system, and zinc deficiency can impair the function of the immune system (142). Zinc deficiency is associated with an increased risk and severity of common infections in children, such as diarrhea and pneumonia, in low-income countries around the world (143). It is a transfer metal that plays an important role in the function of many proteins (144). Zinc intracellular displacement may facilitate the rapid signaling of intracellular signaling in immune cells by facilitating the movement of ions between the intracellular space and the cytoplasm (145).

Previous studies in both early rat and human monocytes have shown that zinc deficiency impairs TLR4 receptors and thus reduces the response to bacterial LPS, which reduces generally phagocytic activity and production of cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and IL-10 (145, 146). In addition, zinc deficiency significantly reduces T cell count and causes thymus atrophy. Zinc deficiency also impairs T cell function and impairs T cell cell receptor (TCR) signaling, thereby reducing T cell proliferation and producing cytokines in response to TCR signaling (147, 148). Studies in humans have shown that deficiencies disrupt cytokine production (Th1, IL-2, TNF- $\alpha$  and IFN- $\gamma$ ), while having less effect on Th2 cytokine production (IL-4, IL-6 and IL-10) (89), so it affects the Th1 / Th2 balance. Numerous studies have reported that these regulated disorders are repaired by zinc supplementation (149). In some cases, zinc therapy in vivo and in vitro reduces immune responses through Th cells (eg, Th2 allergic responses and Th17 autoimmune responses) and increases the number and activity of T regulatory cells (Treg) (150). The effects of zinc deficiency on immune function may be somewhat effective in increasing the risk of infection and the entry of a variety of viruses into the body (151).

A study by Chidchamai et al. showed that zinc supplementation in Laotian rural children had no effect on cytokines or T cell concentration, although the supplement did affect lymphocyte and eosinophil concentrations. These cellular subsets may be useful as indicators of zinc supplementation (152). In another study conducted by Martina Mayward et al., 2017, it

was concluded that all immune cells are directly affected by zinc signals. The most important pathological changes during zinc deficiency indicate that it is the main regulator of cell function and signal transmission. However, the underlying molecular mechanisms still need to be examined in more detail to ensure the beneficial effects of zinc application on patients with different diseases (145).

**Vitamin C.** Vitamin C is an essential nutrient that cannot be synthesized by humans due to the loss of a key enzyme in the biosynthetic pathway (153, 154). Severe vitamin C deficiency leads to potentially fatal disease. Vitamin C deficiency leads to weakening of collagen structures, improved wound healing and immunity (155). People with vitamin C deficiency are more prone to potentially fatal infections such as pneumonia (156). Infections can affect vitamin C levels due to increased inflammation and metabolic needs (156). Although the amount of vitamin C needed to prevent scurvy is relatively low (ie 10 mg per day) the recommended diet for vitamin C is higher than many other vitamins (157, 158). A diet of 100-200 mg per day provides vitamin C saturation of plasma concentrations in healthy individuals and covers general needs to reduce the risk of chronic disease (159). Vitamin C has several activities that can significantly play a role in modulating the body's immune system. Due to its ability to donate electrons quickly, it is known to be a very powerful antioxidant, so it is one of the most important biomolecular molecules (proteins, lipids, carbohydrates and nucleic acids) against the damage of oxidants created during cellular metabolism and exposure to toxins and contaminants protects (160).

Vitamin C is also an effective factor in a family of enzymes that regulate biosynthesis and the gene that regulates monooxygenase and dioxygenase (161). Vitamin C enhances phagocytosis and ROS production enhances the effect of microbial lethality, and in the case of T and B lymphocytes, distinguishes and multiplies and enhances antibody levels (162-164) It also modulates the production of cytokines in relation to inflammatory mediators and reduces histamine levels (164, 165). Vitamin C appears to have beneficial effects on the cellular functions of the innate and adaptive immune system (166). Although vitamin C is a powerful antioxidant that protects the body against endogenous and exogenous oxidative challenges, its high

performance as a cofactor for many biosynthetic regulatory enzymes and regulatory genes is likely to play an important role in immune system modulating effects (166). Vitamin C stimulates the migration of neutrophils to the site of infection, enhances phagocytosis and oxidative production, and kills germs (166). At the same time, by strengthening the neutrophil apoptosis by macrophages, and reducing the neutrophil necrosis, it protects the host tissue against overuse (166). Therefore, it is clear that vitamin C is necessary for the body's immune system to provide a sufficient immune response to pathogens and at the same time to prevent excessive damage to the host (166) It seems that vitamin C can prevent and treat respiratory and systemic infections by strengthening the various functions of immune cells. To prevent infection with vitamin C in the diet, 100-200 mg per day is sufficient that not saturate the plasma surface and optimize the cell and tissue levels (166).

Epidemiological studies show that hypovitaminosis C is still relatively common in Western populations, and vitamin C deficiency is the fourth leading nutrient deficiency in the United States (166). The reasons include reduced consumption along with increased needs due to pollution and smoking, fighting infections and diseases with oxidative and inflammatory components, for example, type 2 diabetes and so on. Ensuring adequate vitamin C intake through diet or supplements, especially in groups such as the elderly or other people who are exposed to insufficient risk factors for vitamin C, is essential for proper immune function and resistance to infections (166).

Although information on vitamin C intake during the outbreak of COVID-19 is contradictory, in one study, Orwell examined the mechanisms of vitamin C's effectiveness in preventing corona. He said that vitamin C can greatly reduce the risk of COVID-19 by boosting and improving the immune system and its anti-inflammatory and antioxidant effects (167).

**Garlic.** Garlic, scientifically known as *Allium Sativum*, is a medicinal plant in the category of onion vegetables that contains about 65% water, 2% protein, 1.5% fat and 28% carbohydrates (168). Garlic is one of the medicinal plants that has been used for food and medicine for many years and contains various compounds such as organosulfur, amino acids, vitamins and minerals that have antimicrobial, anti-inflammatory, anti-

clotting, anti-tumor and anti-oxidant, cholesterol and blood glucose lowering properties (168). Some sulfur-containing compounds, including Allicin, S allyl cysteine, and diallyl disulfide, are responsible for the healing properties of garlic. Allicin is known to be the most important biologically active component of garlic (168). Today, garlic is known to be one of the most important factors in maintaining the immune system (168). Its effects on the immune system include modulation of cytokine secretion, promotion of phagocytosis and activation of macrophages, production of immunoglobulin, control of allergic reactions and proliferation of lymphocytes.

According to studies, garlic-derived compounds including S-allyl-L-cysteine (SAC), caffeic acid (CA), uracil, diallyl trisulfide (DATS) known as alitridin and diallyl sulfide (DAS) by inhibiting the main regulatory factor Inflammation, NF- $\kappa$ B, inhibits the expression of several cytokine genes involved in inflammatory responses, including TNF-1, IL-1 $\beta$ , IL-6, MCP-1, and IL-12 (168).

The allicin in garlic increases the expression of CD4 + T cells (CD4 + T cells) and macrophages. It has also been observed that the allicin in garlic controls the parasitic infection by modulating the cytokines that activate macrophages (168). Researchers have shown that dietary supplementation, by increasing the proliferation of T cells, directly and indirectly increases the proliferation and differentiation of B cells and can be involved in the production of immunoglobulin (168).

On the other hand, lectin in garlic appears to release histamine from mast cells and basophils by interacting with IgE molecules at the cellular level (169). Clement et al. Isolated three immune system regulatory proteins (QR-1, QR-2, and QR-3) from raw garlic. QR-2 releases high levels of histamine from leukocytes due to the activation of mast cells and basophils (169).

In a study, Mehrbod et al.(2009) Investigated the antiseptic and antiviral effects of garlic extract on the flu virus (170). They showed that the antiviral effects of garlic extract were observed by reducing the concentration of cytokines during infection, so they introduced garlic as a potent disinfectant during infection (170). One study looked at the anti-inflammatory effects of fresh and warm raw garlic extract (FRGE and HRGE) on producing NO-induced

LPS and inflammatory cytokines due to decreased alisin function in RAW 264.7 macrophages, results showed that the anti-inflammatory effect and Alicin concentration was more in FRGE than HRGF (171). Therefore, the reduction in NO-induced LPS and anti-inflammatory cytokines in RAW 264.7 macrophages was greater through HO1 induction for FRGE compared to HRGE (171).

**Beeswax and Honey.** Beeswax, which is obtained from the melting of bees' nests, is a yellow, soft, and highly absorbable substance that is usually produced by bees. Waxes contain esters, fatty acids and alcohols, and slightly free hydrocarbons of protein, fiber, minerals, vitamins, and glycosidic flavonoids, and 50 uromatic substances, and are also used for pharmaceuticals (172). Propolis is also a gum substance that bees collect from different plants. The chemical composition of propolis is qualitatively and slightly different and will depend on the plants in that area. Propolis contains a lot of nutrients that are very strong due to the abundance of energy and protein (173). It also has antimicrobial, antifungal and immune-boosting properties. Naturally, propolis is made up of 30% wax, 50% gum, 10% essential fats, aromatic and herbal fragrances, and 5% polen (173). Polyphenols are pharmacologically active components of propolis due to their ability to inhibit a variety of enzymes and are considered in this regard. Clinical studies have also shown that propolis contains high concentrations of flavonoids, which are widely used to produce drugs due to their antimicrobial properties (174). A study entitled the effect of propolis and its isolated compounds on the production of cytokines by macrophages showed that propolis inhibited IL-6 production (175). Depending on the concentration, propolis regulates the immune / inflammatory response. Its efficiency may be due to the increasing effect of its compounds and may play a role in the production of cytokine in propolis (175).

Honey is a delicious and amazing food that bees produce using flower nectar, which has been studied in various studies, including antibacterial effects (176), strengthening the immune system (177), and respiration (178, 179). antioxidants and recent studies have also shown antitussive effects (178, 180, 181). Another review study found that the effect of dextromethorphan on cough in adults and the effect of honey on cough

in children compared with placebo had not been shown to have a better effect in reducing the cough in children than in placebo (182). Moderate, decreased severity and frequency of cough compared with dextromethorphan or no medication (182). Therefore, in addition to its antimicrobial, antifungal, antibacterial and antiviral effects, honey has been introduced by the British Public Health Service (PEH) as a treatment for acute coughs caused by upper respiratory tract infections (180). It is also one of the major symptoms in patients with COVID-19. Therefore, this nutrient can be considered as one of the treatment strategies as well as the prevention of this disease.

**Selenium.** Selenium, abbreviated Se, is widely found in soil, plants, and grains, and has a wide range of commercial uses, including shampoos, photocells, and as an anti-inflammatory agent (Selectoc) (183). The biological necessities of Se were first recognized by Schwartz and Voltz (1957), but clear evidence for its function as a key element was provided by Thompson and Scott (1970) (183).

Selenium (Se) is a powerful nutritional antioxidant that combines its effects on selenoproteins to have biological effects. Given the important roles that selenoproteins play in regulating reactive oxygen species (ROS) and redox status in almost all tissues, it is not surprising that the SE diet strongly influences inflammation and immune responses (184).

Using studies on aging or immunity protection against pathogens, selenium strengthens the immune system (184). The immune system is a very special defense mechanism that recognizes and kills non-native cellular and non-cellular organisms. This process requires specific antigen detection at the molecular level and a complex network of functional immune cells (183). Recent evidence suggests that Se significantly affects the function of all components of the immune system, namely non-specific, humoral and cellular mediators (183). The effects of Se on important safety functions indicate that trace element tracking through its ability to enhance and / or restore effective mechanisms or mediators of host defense, as a safety response modifier, may be of high clinical significance (183).

**Lemon.** Lemon or *Citrus limonum* is the sour fruit of the Rutaceae family, which has volatile oil. It was first cultivated in China and India and has gradually spread to other countries. Lemon

has been considered for its high content of organic acids, especially citric acid, and for creating acidic conditions in the treatment of many inflammatory and infectious diseases. It has also been widely used in epidemics such as cholera in various parts of the world, as it has high antimicrobial properties against the bacterium that causes the disease (*Vibrio cholerae*) (185, 186). Sour lemon essence, which is obtained by squeezing the outer part of fresh sour lemon peel, contains 95-92% of various terpenes. Most of it is limonene with Baflander, Camfen, and Pienen. The pleasant smell of lemon essence is related to the presence of citrate, which is found in the amount of 4-7%. In addition, it contains free geraniol, linalool, citronellol and a small amount of nonylide and antranilic acid (187).

Vitamin C is a powerful antioxidant that, in addition to eliminating harmful cells and free radicals in the body, prevents the formation of cancer cells and cancer (188). Vitamin C and the antioxidants in sour lemons help to eliminate toxins from the body caused by a variety of contaminants such as lead or dust in the air. Sour lemon is a great source of vitamin B complex and a precursor to vitamin A. These vitamins increase the body's immunity. Lemon has a very high fiber, which has been very helpful in maintaining good health. Citric acid in lemon helps digestion (188). Lemon is very useful for irregular heart movements caused by improper digestion and liver toxins. The acids in lemons decrease uric acid and dilute the blood. Sour lemon lowers blood cholesterol levels. Lemon also improves normal and migraine headaches (188). The bioflavonoids in lemons reduce the brittleness of capillaries. People who suffer from sciatica should eat a lemon before a meal. Sour lemon is also effective in improving memory enhancement (188). A study examining the protective effect of lemon on inflammation and oxidative stress in rats showed that malondialdehyde levels, alpha tumor necrosis factor (TNF-a), C-response protein and leptin in the sour lemon supplement group in the comparison with the control group was significantly lower (189). Lemon juice in all three doses significantly improved serum levels of TAC, MDA, TNF $\alpha$  and hs-CRP in the treated groups. Consumption of 7.5 ml of lemon juice also significantly reduced leptin levels. However, lemon juice did not have a significant effect on adiponectin levels. This study suggests that lemon juice as a potential dietary alternative can reduce

leptin levels and oxidative and inflammatory damage in mice (189).

**Magnesium.** Magnesium plays a key role in many cellular responses. More than 300 metabolic reactions require magnesium as a cofactor (190). Magnesium is involved in many processes affecting muscle function, including muscle contraction, protein synthesis, oxygen consumption, energy production, and fluid balance, and is a physiological regulator of cell membrane strength and neuromuscular, cardiovascular, and immune function (191). However, magnesium deficiency is often found in industrialized countries. Numerous studies have reported that athletes may also be deficient in magnesium. Clinical signs of inflammation was one of the early signs of magnesium deficiency in rats. Immunosuppression of immune cells, such as monocytes, macrophages, and polymorphonuclear neutrophils, which produce a variety of biological substances, is also another sign of magnesium deficiency. Some of these cells are powerful inducers of inflammation (cytokines, free radicals, eicosanoids) (192). Large amounts of circulating cytokines such as IL-6 can be detected early in the magnesium deficiency diet and lead to the release of acute phase proteins by the liver (192). It has been observed that under laboratory conditions, high magnesium concentrations reduce the activation

of human leukocytes. Extracellular magnesium can also prevent the activation of leukocytes through calcium, as magnesium is neutralized in many physiological and pathological processes by calcium. The inverse correlation between magnesium uptake and plasma CRP levels has also been observed (193). Magnesium can also reduce anxiety and stress by suppressing the hormone adrenaline, and can be very helpful in stressful situations related to the spread of covid-19 disease (194).

Because magnesium is involved in a wide range of biological activities, it can be a protective factor against asthma and chronic airway obstruction. In a study, Britton et al. Showed that daily magnesium intake for 12 months in adults aged 18-70 years improved lung function and reduced the incidence of chronic airway disease and wheezing (194).

### CONCLUSION

There are currently no approved drugs to treat COVID-19. The drugs available for COVID-19 primarily act as a protease. Herbal medicines and supplements studied in this study can act as COVID-19 inhibitors through anti-inflammatory, Antioxidants effects, as well as boosting the immune system. However, further research on the dosage and other possible uses of these supplements is necessary for patients with COVID-19.

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