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The potential of caffeine contained in the coffee to modulate the immune system of the COVID-19 sufferers: A review

Anis Irmawati [1, *], Mochamad Daffa Athallah [2], Retno Indrawati Roestamadji [1], Awalia Aprilizahrani Patiran [2], Noor Faizah Balqis [3], Tantiana [1], Hendrik Setia Budi [1], Yassir Ahmad Azzaim [4, 5] and Manuel Raynaldy Sihombing [5]

[1] *Department of Oral Biology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2] *Undergraduate Program, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[3] *Postgraduate Program, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia.*
[4] *Department of Dental Material, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[5] *Magister Program, Dental Health Sciences, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.*

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Abstract

Background: The COVID-19 pandemic is a worldwide epidemic caused by the SARS-CoV-2 virus, initially detected in Wuhan City, Hubei, China in December 2019. This presents an unparalleled difficulty in identifying efficacious medications for treatment. Despite numerous clinical trials employing various medicines, there remains a dearth of targeted therapies for COVID-19. The progression of COVID-19 clinical symptoms, for example a severe pneumonia, arespiratory distress syndrome (ARDS), and multiorgan failure, is a result of an exaggerated immune response characterized by increased inflammation, oxidation, and cytokine storm. Presently, coffee beans contain caffeine, which is a highly consumed chemical. Caffeine exerts beneficial benefits on the human body, influencing multiple systems such as the immunological system, central nervous system, digestive system, and respiratory system. The impact of caffeine is contingent upon the quantity and composition of the product in which it is present.

Objective: Analyze the potential of caffeine as an immunomodulator in COVID-19 sufferers.

Discussion: Caffeine functions as an agonist of TAS2R receptors and an antagonist of adenosine receptors. The immunomodulatory properties of caffeine can assist in diminishing the severity of SARS-CoV-2 infection by stimulating adenylyl cyclase, which converts ATP into cAMP. The heightened level of cAMP stimulates the intiation of protein kinase A (PKA), which subsequently suppresses the secretion of pro-inflammatory cytokines. Furthermore, caffeine has the ability to suppress the generation of reactive oxygen species (ROS), hence reducing the unleash of pro-inflammatory cytokines.

Conclusion: Caffeine provides health benefits with its immunomodulating properties to COVID-19 patients and can be regarded as a supplementary treatment in patients with COVID-19.

Keywords: COVID-19; SARS-Cov-2 Kopi; Kafein; Imunomodulator; Badai Sitokin; Sitokin Proinflamasi; Good Health and Well Being.

1. Introduction

The onset of a pneumonia epidemic can be traced back to Wuhan, China in December 2019, with a significant quantity of instances linked to seafood shops that sold live animals. On January 7 2020, scientists in China succeeded in isolating

* Corresponding author: Anis Irmawati

the corona virus from patients in Wuhan. The virus in question is responsible for the onset of a medical condition known as COVID-19, and its transmission is occurring at a swift pace around the globe. The World Health Organization formally designated this virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On March 5 2020, 96,000 cases were recorded worldwide. Out of the individuals who have contracted the infection, 20% are currently in a critical state, 25% have successfully recuperated, and 3.5% have unfortunately passed away [1]. Covid-19 was first identified in Indonesia on March 2, 2020 [2]. Indonesia has experienced a dramatic surge in the tally of verified COVID-19 cases. As of June 2020, there have been 31,186 confirmed cases and 1851 deaths. DK1 Jakarta Province recorded the largest number of cases, with 7,623 confirmed cases and 523 deaths, accounting for 6.9% of the total [3].

The global patient count is steadily rising, with certain infected individuals exhibiting symptoms ranging from moderate to severe. Mild symptoms experienced by COV1D-19 patients include fever, dry cough, cough with phlegm, fatigue, loss of appetite, sore throat, blocked nose and headache. Patients who experience more serious conditions can experience pneumonia, lung inflammation, acute respiratory distress syndrome (ARDS), multiple organ dysfunction before ultimately dying, and acute kidney failure [4,5,6]. The occurrence of severe symptoms in patients can be attributed to the virus triggering an abnormal immune response in the host. To overcome this, it is necessary to regulate the host immunological response. Based on the pathophysiology of SARS-CoV-2, it is thought that tissue damage occurs as a result of impaired inflammatory systems and cytokine storms [5,7,8].

Several actions taken to treat Covid-19 patients include self-isolation or quarantine, symptomatic treatment, intensive care and vaccination. The purpose of self-isolation or quarantine is to mitigate the transmission of the virus to individuals, but can cause stress and anxiety in patients [9]. Symptomatic treatment such as administering symptom-relieving drugs and antibiotic or antiviral medication may induce adverse symptoms such as nausea, vomiting, diarrhea, and headaches [10]. Meanwhile, side effects from the Covid-19 vaccine include headaches, fever and fatigue [6].

Therapeutic options to modulate the immune system are urgently needed. Numerous research have examined the capacity of caffeine to function as a medicinal agent. Caffeine in *coffee* has several benefits, including increasing alertness, eliminating drowsiness, improving mood, increasing endurance and increasing muscle contractions [11]. In addition, caffeine can function as an anti-inflammatory agent in individuals with COVID-19. Caffeine suppress the generation of Tumor Necrosis Factor a (TNF-a) and the expression of inflammatory NOD like receptor protein 3 (NLRP3) by acting on the MAPK/NF-kB pathway. As a result, there is a decrease in the synthesis of Interleukin IL-18, 1β(IL-1β), TNF-a, and IL-6 [12]. Caffeine also acts as an immunomodulator because it acts as an adenosine receptor (AR) antagonist and type 2 taste receptor (TAS2R) agonist [13]. The inhibitory effects of coffee on adenosine receptors and TAS2R receptors contribute to the mitigation of SARS-CoV-2 by modulating the immune response associated with these receptors [12].

2. Literature Review

2.1. COVID-19

SARS-CoV-2 is the pathogen responsible for the onset of Coronavirus Disease 2019 (COVID-19), an extremely transmissible respiratory ailment. SARS-CoV-2, also known as Coronavirus 2, belongs to the genus Beta corona viruses because the genome of this virus is about 30,000 base pairs long, has a "spike" protein, and can spread from animals to humans (S). The SARS-CoV-2 virus composed of four structural proteins called envelope (E), spike (S), nucleocapsid (N), and membrane (M) proteins, is an RNA virus characterized by its crown-like and is between 60 to 140 nanometers in diameter. Being zoonotic means that the SARS-CoV-2 virus can infect humans and vice versa. Direct contact with diseased animals or animal products, such as milk or meat, can spread zoonoses. not properly processed. According to scientific data, coughing or sneezing (droplet) can spread COVID-19 from person to person [5,14].

COVID-19 patients show various clinical manifestations, including those who do not show symptoms (asymptomatic), to those who experience severe symptoms, sepsis, ARDS, septic shock, pneumonia, and severe pneumonia. Patients who experience mild symptoms have an acute infection of the upper respiratory tract without complications, and may experience symptoms such as fever, exhaustion, and cough (with or without discharge), loss of appetite, feeling unwell, sore throat, blocked nose, or headache. Additionally, some instances have mentioned having gastrointestinal symptoms as nausea, vomiting, and diarrhea [15].

Individuals who have contracted the SARS-CoV-2 virus exhibit respiratory symptoms such as fever, cough, sneezing, and difficulty breathing. The predominant symptoms are pyrexia, unproductive cough, and lethargy. Patients can also experience other symptoms such as coughing up sputum, difficulty breathing, sore throat, and even ARDS. SARS-CoV-2 induces respiratory infections that result in the formation of ARDS. This condition causes the lungs to become damaged

and inflamed, causing difficulty breathing. ARDS is the primary factor leading to mortality in individuals with COVID-19 [6]. The primary cause of ARDS in SARS-CoV-2 infection is an excessive release of cytokines, known as a cytokine storm, which refers to an excessive and unregulated systemic inflammatory reaction. The cytokine storm also leads to multiorgan damage [5]. COVID-19 may result in severe consequences, such as hypoxia, acute respiratory syndrome, kidney failure, liver damage, pneumonia, shock, heart attack, and even death [16].

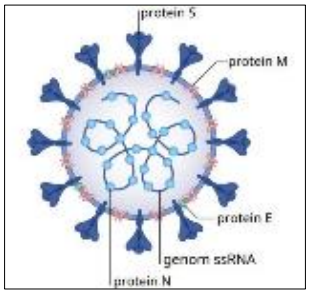

Figure 1 Structure of SARS-CoV-2 [5].

COVID-19 develops in the human body starting with the SARS-CoV-2 virus infiltrates the human body via the respiratory tract, such as the nose or mouth. The primary mode of transmission for SARS-CoV-2 is through direct transfer between individuals, leading to increased aggressiveness in its transmission. SARS-CoV-2 is transferred via respiratory droplets that are expelled while coughing, sneezing, and talking [6].

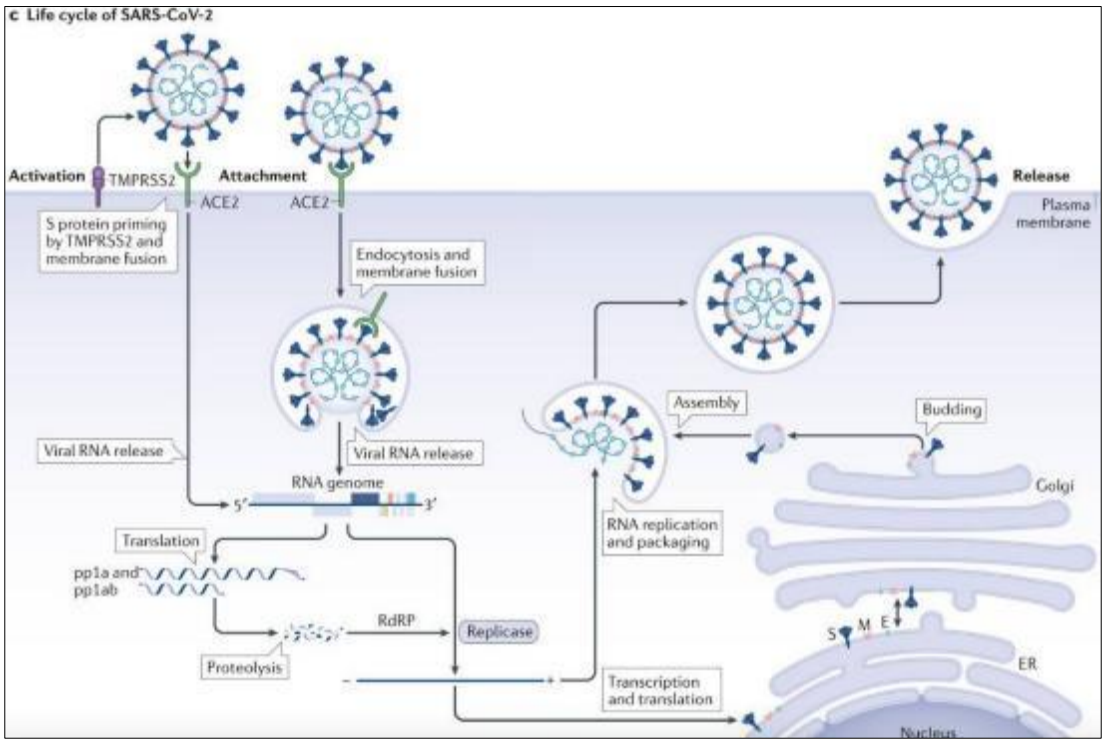

Figure 2 The lifespan of SARS-CoV-2 [5].

The initiation of the SARS-CoV-2 entry process occurs when the viral spike (S) protein attaches to Angiotensin-Converting Enzyme 2 (ACE2) on the outer layer of host cells [5]. SARS-CoV-2 will attach to receptors and penetrate cells. The glycoproteins included in the viral spike envelope will attach to the ACE2 cellular receptors located in the mouth cavity and respiratory tract. The viral complex enters the cell and either directly fuses with the cell membrane or undergoes endocytosis to enter the cytoplasm, after which it is subsequently discharged into the cytoplasm. The spike protein (S) is an outwardly projecting protein situated on the surface of the virus, with the function of binding the virus to the receptor on the host cell. The S protein is composed of two subunits: the S2 subunit facilitates the fusion of the viral membrane with the host cell membrane, and the S1 subunit contains the receptor-binding domain (RBD) that interacts to ACE2. The S protein gets cleaved at the point where S1 transitions into S2. The viral genome RNA is liberated within the cytoplasm, initiating translation at the first Open Reading Frame (ORF). ORFla/b found in the genome of

SARS-CoV-2. The ORF is initially translated into two polyproteins, ppla and pplab. The viral proteases subsequently cleave these polyproteins, resulting in the production of 16 tiny non-structural proteins, including RNA dependent RNA Polymerase (RdRP). Afterwards, the viral RdRP duplicates the viral genomic RNA, while the host cell's endoplasmic reticulum and Golgi complex produce the four structural proteins (E, S, N, and M). The S protein's role involves attaching to and penetrating host cells. The E protein encodes the viral envelope protein that forms the outer layer of the virus. The M protein encodes a membrane protein that forms the inner layer of the virus and contributes to the formation of the virus's structure. The N protein helps protect the viral genome and forms the nucleocapsid. Following that, the genomic RNA and structural proteins undergo a transformation, resulting in the formation of new virus particles, which are then released through exocytosis [5].

The factors that impact SARS-CoV infection include the characteristics of the virus itself and the overall health condition of the affected person. The virulence of the infection is governed by the virus's capacity to harm host cells and elude the immune response. Disruptions to the immune system are also involved in causing tissue damage during COVID-19 infection. If the immune response is inadequate, the virus can reproduce freely and damage body tissue. Conversely, an excessively robust immune response might result in harm to tissues and organs [13].

2.2. Immune system

The immune system provides protection against bacterial pathogens, viral, and parasitic illnesses, as well as eliminates other foreign substances that can interfere with the healthy function of cells and tissues. There are 2 types of defense systems in living creatures, namely the innate defense system or innate immunity and specific defense systems or adaptive immunity. Both play a crucial part in preserving health and reinforcing the body's defense against diseases and other ailments [17]. Nonspecific immune response is innate immunity, which means the body can respond to foreign substances that enter the body even though the body has never been exposed to these substances. The nonspecific immune response can detect the presence of foreign substances and safeguarding the body from the consequent harm, but is unable to recognize and remember these foreign substances. Nonspecific immune responses involve several main components, such as physical, physiological, and cellular defenses. These components include the epithelium and the antimicrobial substances produced on its surface, various types of proteins in the blood such as the complement system, inflammatory mediators and cytokines, phagocytic cells such as polymorphonuclear cells, natural killer (NK), and macrophages cells are also part of this defense [17,18].

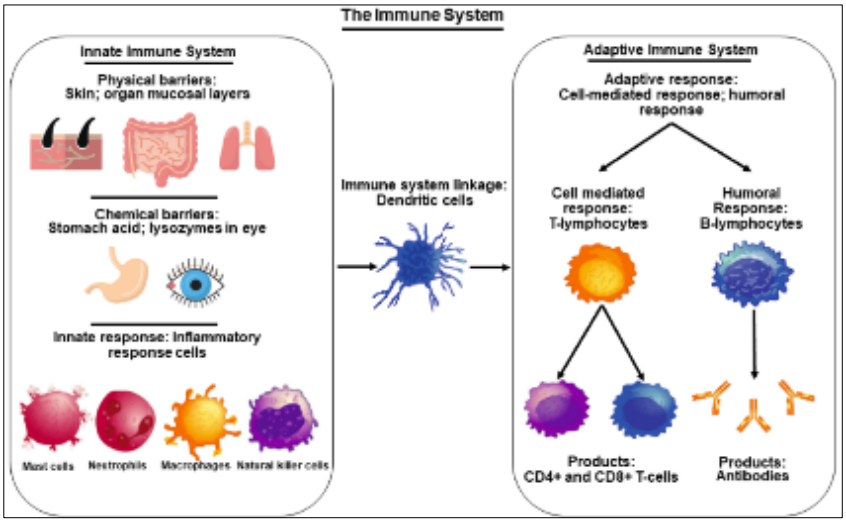

Figure 3 Adaptive and innate immune system [19].

The skin serves as the primary barrier against diseases that invade the human body. The skin acts as a physical barrier, mostly relying on a layer of dead cells on its surface, to provide defense. New cells are continuously produced from cell division, moving from within the skin to the surface of the skin. Apart from that, the skin also produces a strong protein compound called keratin. The very strong structure of keratin makes it difficult for pathogenic microorganisms to decompose. In addition, the skin also produces oil and sweat glands that help maintain an acidic environment (pH3-5) to prevent microbial colonization [17].

Salivary glands, tears, and mucosa are included physiological barrier which plays an important role in inhibiting microbial colonization on body surfaces. This secretion wets the exposed area and contains the enzyme lysozyme which

is able to destroy the cell walls of bacteria that try to enter the respiratory system and the area around the eyes. Mucus is a viscous substance secreted by cells in the mucous membranes. In the trachea, cilium epithelium cells assist clear mucus with microorganisms stuck in it, thus avoiding bacteria from invading the lung. If microorganisms enter through food, the microbes will be exposed to stomach acid (HCI) which can kill the bacteria [17,18].

Microorganisms that successfully penetrate the body's defenses then need to pass through a second defense. Main mechanism of cellular barrier or non-specific internal defense system relies on phagocytosis, which is the process in which certain white blood cells engulf microorganisms that attack the body. In addition, internal non-specific defense also involves natural killer (NK) cells, inflammatory responses, and antimicrobial compounds [17]. Some internal innate immunity. including:

1. Neutrophils are a subset of leukocytes, play a vital role in the body functions. These cells act as phagocytic cells, which means they have an ability to engulf and digest microbes or other foreign substances in the body. Neutrophils constitute around 60-70% of the overall count of white blood cells and are the predominant kind of phagocytic cell. When there is a chemical signal (chemotaxis), neutrophil cells approach the area infected by the microbe. Neutrophil can also leave the blood circulation to enter infected tissue and kill the microbes that cause infection [18].

2. Monocytes. Although they account for only 5% of the total white blood cells, but they are capable of providing very effective phagocytic defense. Monocytes are a type of phagocytic cells that play a vital role in the immune system's fight against infection and inflammation. Once mature, monocyte cells undergo circulation in the bloodstream for a duration of many hours prior to their migration into the tissues of the body and turning into macrophages. Similar to Amoeba, these cells are able to form elongated pseudopodia to capture and digest microbes using their digestive enzymes. However, some types of microbes have evolved to avoid macrophage attacks, such as bacteria with capsules that prevent attachment of pseudopodia, as well as bacteria that exhibit resistance to macrophage digesting enzymes and are capable of intracellular reproduction [17].

3. Eosinophils, a small part of white blood cells, only around 1-6% of the overall quantity of white blood cells can be found in the bloodstream. Eosinophils are also phagocytic cells, which means they have the ability to engulf and digest microbes or foreign substances in the body. Eosinophils are activated by cytokines and chemokines released by other immune cells during infection or allergy. In an allergic response, eosinophils respond to allergen exposure and release chemical compounds such as histamine, prostaglandins, and leukotrienes, which cause allergy symptoms such as itching, rash, swelling, and difficulty breathing [20].

4. Natural Killer (NK) cells are a specific type of lymphocytes that form a component of the innate immune system. Natural killer (NK) cells are found in the circulatory system and can be identified in several bodily tissues, such as the liver, spleen, and lungs. NK has the ability to kill cells that change or behave abnormally, such as cells infected with viruses, tumor cells, and cells that have been damaged. NK cells recognize these cells through a different target recognition mechanism than T and B lymphocytes, namely by detecting the presence of abnormal cell surface molecules. NK can damage target cells by releasing cytotoxic compounds or by inducing apoptosis, namely normal and controlled programmed cell death [21].

5. Inflammation, is the body's response to tissue damage that occurs due to various factors, such as infection, injury, or chemical stimulation. The inflammatory process is influenced by histamine and prostaglandins. Histamine, which is produced by body cells, functions to increase muscle strength and permeability of capillary blood vessel walls in the infected area. This speeds up blood flow and enhances the migration of phagocytes cells from the bloodstream to the damaged tissue. The first phagocytes to cover a wound are neutrophils, then monocytes will develop into macrophages which will clean damaged tissue cells. Signs of inflammation usually include redness, swelling, pain, and fever [22].

6. Antimicrobial Proteins, is a proteins that contribute to the body's nonspecific defense system are called the complement system. These proteins can kill microorganisms directly or prevent their reproduction. Complement proteins are inactive when circulating in the blood, but a few molecules of one type of protein can trigger a large wave of reactions and activate many other complement protein molecules. Complement proteins are activated when they bind to antigens belonging to pathogens or to the surface of bacteria. Some complement proteins can form complex pores that induce lysis in pathogens or cause nonspecific host defense responses such as inflammation and attraction of phagocytic cells to damaged cells or tissues [17].

The adaptive immune system, also known as the specific immune system or antigen-regulated immune system, is the body's complex defense system that responds specifically to antigens (foreign substances) that enter the body. This

process operates when the pathogen has effectively surpassed the body's general defense mechanisms. The adaptive immune system possesses the capacity to identify and retain memory of previously encountered antigens, so that a faster and stronger immune response can be triggered if the antigen re-enters the body. The body's defense is specifically carried out by antibodies formed by lymphocytes due to antigens entering the body [17].

Lymphocytes consist of two types, T lymphocytes (T cells) and B lymphocytes (B cells). B cells are the humoral component of adaptive immunity which functions to secrete antibodies and release cytokines and act as antigen presenting cells (APC). B cells originate from hematopoietic stem cells situated within the bone marrow. When they are fully developed, they emerge from the bone marrow with distinct cell membrane antigen-binding receptors. B cells can be classified into three distinct types: dividing, plasma, and memory B cells. B cells undergo cellular division and serve the purpose of generating memory B cells and plasma B cells. Plasma B cells serve the purpose of generating antibodies. Memory B cells function to remember antigens that have entered the body and stimulate the formation of plasma B cells if a second infection occurs [17,23,24].

T cells come from the thymus, which refers to a gland located above the heart in the thorax cavity, which plays an important role in helping to mature T lymphocytes produced by the bone marrow. The main function of T cells is to help build the cellular immune system, which is carried out through direct attacks on antigen-producing cells. Apart from that, T cells also help the production of antibodies by plasma B cells. Three distinct types of T lymphocytes can be identified., namely cytotoxic T cells, helper, and suppressors. Cytotoxic T cells has the capacity to identify and eliminate cells that are contaminated by viral agents or malignant cells. Cytotoxic T cells carry out their function by releasing substances that can kill target cells, like enzymes and cytotoxic proteins. T cells helper functions to help other immune cells, like plasma B cells and cytotoxic T cells, in responding to infection or disease. Suppressor T cells function to reduce and stop the immune response by inhibiting the initiation of helper T cells and cytotoxic T cells to reduce excessive immune responses and prevent tissue damage. Suppressor T cells can also inhibit B cell activation to prevent excessive antibody production and protect normal tissue. Suppressor T cells will work after the infection has been successfully treated [17,25].

Antibodies are protein molecules that are formed as response to the presence of antigens, namely unwanted foreign objects in our body. The process of forming antibodies takes around 10-14 days and is carried out by B cells or B lymphocytes. The function of antibodies is to neutralize or destroy antigens that enter into the body. Every second, about 2,000 antibody molecules are produced by B cells. Antibodies are found in the bloodstream and noncellular fluids and have a molecular structure that matches that of the antigen. Each type of antibody is specific for a certain type of antigen [17].

Antibodies are also called immunoglobulins (Ig) or serum protein globulins, because they function to protect the body through the immune process. There are five types of immunoglobulins, namely IgM, IgG. IgE. IgD, and IgA. Immunoglobulin G (IgG) circulates in the body, especially in the blood, lymph system and intestines. This compound has a strong anti-bacterial and viral effect, and neutralizes toxins. IgG can spread into white blood cells and body tissues, and can cross the placenta and provide immunity to the unborn baby [17]. Immunoglobulin M (IgM) is the first type of immunoglobulin produced by the body, this is because IgM plays a role in removing waste, particles (smaller than 2μM), and dying cells by coating them and facilitating their engulfment by macrophages through opsonization and antibody-dependent phagocytosis. In the mucosa IgM plays a role in establishing a healthy microbiota [26]. The principal antibody generated by the mucosa is immunoglobulin A (IgA), which is the second most prevalent antibody in the circulation. Its major role is to protect the mucosal surfaces, such as the respiratory tracts and gastrointestinal, from invading pathogens. Immunoglobulin A (IgA) is a type of immunoglobulin found in mucus and other body fluids such as tears, milk, and digestive and respiratory tract mucus [27]. Immunoglobulin E (IgE) is a type of immunoglobulin involved in allergic responses and protecting the body from parasites. IgE is produced when the body is exposed to allergens or parasites. Immunoglobulin D (IgD) is the least abundant type of immunoglobulin found in human blood. IgD is present on the membrane of B cells and functions in the stimulation of B cell activity to produce other antibodies, such as IgM and IgG, when the body is exposed to foreign objects or antigens [17].

Adaptive immunity is divided into 2 types, namely passive immunity and active immunity. Active immunity is the immune response generated by the body itself. The body produces antibodies in response to infectious antigens. This type of immunity can occur naturally or artificially or artificial active immunity. Natural immunity formed through diseases, such as smallpox, in which the body develops humoral immunity and cellular immunity after being infected with the smallpox virus. Once someone recovers from smallpox, they will not get smallpox again. On the other hand, artificial active immunity obtained through vaccination or immunization against certain microorganisms. Vaccination involves the introduction of a weakened or inactivated antigen into the body to promote the development of immunity [17].

Passive Immunity is immunity obtained not from antibodies synthesized in the body. As well as active immunity, passive immunity also occurs naturally or natural of passive immunity and artificially or artificial passive immunity. Natural of passive immunity is immunity obtained not from one's own body, but from another person's body. For example, a baby's immunity is obtained from his mother. While still in the womb, babies get antibodies from their mother through the placenta and umbilical cord. Then after birth, the baby gets antibodies from exclusive breast milk through the breast feeding process. Whereas artificial passive immunity is immunity obtained through the injection of antiserum containing IgG antibodies or other immunoglobulins. Artificial passive immunity only lasts a few weeks because the immunoglobulin that comes from the body will be broken down by the body [17,28].

During an infection, the body will respond by increasing the production of cytokines, namely proteins that act as signals to help the body fight infection. Excessive cytokines can cause excessive inflammation (cytokine storm) which can damage the body's organs.

2.3. Immunomodulators

Immunomodulators are a certain type of compound that can balance the body's defenses both non-specifically and specifically, through immune mechanisms or cellular or humoral defense. Immunomodulator or biological respons modifier consists of various kinds of ingredients, both chemical, synthetic and natural, which are used in immunotherapy to restore the body's immune imbalance [29].

Immunomodulators consist of immunostimulators, immunorestorators and immunosuppressors. Immunostimulators work by activating nonspecific and immunopreventive immunotherapy. They stimulate important components of the immune system such as properdin, protective secretory IgA antibodies,complement systems, phagocytosis, and protective secretory IgA antibodies, release of alpha and gamma interferons, B and T lymphocytes, synthesis of cytokines and specific antibodies. The utilization of immunostimulants in managing different infectious diseases is motivated by multiple factors, such as bacterial antibiotic resistance, allergic responses to antibiotics, immunosuppressive impact of drugs, and suboptimal effects of antibiotics on viral infections [30].

Immunosuppressants have the ability to control different aspects of the immune response. They can affect the rate at which genes that encode proteins necessary for lymphocyte function are transcribed. Additionally, they can regulate the later stages of the humoral response, such as the levels of antibodies produced and their affinity. These substances are employed in different medical fields, such as the management of autoimmune disorders and organ transplantation. Examples of these substances include corticosteroids, histamine antagonists (HA), nonsteroidal anti-inflammatory drugs (NSAIDs), and numerous inhibitors of cellular signaling [31].

In general, the use of the immunomodulator group of drugs is synthetic or chemical drugs such as isoprinosine, levamisole, BCG vaccine and many more. The use of this synthetic immunomodulator has several disadvantages such as causing allergic reactions and hypersensitivity. In long-term consumption, use of synthetic immunomodulators can cause digestive disorders, dizziness, fever, skin rashes, constipation, increased uric acid levels, and so on [32].

Various immunomodulatory compounds derived from plants with enhanced bioavailability and minimal toxicity could be a solution to overcome the cytokine storm syndrome observed in COVID-19 Immunomodulators have the ability to activate, inhibit, or control different elements of the host immune system, such as adaptive immune system and innate immune system . Given the relationship between the immune-inflammatory axis and viral infection, it is suggested that natural compounds with anti-inflammatory and immunomodulatory properties should be investigated for their potential use in preventing and treating COVID-19. Contemporary medication research and development rely on chemicals, biologics, and individual components that are deemed crucial in the treatment of a disease. Nevertheless, it is unattainable to acquire a solitary chemical that exhibits both high effectiveness and minimal toxicity in order to specifically target cellular pathways responsible for generating diseases. In such situations, natural substances exhibiting favorable immunomodulatory effects can serve as fundamental components or models for the identification and advancement of novel pharmaceuticals. Plant-derived immunomodulatory chemicals can serve as substitutes for manufactured drugs, which often come with notable adverse effects [33].

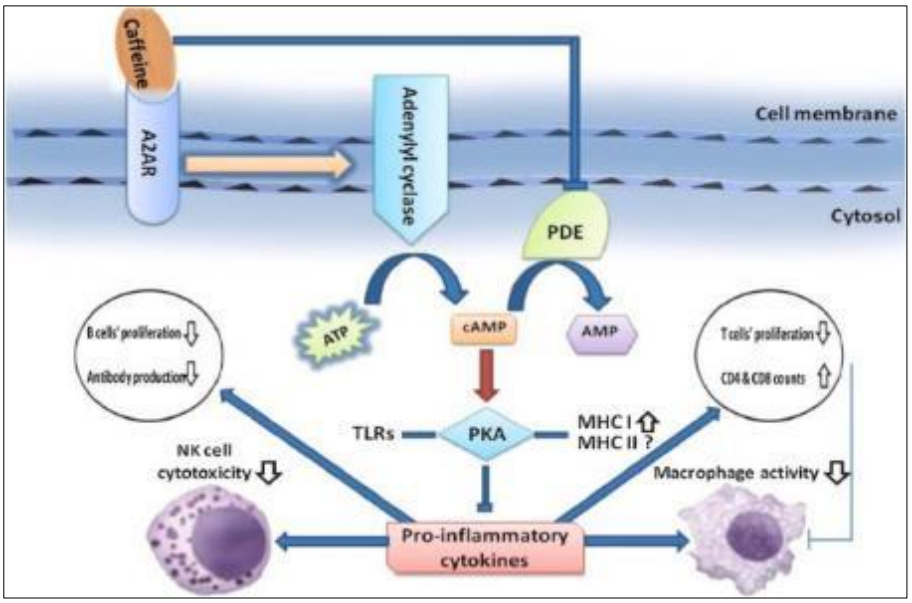

Figure 4 Mechanism of immunomodulation by caffeine [34]

Caffeine, upon binding to A2A receptors, stimulates adenylate cyclase, leading to the conversion of ATP into cyclic adenosine monophosphate (cAMP). This phenomenon triggers a series of intracellular signaling processes by increasing the levels of cAMP, achieved by inhibiting phosphodiesterase (PDE). Therefore, the binding of caffeine outside the cell is increased inside the cell due to the presence of the second messenger cAMP. Elevated levels of cAMP stimulate protein kinase A (PKA) and impede the secretion of proinflammatory cytokines. Inhibited inflammation diminishes the functioning of diverse immune cell, including natural killer (NK) cell, B and T cell proliferation cell ability to destroy cells, macrophages, and the generation of antibodies. Furthermore, it regulates the amounts of major histocompatibility class I (MHC I) and toll-like receptors (TLRs) molecules [34].

2.4. Cytokine storm

The phrase "cytokine storm" denotes a collection of immune dysregulation illnesses that exhibit various systemic inflammation, constitutional symptoms, and malfunction in several organs. If these disorders are not appropriately treated, multiorgan failure may result. Depending on the cause and kind of treatment used, cytokine storms might differ in appearance and length. Although the triggers may be different in the early stages, the clinical manifestations of cytokine storm in the late stages often converge and frequently overlap. Almost all patients who experience a cytokine storm will experience a fever. In addition, patients can experience symptoms such as fatigue, loss of appetite, headaches, skin rashes, diarrhea, joint pain, muscle pain, and neuropsychiatric disorders. These symptoms may be brought on by the immune system's reaction, cytokine-induced tissue damage, or acute phase physiological abnormalities. When the illness is severe, it can quickly worsen and cause serious bleeding or disseminated intravascular coagulation, which is a clogging of the blood vessels. Patients can also experience shortness of breath, hypoxemia, low blood pressure, impaired hemostatic balance, vasodilatory shock, and death. Numerous individuals also have respiratory issues, such as coughing and elevated heart rate, which can develop into ARDS with hypoxemia and necessitate the use of a mechanical ventilator for treatment. In individuals undergoing cytokine storms, the confluence of blood coagulation issues, hyperinflation symptoms, and a reduction in platelet counts may heighten the likelihood of spontaneous bleeding. In very severe cytokine storm situations, complications such as kidney failure, acute liver damage or impaired bile flow, as well as stress-induced cardiomyopathy or takotsubo syndrome, may also occur. Capillary leak syndrome and the development of anasarca can result from endothelial cell destruction, decreased albumin levels in the acute phase, and kidney function issues. These changes are comparable to those observed in cancer patients receiving high doses of interleukin-2 therapy [35].

The laboratory test results in patients who are experiencing cytokine storms differ based on the root reason. Elevations in nonspecific inflammatory indicators, like a C-reactive protein (CRP), typically indicate a rise and are associated with the intensity of the cytokine storm. In addition, numerous individuals also encounter hypertriglyceridemia and a range of abnormalities in their blood counts, such as leukocytosis, leukopenia, anaemia, thrombocytopenia, as well as elevated levels of ferritin and d-dimer in their blood. The fluctuations in the quantity of cells present in the bloodstream are most likely a result of an intricate interplay between the impact of cytokines on the generation and discharge of cells from the bone marrow, cell damage induced by the immune system, and cell migration influenced by chemokines. Marked

increases in serum levels of inflammatory cytokines may also occur, such as interferon-y (or interferon-y-induced chemokines CXCL9 and CXCL 10), IL-2, IL-10, and soluble IL-6 receptor alpha, which are markers of T cell activation. In particular, serum levels of IL-6 can reach very high levels in patients experiencing a cytokine storm [35].

Table 1 Clinical presentation of cytokine storm [36].

Lung	**Liver**	**Nervous System**
Pneumonitis Pulmonary edema Dyspnea, hypoxemia ARDS	Hepatomegaly Elevated liver enzymes Increas hepcidin Hypoalbuminemia Liver injury Cholestasis Liver Failure	Confusion Delirium Aphasia seizures
Kidneys	Constitutional symptoms	Heart
Acute renal dysfunction of injury Renal failure	Fever Anorexia Fatigue	Hypotension Tachycardia cardiomyopaty
Gastrointestinal system	Rheumatologic system	Skin
Nausea Vomiting Diarrhea Ascites	Vasculitis Arthritis, arthralgia	Rash Edema
Vascular and lymphatic systems		
Cytopenia, anemia, leukocytosis Coagulopathy Hyperferritinemia, increase in other acute-phase reactants (e.g., CRP, D-dimer) Elevated cytokines (e.g., interleukin-1, interleukin-6, interferon-γ) and growth afctors (e.g., VEGF) Endothelial damage and vascular permeability Capillary leak syndrome Vasodilatory shock Spontaneous hemorrhage lymphadenopathy		

A cytokine storm refers to an exaggerated and uncontrolled inflammatory reaction from the immune system to a viral or bacterial infection, one of which is the SARS-CoV-2 virus, which can cause severe inflammatory conditions throughout the body. Exposure to the SARS-CoV-2 virus that is spread in the air or objects expelled through coughs and sneezes by COVID-19 patients can enter the respiratory tract of someone who is not infected through the mouth, nose or eyes. The spike protein present on the virus's surface facilitates the attachment to ACE2 cellular receptors, which are found throughout the respiratory tract, digestive tract, and other organs [5,6].

Pattern Recognition Receptor (PRR) is a receptor that detects various molecular structures that are characteristic of viruses. These molecular formations are referred to as Pathogen Associated Molecular Patterns (PAMPs). Upon binding of PAMPs to PRRs, an immune response is initiated, leading to inflammation in response to the virus. This results in the stimulation of numerous signaling pathways and transcription factors, initiating the production of genes responsible for creating a diverse array of proteins crucial for the host's immune reaction against the virus. These genes include those that encode pro-inflammatory cytokines [37].

Activation of PRRs initiates the activation of key transcription factors that control the expression of genes responsible for producing adhesion molecules, chemokines, and inflammatory cytokine. As a consequence of these processes,

leukocytes and plasma proteins are attracted to the site of infection, where they carry out different effector activities to combat the source of the infection. This response is initiated by chemokine molecules and adhesion molecules. This sequence of occurrences leads to the enlistment of leukocytes and plasma proteins to the location of the infection in order to counteract the cause of the infection [37].

When a patient is infected, the body responds by producing pro-inflammatory cytokines. An uncontrolled systemic inflammatory response, where chemokines and pro-inflammatory cytokines are produced excessively by the immune system, an intensify in the amount of these cytokines results in the migration of various types of immune cells, including neutrophils, T cells, and macrophages from the bloodstream to the site of infection. This has the potential to inflict harm on human tissue because it disrupts endothelial cell to cell interactions, damages blood vessels, and causes damage to capillaries. This damage includes diffuse alveolar damage, multiple organ failure, and ultimately can be fatal [37].

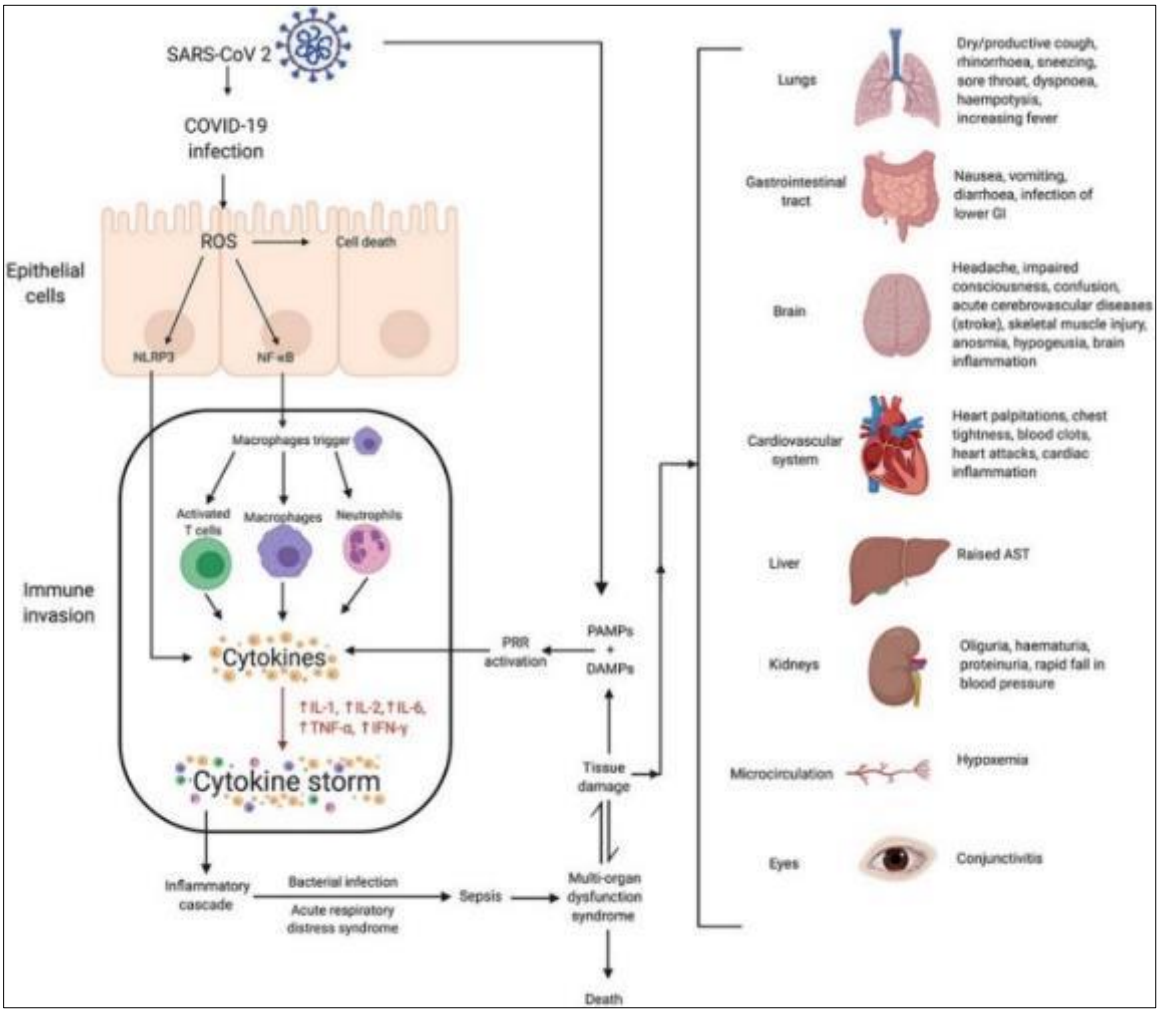

Figure 5 Cytokine storm in COVID-19 [38].

The excessive release of cytokines can lead to pulmonary injury, fibrosis leading to impaired function, and damage to several organs. Severe instances of COVID-19 can result in ARDS, pneumonia, renal failure, and ultimately mortality [5,37].

2.5. Caffeine

Caffeine, specifically defined as 1,3,7-trimethylxanthine, is the most well-known bioactive ingredient in coffee. Caffeine is an alkaloid compound that is part of the type metilxanthine. Caffeine, in its pure state, exists as a white powder composed of hexagonal prism crystals. It is a substance that lacks odour but possesses a bitter flavour (12). Caffeine occurs naturally in varied quantities in the nuts, leaves, and fruits of 60 distinct plant species. The main sources of caffeine are coffee beans that have been roasted and tea leaves. Apart from that, caffeine can also be found in cocoa beans, kola nuts, guarana fruit, and yerba mate. However, Compared to tea leaves and mate, coffee has a greater caffeine level, which is around 1.6% - 2.5% [6].

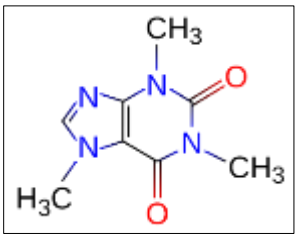

Figure 6 Chemical structure of caffeine (38).

Several types of the coffee that contain caffeine include Arabica coffee at 1g/100g and Robusta coffee at 2g/100g. Several types of tea that contain caffeine include oolong tea at 10 mg-45 mg/100g , black tea at 20 mg-90 mg/100g, instant tea at 10 mg-45 mg/100g, and green tea at 6 mg-30 mg/100g. Therefore, the effects obtained are higher when someone consumes coffee compared to other food ingredients, besides that coffee contains various chemical components that are beneficial for the body [6,12,39].

Caffeine in coffee is known to have benefits when consumed, but excessive consumption can have a bad impact on the body. The European Food Safety Agency (EFSA) has defined permissible amounts of caffeine intake that are considered safe. Considering the amount of caffeine consumed is crucial, and it is recommended that the daily consumption of caffeine does not surpass the recommended adults should take no more than 400 mg daily, while pregnant and 200 mg should not be given to breastfeeding mothers (equal to fewer than 2 cups per day). The recommended dosage for children is 3 mg/kg/day [7,34,39].

Ingesting a quantity of caffeine above 300 mg in a single instance might result in caffeine toxicity. The predominant symptoms include agitation, sleeplessness, excessive urination, indigestion, muscular tremors, disorganized thinking and speech, irritability, irregular heartbeat, rapid heart rate, and restlessness. Problems that often occur as a result of consuming 1-2 grams of caffeine are seizures or arrhythmia. In the end, there were reports of deaths due to consuming large amounts of caffeine, namely around 5-10 grams. However, caffeine poisoning can occur at various different doses and is influenced by varying caffeine metabolism, the presence of disease, and interactions with drugs [40].

Regular caffeine intake was linked to an elevated pain threshold, increased tolerance to heat-induced pain, and a higher threshold for pressure-induced pain. The presence of caffeine can diminish the perception of pain by directly affecting adenosine receptors. This is mostly achieved through the central inhibition of receptors that regulate pain signals, as well as the inhibition of peripheral adenosine receptors on sensory nerve fibers. Studies have explored whether caffeine could have either a beneficial or harmful impact on psychiatric disorders. These findings indicate a correlation between the amount of caffeine taken and the likelihood of developing depression. Individuals who consumed more than two servings of caffeinated coffee daily had a 24% reduced likelihood of experiencing depression compared to those who abstained from coffee consumption. As the amount of caffeine consumed increases, the occurrence of depression reduces. Caffeine can enhance trans-diaphragmatic pressure by increasing muscular contractility, so affecting the respiratory system. These findings indicate that caffeine may be employed as a therapeutic intervention for those with respiratory muscle dysfunction [41].

Caffeine plays an important role in mechanisms involving central and peripheral systems, causing changes in metabolic and physiological processes. Caffeine has two primary effects on the body: it activates the central nervous system and functions as a gentle antidepressant. This occurs through its ability to enhance the synthesis of specific neurotransmitters like serotonin and noradrenaline in the brain. Specifically, within the central nervous system, particularly in the autonomic nervous system, there's a neurotransmitter system dependent on epinephrine that manages body temperature, blood pressure, and heart rate. Caffeine functions by blocking the receptors of the epinephrine neurotransmitter that are present in nerve cells. The presence of caffeine triggers many physiological reactions that oppose the effects of epinephrine, resulting in heightened energy levels, disrupted sleep patterns, and heightened states of alertness. Caffeine also affects nerve cell firing and releases several neurotransmitters and other hormones, including adrenaline [42].

Among the many possible benefits of caffeine, many studies have examined its potential to influence the immune system and function as an immunomodulator [29,43]. Caffeine is known as an adenosine receptor antagonist and TAS2R receptor agonist. The immunomodulatory feature of coffee can contribute to lowering the severity of COVID-19, caffeine has the potential to act as an immunosuppressive agent that can reverse excessive cytokine expression [12,31]

3. Discussion

Coffee is the most widely consumed beverage worldwide because coffee has a distinctive taste and aroma, and has various benefits for the body's health. Coffee has possesses antitumor, antibacterial, anticancer, anti-inflammatory, antioxidant, and antifungal properties, and research has revealed certain distinctive effects. Research has demonstrated its impact on cardiometabolic diseasesconditions like a chronic kidney disease, cardiovascular disease, and diabetes [44]. Coffee has various chemical components, one of the chemical components of coffee is caffeine. Increasing research evidence shows that the caffeine contained in coffee plays an important role in preventing cytokine storms. In COVID-19 patients, caffeine contributes to lowering the risk and COVID-19 symptoms adverse effects, so that COVID-19 patients have a higher chance of recovering. Research so far shows strong evidence that caffeine as an immunomodulator can reduce excessive or uncontrolled inflammatory responses [12].

In the research with types of cross-sectional, caffeine was found to show anti-inflammatory effects from consumption at low concentrations (<250pM) or equivalent to 48.55mg which was characterized by lower plasma CRP levels and a decrease in pro-inflammatory cytokine products [41,45]. Usually low doses of caffeine can be found in coffee drinks containing espresso because in 1 shot Espresso usually contains 40-75 mg of caffeine, although the concentration of caffeine in espresso can vary based on several factors, including the variety of coffee beans utilized, the brewing process employed, technique, and the thickness or length shot duration of the espresso shot [46].

Although epidemiological studies show that the presence of caffeine present in coffee adds to the anti-inflammatory response, the physiological processes and causal pathways that explain the connection between caffeine and decreased susceptibility to cytokine storm in individuals with COVID-19 are not fully understood and need to be studied further.

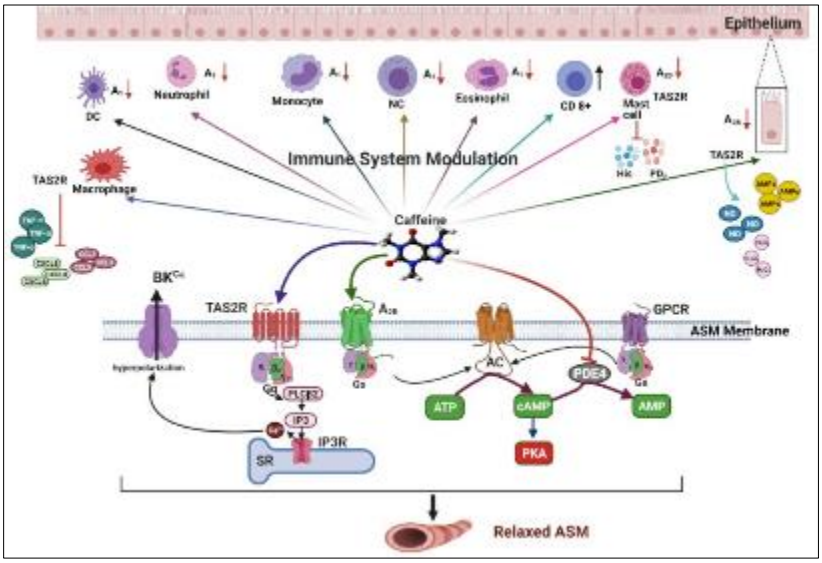

Figure 7 Modulation of the immune system by caffeine [49].

Several literatures have researched and discussed the relationship of caffeine contained in the coffee to reducing inflammatory conditions by examining one type of receptor protein in the human body participating in the processes of inflammation and regulation control of inflammation reactions and responses and the generation of pro-inflammatory cytokines that promote inflammation, where excessive pro-inflammatory cytokines can cause a cytokine storm. On research Translational Physiology with rat animal subjects, then the subjects were randomly divided into groups given caffeine for 6 weeks (20mg/kg/day) or the equivalent of administering 2-3 cups of coffee daily via oral gavage. The results showed outcomes demonstrated that administration of caffeine greatly inhibited considerably reduced the overexpression upregulation of inflammatory cytokines in mouse PBMC/monocyte cell lysates collected from mice. PBMC, or peripheral blood mononuclear cells, are a collection of leukocytes that consist of monocytes and lymphocytes. Furthermore, this study found a strong correlation between elevated levels of ICAM, IL-6, MCP-1, and TNF-a in the blood, muscle, adipose tissue, and liver, indicating the presence of both systemic and local inflammation in mice that could be effectively inhibited by caffeine treatment [47]. Monocytes and lymphocytes make up the white blood cell population known as PBMC. Furthermore, systemic and local inflammation in mice was linked in this study to considerably greater levels of ICAM, MCP-1, IL-6, and TNF-a in the serum, muscle, adipose tissue, and liver[48]. These inflammations may be successfully suppressed by caffeine therapy [47].

Proteins called ICAM, MCP-1, IL-6, and TNF-a is a group of protein constituents that have a vital function in the inflammatory response and immune system. Because of the immunomodulatory properties associated with the Taste 2 Receptor (TAS2R), caffeine as a TAS2R agonist, may help reduce the severity of SARS-CoV-2 because of the immunomodulatory actions associated with the TAS2R. TAS2R is a bitter taste receptor located in the taste buds of the tongue that is involved in detecting harmful substances that typically have a bitter flavor. The TAS2R is a member of the G-protein coupled receptor (GPCR) which can help us avoid toxic foods by recognizing dangerous compounds [30].

When caffeine is consumed, it binds to a bitter taste receptor on the human tongue called TAS2R. Activation of TAS2R by caffeine triggers intracellular signals via G protein (G protein). This process then stimulates adenylate cyclase to produce cAMP. cAMP functions as a regulator capable of activating PKA. PKA possesses the capability to impede the initiation of the NF-kB pathway, a signaling system implicated in the creation of pro-inflammatory cytokines. By inhibiting activation of the NF-kB pathway, that promote inflammation, from being activated. Caffeine activation of the TAS2R receptor via caffeine may reduce the production lessen the productuion of pro-inflammatory cytokines and contribute to aid in anti-inflammatory responses by blocking the initiation of the NF-kB pathway. Research by Gibbs et al., states that caffeine suppresses plasma levels of TNF-a via the cAMP/PKA pathway, upon activation of the TAS2R receptor. Research by Gopallawa et al. (2021), also showed similar results, where caffeine can reduce plasma levels of TNF-a by affecting the cAMP/PKA pathway through activation of the TAS2R. Thus caffeine may function as an immunosuppressive agent that can reverse excessive cytokine expression through activation of the TAS2R [41,49,50,51].

Apart from that, caffeine is also known as an adenosine receptor antagonist. Adenosine receptors are membrane proteins that are present in various cells in the body and interact with adenosine molecules, which are organic compounds composed of the nucleosides adenine and ribose. Adenosine receptors are involved in a number of physiopathological responses, including blood vessel expansion, pain regulation, and inflammatory processes. There are four adenosine receptor variants that have been identified, namely Al, A2A, A2B, and A3 [7,52,53].

Caffeine can block adenosine receptors Al, A2A, and A2B. When caffeine binds Adenylyl cyclase is triggered by caffeine's binding to A2A receptors, adenylyl cyclase is activated thereby converting which results in the conversion of ATP into cyclic adenosine monophosphate (cAMP). By inhibiting phosphodiesterase (PDE), this action triggers initiates intracellular signaling that is regulated by upregulation the increase of intracellular cyclic AMP (cAMP) via inhibition of phosphodiesterase (PDE). Thus, the second messenger, cAMP, enhances the binding of extracellular caffeine within cells. The initiation of PKA occurs intracellularly through the strengthening effect of the second messenger, cAMP. Increased concentrations of cAMP trigger the initiation of PKA activation. PKA possesses the capacity to impede and subsequently obstruct the initiation of the NF-kB pathway, which represents a signaling route engaged in generating pro-inflammatory cytokines. This has the ability to inhibit the secretion of pro-inflammatory cytokines. Suppressing the secretion of these proinflammatory cytokines can diminish the function of several immune elements, including natural killer (NK) cells, macrophages T and B cell replication, and antibody synthesis [34].

Besides that caffeine also can reduce NLRP3 expression and caspase cleavage associated with the NLRP3 inflammasome. In addition, caffeine can also inhibit. In addition, caffeine has the ability to lower caspase cleavage linked to the NLRP3 inflammasome and NLRP3 expression. In addition, coffee can hinder the initiation of the NLRP3 inflammasome by blocking the MAPK/NF-kB signaling pathway. As a result, IL-1β and IL-18 production can be suppressed [12,41,43,54].

4. Conclusion

The caffeine contained in coffee has the potential to modulate the immune system in COVID-19 sufferers.

Compliance with ethical standards

Disclosure of Conflict of interest

No Conflict of interest to be disclosed.

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