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*Review Article*

## **Analysis of Some Natural Products for Prevention of Diseases Associated with COVID-19**

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### **ABSTRACT**

Coronavirus, also known as COVID-19, is a new disease that has crippled almost every aspect of human activities today. Common symptoms of the virus include high fever (38°C and above), dry persistent cough, shortness of breath and sore throat. Recently, additional symptoms which include diarrhea, fever and headache have been reported in South Africa. Medicinal herbs have been in use since ancient times for the management of viral infections related to COVID-19. Nutrient deficiency has been observed in worst cases of COVID-19 infection. This review therefore explores the scientific-related literature on the use of garlic, ginger and lemon which are regarded as the healthiest of all-natural herbs. They contain several natural vitamins (vit A, B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub>, B<sub>5</sub>, B<sub>6</sub>, C, E), minerals (potassium, magnesium, selenium, iron and zinc), and phenolic compounds (quercetin, gingerol, shogaol, paradol, limonene, limonins and hesperidin), omega-3s and -6s, allicin, ajoene and S-allylmercapto- L-cysteine. All these compounds are potent antiviral agents that can penetrate the mucous secretions of the respiratory system to strengthen the immune system and possibly prevent the replication of COVID-19. The combination of these natural herbs can block all the different pathways of COVID-19 infection and could provide instant relief to the early symptoms associated with the disease.

**Keywords:** *Natural products, nutrients, anti-inflammation, SARS-CoV-2, COVID-19*

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### **INTRODUCTION**

According to the World Health Organization (WHO), it has been estimated that about 80% of the population in developing countries depends on natural medicine for their Primary Health Care (PHC) needs (WHO, 2002). Natural herbs have served for many years as a first aid remedy to treat severe acute respiratory syndrome (SARS), and have been passed down from forefathers to children (WHO, 2003). As a continent, Africa has its own traditional ways of managing diverse health issues she has been confronted with over time, most of which are undocumented, which to a very large extent today, are being recognized as indigenous knowledge. Apart from this, there is a general perception that since most orthodox medicines are processed forms of traditional herbs and roots, the latter is better to be preferred because it is still in its natural state.

COVID-19 is a disease caused by a novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Chen *et al.*, 2020). SARS-CoV-2 belongs to the family of RNA viruses called coronaviruses, which also includes the viruses that cause the common cold and flu (Chan *et al.*, 2020). The virus is characterized by spike proteins (Spro) on its surface that helps it replicate through some unique processes: first, the virus targets the human cell membrane by using its spike protein to bind to the angiotensin converting enzyme 2 (ACE2) found in the lungs and arteries. It then forms endosomes that penetrate the mucosal lining of the upper respiratory system. While inside the respiratory system, the virus genome synthesizes new viral polyproteins and RNAs, which subsequently multiplies and spread to every other parts of the body (Wu *et al.*, 2020). Serious infection becomes severe when other deadly diseases, such as pneumonia, acute respiratory distress syndrome (ARDS), chronic obstructive

pulmonary disease (COPD), high blood pressure, diabetes, asthma and kidney failure are associated (Chan *et al.*, 2020). The virus has also been observed to easily kill through all other multiple channels; through blood clot and mucus formation, which then strain the oxygen supply, causing difficulty in breathing (hypoxia) and suffocation (WHO, 2020). COVID-19 may also impact cells in the heart, liver and kidney, resulting in inflammatory responses known as a cytokine storm, which has been implicated to cause damage in the stage of the disease progression (Wu *et al.*, 2020). While there are still some doubts on how the disease came about, COVID-19 originated from Wuhan Province, China, in 2019 and has spread throughout the world (Li *et al.*, 2020), resulting in the World Health Organization (WHO) declaring it a pandemic in 2020 (WHO, 2020). It is widely accepted that the number of cases currently reported (over 26 million) is a vastly underrepresented number, with many more going undetected (WHO, 2020). According to WHO media statement in March, 2020, some people do develop mild symptoms, but some may have a more severe reaction-risk from the ages of 60 and above, people with a weakened immune system (e.g. HIV/AIDS, TB), and people with other underlying diseases such as diabetes, heart and lung diseases (Huang *et al.*, 2019).

COVID-19, a novel deadly virus, is said to be airborne. It spreads through the mucus or saliva droplets from an infected individual's cough or sneeze, which then penetrates through another person's nose or mouth (Wu and McGoogan, 2020). Physical contact with contaminated surfaces, metal, glass and plastic are also reported as sources of transmission (Tian *et al.*, 2020). WHO has recommended the wearing of a facemask, the use of an alcohol-based sanitizer or washing of hands with soap and water for 20 seconds to prevent the spread of the virus (WHO, 2020). The South African Government has made wearing of facemask in public places mandatory for every South African, and that failure to comply, will be a criminal offence. In the absence of prevention, the virus gain access through the body cells and invades the respiratory tract system (RTS) (Angeletti *et al.*, 2020). Common symptoms of the infection can begin within 14 days with high temperature, continuous coughing, tightened lungs, shortness of breath, fever, fatigue, sore throat, running nose, sneezing, tiredness, and difficulty to sleep (Wu and McGoogan, 2020). According to WHO, the prevalence of COVID-19 infection spread may increase during very cold weather conditions (WHO, 2020). This may be a valid reason why the World Health Organization recommends regular exercises for about 30 minutes and drinking of warm water to help the body keep warm (WHO, 2020). WHO also recommends that individuals with symptoms not consume cold water, cold drinks or ice-cream. Infected patients living in a cold environment, such as hotel, airplane cabins, air-conditioned offices or homes can easily be killed by COVID-19. At present, there is no vaccine available for COVID-19 treatment, but there are some commercial drugs that have been tried.

The National Institute of Allergy and Infectious Diseases (NIAID) with the National Institutes of Health (NIH) supported a clinical trial on the combination of hydroxychloroquine, a less toxic form of chloroquine which is normally used to treat or prevent malaria and azithromycin, an antibiotic prescribed for bacterial infections, such as

respiratory infections, skin infections, ear infections, and sexually transmitted diseases. They observed the combination to be helpful against COVID-19, although it still needs confirmation (NIH, 2020). In this trial, patients confirmed to have COVID-19, were given 600 mg of hydroxychloroquine daily. Depending on the symptoms of participants, azithromycin was also added to their treatment. Untreated patients from another centre and patients who refused the treatment with hydroxychloroquine and azithromycin were included in the study as negative controls. All 20 patients treated, demonstrated significant reduction of the viral infection compared to the negative controls. In cases where azithromycin was added to hydroxychloroquine, the combination was found to be significantly more efficient for virus elimination. Based on the findings, the following dose treatment for individuals already infected with COVID-19 was recommended: Hydroxychloroquine sulfate (200 mg thrice a day for 10 days) and azithromycin (500 mg once a day, then 250 mg orally on additional days). Unfortunately, three professional cardiology groups issued a statement warning that either of these drugs can cause serious arrhythmias that may lead to sudden cardiac death and that taking these two medications together might be even more dangerous for some people who already have cardiovascular disease (Gautret *et al.*, 2020).

According to medical doctors, chronic conditions including cardiovascular disease, hypertension and diabetes weakens the immunity system, and can worsen those infected with SARS-CoV-2 (Childs *et al.*, 2019). Building a healthy immune system with healthy natural diets and herbs rich with high a content of vitamins and minerals have always been the best way for a healthy living (Wu *et al.*, 2020). This paper reviews the nutritional contents and health benefits of natural products/or spices bio-medically used for inflammatory diseases associated with COVID-19 symptoms: an attempts to validate their individual and combined effects on inflammation.

## NUTRITIONAL PROPERTIES AND HEALTH BENEFITS OF GARLIC

A variety of components, including non-sulfur compounds, work synergistically to provide various health benefits (Pure *et al.*, 2017). Garlic also known as *Allium sativum* is an edible bulb herb, consisting of 10-20 smaller sections of cloves, enclosed in a white parchment-like-skin (Ouroudi *et al.*, 2017). Each clove contains valuable amount of nutritional components. Three crush garlic cloves can contain vitamin C (8 mg), vitamin B<sub>6</sub> (1 mg), calcium (16 mg), potassium (36 mg), phosphorus (13 mg), quercetin (2 mg), omega-3 fatty acids (8 mg), carbohydrates (3 g), calories (13 mg), trace amount of vitamin A and K, allicin, ajoene, S-allyl-cysteine (SAC) and its derivative, S-allylmercapto-L-cysteine (SAMC) (Lawson and Hunsaker, 2018). Garlic is an ancient natural herb that have received support from both the scientific community and natural healers from around the world (Petrovskal and Cekovska, 2010). Because of its medicinal properties, it has kept many people healthy. According to Parcival, (2016), the vitamins, minerals and other phyto-compounds in garlic have the power to boost the immune

system, fight common virus infections and reduce inflammation.

**Potassium:** Garlic is rich in potassium, one of the seven essential minerals needed to maintain consistent blood pressure (Khaerunnisa *et al.*, 2020). Potassium helps the proper functioning of nerve and muscles cells, particularly heart muscles cells. The normal average amount of potassium level in the blood is between 3.6 to 5.2 millimoles per liter (mmol/L), but when it becomes lower than 2.5 mmol/L, can result in life-threatening hypokalemia (Wu *et al.*, 2020). Severe cases of COVID-19 have been diagnosed of hypokalemia (Chen *et al.*, 2020). Hypokalemia can cause heart dysfunction and hypertension, which are major problems associated with COVID-19 (Chen *et al.*, 2020). In a recent study of 175 patients hospitalized with COVID-19 in China, about 93% of critically ill patients who had breathing difficulties, had hypokalemia and angiotensin converting enzyme 2 (ACE2) degradation (Wu *et al.*, 2020). ACE2 is the messenger enzyme that regulate blood pressure through the help of sodium and potassium in the lungs, intestines, kidneys, brain and heart (Gupta *et al.*, 2020). When SARS-CoV-2 succeeds in inactivating ACE2, it can lead to excessive loss of potassium in COVID-19 patient (Gurwitz, 2020). The high amount of potassium in garlic and from other foods, such as spinach, broccoli, potatoes, sweet potatoes, mushrooms, peas, cucumbers, zucchini, eggplant, pumpkins and fruits may increase ACE2 in the heart and lungs, and are more likely to prevent SARS-CoV-2 infection, replication and spread (Khaerunnisa *et al.*, 2020).

**Quercetin:** Quercetin found in garlic, is a flavonoid compound that has been tested to have a broad spectrum of antiviral activities, including COVID-19. Liu *et al.* (2020) recently crystallized the main protease (Mpro) active site (3-chymotrypsin-like protease (3CLpro) of COVID-19. They observed that Mpro in CoV regulates the proteolytic maturation of the virus and hence should be the potential target protein to prevent the spread of infection (Liu *et al.*, 2020). Phyto-medicinal products, including quercetin were tested on COVID-19 Mpro, using a molecular docking approach (Khaerunnisa *et al.*, 2020). The result of the docking analysis shows that quercetin H-bonds interacted with 6LU7 amino acids (His164, Glu166, Asp187, Gln192 and Thr190) in the COVID-19 Mpro active site (Khaerunnisa *et al.*, 2020). The high affinity binding of quercetin was comparable to the commercial nelfinavir used as positive control (Khaerunnisa *et al.*, 2020). Hence, the authors concluded that quercetin may be a potential inhibitor of COVID-19 Mpro, and should be explored in future research. The high doses of quercetin treatment injected in mice infected with lethal dose of the Ebola virus, survived Ebola infection compared with the placebo control group that were not given quercetin treatment (Qui *et al.*, 2016). Another research study conducted by Lopes *et al.* (2020), observed that quercetin may have immunomodulating properties that prevents viruses from replicating and reduces resistance to treatment with antiviral medication. It was also observed that quercetin derivatives have similar molecular structures and biological activities as nelfinavir, an

antiviral drug used to treat HIV/AIDS (Khaerunnisa *et al.*, 2020).

**Omega-3-fatty acids:** Omega-3-fatty acids are one of the most essential nutrients found in garlic, they are long-chain polyunsaturated fatty acids ranging from 18-22 carbon atoms in chain length, with double bonds (C=C) beginning at the third carbon from the methyl end of the fatty acid structure (Molfino *et al.*, 2016). Omega-3s are incredibly important, as they are made up of three vital nutrients, which includes  $\alpha$ -linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Molfino *et al.*, 2016). These three components are essentially needed for a healthy respiratory function, body temperature and blood pressure. The human body are unable to synthesize them, the only way to get their health benefits is to consume natural herbs, certain foods or probiotic supplements (Molfino *et al.*, 2014). ALA's are primarily found in plant sources like garlic, vegetables, avocado, seaweed, legumes, walnuts, flaxseed, canola oil and soy products. EPA and DHA are found in fish, like anchovies, sardines, salmon and tuna (Kiefer and Pantuso, 2012).

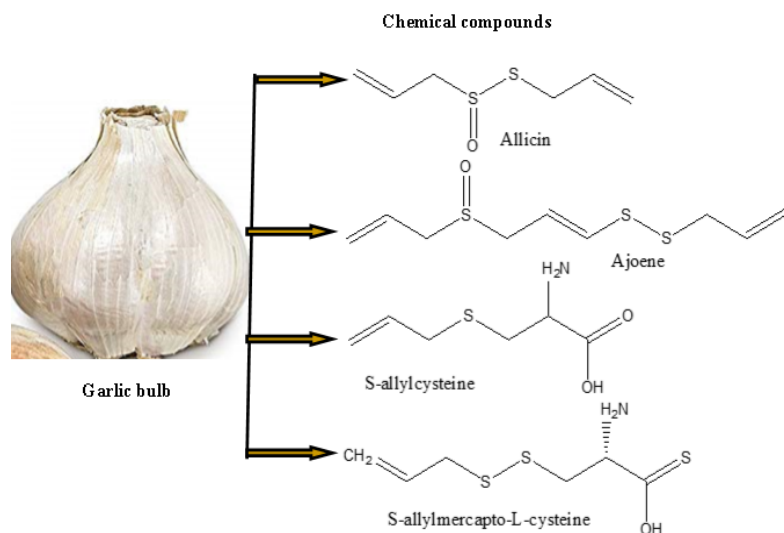
Omega-3s provide many health benefits, including hormonal repair, production of prostaglandins that fight inflammatory diseases of COVID-19, prevent plaque that harden the arteries and keep body cells healthy and resilient (Freitas and Campos, 2019). In an effort to stop the spread of the global COVID-19 pandemic, medical scientists are currently testing treatments containing omega-3-fatty acids as an alternative agent (Iddir *et al.*, 2020). COVID-19 complications that has resulted to intensive care have been linked to a malfunction of the immune system known as a cytokine storm. Inflammatory cytokine storm has been implicated in the progression of viral infections (Channappanavar and Perlman, 2017). It is an excessive-reaction to infection in the body, in which the immune system overproduces cytokines and immune cells that help to fight infection. This excessive reaction can start attacking healthy tissue as well as cells infected with the virus and can lead to serious damage to the heart, lungs, and other vital organs (Mehta *et al.*, 2020). Sick patients with diabetes, heart disease, high blood pressure, asthma are more likely to suffer from a cytokine storm. Research have documented that omega-3 fatty acids generates pro-resolving mediators and bioactive metabolites that could reduce proinflammatory cytokines (McGlory *et al.*, 2019). Resolvins, a derivative from omega-3 fatty acids are a specialized pro-solving lipid mediators (SPMs) that have shown to reduce chronic inflammation and the risk of cytokine storms caused by the COVID-19 infection (Iddir *et al.*, 2020). Omega-3 fatty acids derivatives have also been found effective against Nontypeable *Haemophilus influenza* (NTHi), a disease that often plagues people with chronic obstructive pulmonary disease (COPD) (Kris-Etherton *et al.*, 2019). COPD is a common condition seen along with COVID-19 patients, it is characterized by excessive mucus in the lungs that blocks airflow, as a result of smoking (Hadzic *et al.*, 2020; Ward *et al.*, 2020). Acute coronary heart disease (CHD) is another deadly disease associated with COVID-19 (Madjid *et al.*, 2020). It results in blood clots that clog inside the coronary arteries to cause a narrow flow of blood and oxygen to the heart muscle.

Infection of CHD has resulted in severe chest pain, heart attack, or cardiac arrest in COVID-19 patient (Madjid *et al.*, 2020). Clinical trials of omega-3 fatty acids on patients with CHD have shown to lower the rate of infection (Molifino *et al.*, 2017). The most effective way to consume garlic is to crush the cloves and let it stand for 10 to 15 minutes, then, mix the crushed garlic with either yogurt, applesauce, honey, or some other carrier agent that makes it easier and tastier to ingest (Ried, 2016). This serves as a quick remedy for asthma, dry cough or chest congestion (Ried, 2016). Cooking garlic is also completely acceptable, if crushed and allow to stand for 10 minutes before cooking at a low heat for 5-10 minutes (Bayan *et al.*, 2014). This process enhances the formation of allicin synthesis and also makes it more stable and resistant to the heat of cooking (Kotheri *et al.*, 2019).

**Allicin:** Allicin is one of the most potent compound present in garlic. It is released by an enzyme known as alliinase when garlic is crushed or chopped (Livingstone *et al.*, 2019). It becomes highly volatile as it oozed out its pungent odor in garlic (Kotheri *et al.*, 2019). The breakdown of allicin forms other varieties of fat- and water-soluble sulfur-containing compounds, known as ajoene, *S*-allyl-cysteine and *S*-allylmercapto-L-cysteine, Fig 1. Allicin is a blood thinner that has drastically reduced the lead levels in blood clots, allowing better blood flow (Mikaili *et al.*, 2013). Garlic allicin has been found to significantly decrease the blood sugar levels of individuals suffering from diabetes (Mikaili *et al.*, 2013). Allicin is also well known for its antiviral activity against viruses capable of causing respiratory diseases worldwide, including, herpes simplex virus type 1 and 2, parainfluenza virus type 3, vaccine virus, vesicular stomatitis virus, cytomegalovirus and human rhinovirus type 2 (Al-Snafi, 2019). Allicin was recently found as a potential inhibitor of the COVID-19 3CLpro/Mpro (Khaerunnisa *et al.*, 2020). The result obtained from the docking experiment showed that allicin binding affinity to the 6LU7 COVID-19 amino acids was -4.30 kcal/mol. According to Bezerra *et al.* (2018), allicin in garlic have shown to decrease virus replication by reducing the production of proteins involved in HIV replication.

**Ajoene:** According to a study published by Koca and Tasci, (2016), ajoene was found 100 times more powerful than two common types of antibiotics used for bacterial infection. Ajoene is another active allicin-derived compound found in chopped fresh raw garlic (Papu *et al.*, 2014). The potential antiviral activity of ajoene was first discovered in 1992 to interrupt the propagation of HIV-infected cells in an *in vitro* system (Tetarintseu *et al.*, 1992). Walder *et al.* (1997), later showed that the compound was able to suppressed HIV-1 replication by blocking the virus destruction of CD4 T-cells and virus-cell attachment *in vitro*. Further study of the compound against simian immunodeficiency virus-mediated cell fusion and virus-induced cytolysis, observed that ajoene was effective in inhibiting the early life cycle of the virus replication (Walder *et al.*, 1998). Ajoene has also been shown to block the human cytomegalovirus spread in infected cells (Terrasson *et al.*, 2007).

**SAC and SAMC:** Due to the activities of organosulfur compounds such as *S*-allyl-cysteine (SAC) and its derivative, *S*-allylmercapto-L-cysteine (SAMC), garlic has received great attention from a large number of pharmaceutical companies because of its broad spectrum to conquer chronic diseases. Both SAC and SAMC accounts for approximately 80% of cysteine sulfoxides in aged garlic (Rodrigues and Percival, 2019). The compounds are best known to reduce cholesterol, blood pressure and platelet aggregation that causes stroke and heart attack (Parcival, 2016). Aged garlic extract of SAC and SAMC have shown to suppressed inflammation by downregulating AKT1/TGF- $\beta$ -activated kinase-mediated NF $\kappa$ B and MAPK signaling pathways (Zeng *et al.*, 2017). Inflammation is mainly triggered by oxidative stress leading to many disease states. Several reports have shown that SAC and SAMC inhibit the oxidative damage implicated in aging (Kosuge, 2020). They have scavenged superoxide anion, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), hydroxyl radical (OH), peroxyxynitrite anion (ONOO) and hypochlorous acid (HOCl) (Hsia and Yin, 2015). In addition, SAC and SAMC have enhanced catalase and glutathione peroxidase activities in kidney and liver (Upadhyay, 2016).



**Figure 1:**  
Major phytochemical compounds found in garlic

## NUTRITIONAL PROPERTIES AND HEALTH BENEFITS OF GINGER

Ginger (*Zingiber officinale*) belongs to the family of *Zingiberaceae*. The herb is one of the most valued medicinal plant in Ayurvedic, Chinese and Unani to treat different kinds of diseases (Jayawardena *et al.*, 2020). The nutritional components present in ginger/100g contains, vitamin C (1.0 mg), magnesium (43 mg), manganese (0.229 mg), iron (279.7 mg), copper (8.8 mg), calcium (280 mg), folate (0.2 mcg), niacin (0.750 mg), choline (0.6 mg), zinc (64.0 mg), omega-3- fatty acids, (0.7 mg), omega-6- fatty acids (2.4 mg), gingerols, shogaols and paradols (Wagesho and Chandravanshi, 2015).

**Magnesium:** Magnesium present in ginger, plays an important role in maintaining a strong immune system (NIH, 2019). The mineral is involved with over 200 reactions in the body, including exerting a marked influence on immunoglobulin synthesis, immune cell adherence, antibody-dependent cytotoxicity, immunoglobulin M (IgM) lymphocyte binding, macrophage response to lymphokines and T helper-B cell adherence (Jayawardena *et al.*, 2020). Magnesium act as a cofactor enzyme involved in vitamin D metabolism to prevent respiratory tract infections (Martineau *et al.*, 2017). Without enough magnesium in the body, vitamin D will remain inactive, hence unable to boost the immune system (Uwitonze and Razzaque, 2018). According to Jayawardena *et al.* (2020), magnesium including other vitamins are important to enhance immunity in viral infections, with special emphasis on COVID-19. Magnesium deficiency can increase the risk of high blood pressure, heart disease and type 2 diabetes (Geiger and Wanner, 2012), and all these are comorbidities associated with COVID-19 deaths.

**Zinc:** According to the National Institute of Health (NIH), zinc is a vital mineral that people need to stay healthy (NIH, 2018). The body cannot produce or store zinc, it must be supplied through natural plant sources or from diets (NIH, 2020). Of all the minerals, zinc is regarded as the most potent element for the body's first line of defense against respiratory tract infections (NIH, 2020). Zinc is involved in numerous aspects of cellular metabolism. A little amount of zinc (15-30 mg) can penetrate the mucous secretions of the respiratory system and on the surfaces of throat and lungs to boost immunity against inflammatory diseases (NIH, 2019). Zinc could reduce the severity and duration of cold symptoms by directly inhibiting rhinovirus replication in the nasal mucosa, suppressing its inflammation by 35% (Gombart *et al.*, 2020). According to Gombart *et al.* (2020), the body requires zinc in the production of white blood cells (natural killer cells) and activate T-lymphocytes (T-cells) to aid control over age-related diseases, such as pneumonia and cancerous cells (Skrajnowska and Bobrowska-Korczak, 2019). A study by Bjorklund *et al.* (2019), found that zinc can balance most hormones, including insulin needed in the regulation of blood sugar levels in diabetes patient. According to Higashimura *et al.* (2019), zinc deficiency causes alterations in the immune

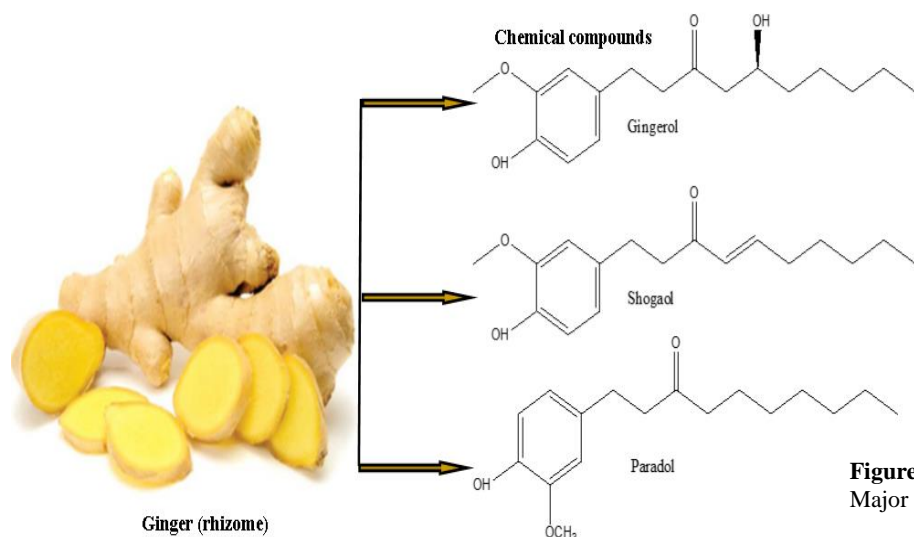
response which contribute to the increase in acute diarrhea with high mortality rates among children under the age of five in developing countries. WHO and UNICEF now recommend a short-term intake of zinc supplements to treat acute childhood diarrhea all over the world (US Food and Drug, 2017). Research has shown that zinc can interfere with the body's molecular pathways, by fusing its self to the receptors in nasal epithelial cells blocking virus infection (Zhang and Liu, 2020). Zinc have been used to support the treatment of measles and SARS-CoV, which was first identified in 2003 (Read *et al.*, 2019). This is a disease similar to the current pandemic (SARS-CoV-2) (Zhang and Liu, 2020). Low zinc levels have been linked to some chronic conditions that account for over 99% of deaths from SARS-CoV-2 (COVID-19) (Zhang and Liu, 2020).

**Gingerol:** Gingerol in ginger can be best described as capsaicin, a compound that gives chillies their spiciness and piperine found in black pepper (Fig 2). Gingerol is an active compound that has exhibited numerous healing activities against respiratory syncytial virus (RSV) (Mao *et al.*, 2019), type-2 diabetes (Vagedes *et al.*, 2018), osteoarthritis and rheumatoid arthritis through a mechanism which inhibits the formation of inflammatory cytokines and chemical messengers of the immune system (Terry *et al.*, 2011). Khaerunnisa *et al.* (2020), reported that gingerol showed the highest binding affinity of -15.7591 kJ/mol with 5R7Y COVID-19 main protease essential for replication and reproduction of SARS-CoV-2. The researchers further revealed that gingerol exhibited binding affinity of -11.4082 kJ/mol, -12.9523 kJ/mol and -12.8835 kJ/mol with COVID-19 viral RNA binding protein (6W4B), N-terminal RNA binding protein (6VSB), spike glycoprotein (6M3M) respectively. Thus, the compound could be a promising drug candidate to treat COVID-19.

**Shogaol:** Shogaol is another active compound that is produced when ginger is cooked or dried. Shogaol extract exhibited antioxidant activity through the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway (Semwala *et al.*, 2015). The Nrf2 is a transcription factor that play a key role as the master antioxidant regulator, it has the ability to reduce oxidative stress in impaired type 2 diabetes and obesity through binding to antioxidant response elements present in the promoter region of many cytoprotective genes (Chatterjee and Chatterjee, 2020). AMP-activated protein kinase  $\alpha$  (AMPK $\alpha$ ) is a major protein that regulate cellular glucose and lipid homeostasis, including insulin in 3T3-L1 adipocytes and C2C12 myotubes (Sakulnarmrat *et al.*, 2015). In 3T3-L1 adipocytes and C2C12 myotubes, shogaol significantly increase glucose utilization by increasing AMPK phosphorylation (Wei *et al.*, 2017). The activity was seen related to phosphatidylinositol-3-kinase (PI3K) activation, which also cause increase in glucose uptake by adipocytes (Akinyemi *et al.*, 2013). In addition, the compound inhibited the lipid synthesis in 3T3-L1 cells by reducing the cellular lipid accumulation (Hosseinzadeh *et al.*, 2017). The advanced



glycation end-products (AGEs) are another complication that accumulate more highly in the periodontal tissues of patients with periodontitis and diabetes mellitus.



**Figure 2:** Major phytochemical compounds found in ginger

It aggravates periodontitis with diabetes by increasing the expression of inflammation-related factors in periodontal tissues (Zhu *et al.*, 2015). Among the compounds tested, shogaol exhibited the best inhibition against the production of AGEs by trapping methylglyoxal (MGO), a precursor of AGEs (Zhu *et al.*, 2015). In another clinical trial, the compound was shown to decrease hepatitis C virus (HCV) loads in an Egyptian HCV patients (Mao *et al.*, 2019).

**Paradol:** Paradol is yet another potent compound found in ginger. The compound has similar healing activities with shogaol. In human body, cyclooxygenase is seen in two forms, including cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is expressed in most tissues and maintains the protective lining of the stomach, regulate blood flow through the kidneys, and promote platelet aggregation, whereas COX-2 is an inducible isoform that is mainly produced in inflamed tissues (Dannerberg *et al.*, 2001). Paradol was reported as the best antiplatelet inhibitor that suppresses prostaglandin synthesis by inhibiting cyclooxygenase-2 (COX-2) enzymes as well as interleukin-1beta (IL-1 $\beta$ ) gene in vitro. Paradol compared with aspirin, exhibited more inhibition activity against the arachidonic acid (AA) metabolism via the COX-1/thromboxane synthase system (Huss *et al.*, 2002). The antiviral activity of ginger paradol showed significant effect on feline calicivirus (FCV), a surrogate for human norovirus (Aboubakar *et al.*, 2016). Obesity is a complex life-threatening condition that is likely associated with heart ailments, strokes, type-2 diabetes and osteoarthritis. Research study by Wei *et al.* (2017), reported that paradol present ginger showed potent anti-lipolytic activity. The study further showed that the compound dissolves body fat, in high fat diet fed animals. Traditionally, ginger paradol tea helps the body to fight off fever and stress associated with colds and flu (Lete and Allue, 2016).

Lemon belong to the family of Rutaceae, with a scientific name *Citrus limonum* risso. It is one of the healthiest fruit on planet earth with wide range of health benefits (<https://foodrevolution.org/>). Lemon is chock-full of essential vitamins and minerals. According to the United States Department for Agriculture database, 124g squeezed lemon contains vitamin A (45 IU), vitamin C (112 mg), vitamin E (0.4 mg), vitamin B<sub>3</sub> (0.2 mg), vitamin B<sub>1</sub> (0.01 mg), vitamin B<sub>2</sub> (0.01 mg), vitamin B<sub>5</sub> (0.06 mg), vitamin B<sub>6</sub> (0.1 mg), folate (31.7 mcg), pantothenic acid (0.3 mg), choline (12.4 mg), potassium (303 mg), calcium (17.1 mg), sodium (2.4 mg), magnesium (14.6 mg), copper (0.1 mg), phosphorus (14.6 mg), selenium (0.2 mg), zinc (0.1 mg) and iron (0.1 mg).

**Vitamin A:** The high content of vitamin A (45 IU) in lemon can support the healthy mucosal tissues and barrier function through which most infections enters the body (Kantoch *et al.*, 2002). Since ACE2 represent the cellular receptor for SARS-CoV-2, an animal study suggests that ACE2 receptor may be upregulated by all-trans retinoic acid, a vitamin A derivate (Zhong *et al.*, 2004). Vitamin A has offered protection against other life-threatening infection, such as lung infection (Villamor *et al.*, 2002). Lymphocytes (a type of white blood cell) needs vitamin A to work more effectively in fighting diseases. With improved cell strength from vitamin A, the linings of the lungs, urinary tract and intestinal tract become much stronger, which can in turn block many viruses and bacteria from entering the body (Villamor *et al.*, 2002). Vitamin A deficiency had rendered a bovine coronavirus vaccine to become ineffective in calves, exposing the calves to more susceptible infectious diseases (Jee *et al.*, 2013). A study conducted by West *et al.* (1992), revealed that the effect of adequate vitamin A diet fed to chickens, showed more resistance to bronchitis virus (IBV), than those not fed. Therefore, vitamin A should be considered for the treatment of lung infection relating to virus infections.

## NUTRITIONAL PROPERTIES AND HEALTH BENEFITS OF LEMON

**Vitamin E:** Vitamin E generally is not an antiviral nutrient; it is a fat-soluble group of tocopherols with most effective antioxidant activities that plays important role in lungs and liver protection. As a fat-soluble nutrient, vitamin E can accumulate in lipid membranes and react quickly with free radicals that trigger nuclear factors that produces cytokines (Galmes *et al.*, 2018). Vitamin E has much to do with the immune system response. It promotes blood health by dilating the blood vessels and reducing platelet aggregation (Galmes *et al.*, 2018). Vitamin E deficiency has been reported to intensify the myocardial injury of coxsackievirus B<sub>3</sub> (a kind of RNA viruses) infection in mice (Beck *et al.*, 1994). Decreased in vitamin E and D levels in calves have also led to the infection of bovine coronavirus (Nonnecke *et al.*, 2014).

**B-vitamins:** The B vitamins are water-soluble medicines that plays special functions. For example, vitamin B<sub>1</sub> (thiamine) is used to treat beriberi, a serious condition similar to sepsis in COVID-19 mortality (Lu *et al.*, 2020). Fatigue is another vague symptom that is associated with COVID-19 infection, it is treated with vitamin B<sub>1</sub> supplements (Poston *et al.*, 2020). Vitamin B<sub>1</sub> has been shown to limit *Mycobacterium tuberculosis* by regulating the innate immunity. Deficiency in vitamin B<sub>1</sub> can result to pulmonary tuberculosis (Poston *et al.*, 2020). Vitamin B<sub>2</sub> (riboflavin) and UV light have been used as medicine to reduce the Middle East Respiratory Syndrome-related coronavirus (MERS-CoV) in human plasma products (Keli *et al.*, 2016). Vitamin B<sub>3</sub> (niacin), B<sub>5</sub> (pantothenic acid) and B<sub>6</sub> (pyridoxine) enhances protein metabolism, participates in over 100 reactions in body tissues. They are necessary in the production of hemoglobin which carries oxygen in the blood, they help the blood work better and possibly increasing a patient life span (Kyme *et al.*, 2012). Treatment with these vitamins have significantly inhibited neutrophil infiltration into the lungs with a strong anti-inflammatory effect during ventilator induced lung injury (Jones *et al.*, 2015). Lemon containing B vitamins could be considered as a basic option for the treatment of virus infections (Zhang and Liu, 2020).

**Selenium:** Selenium present in lemon is another immune booster that helps defend viral and bacterial infections, autoimmune diseases and allergies (Beck and Matthew, 2002). For instance, in HIV patients, selenium has been shown to slow down the progression of the virus replication (Guillin *et al.*, 2019). Deficiency in selenium have been found to impair the immune system, causing rapid mutation of benign variants of RNA viruses to virulence (Harthill, 2011). A similar study by Beck *et al.* (2001), reported that selenium deficiency could not only increase the pathology of an influenza virus infection but also permit an avirulent virus to acquire virulence due to genetic mutation (Beck *et al.*, 1995). Another study by Ma *et al.* (2019), reported that synergistic effect of selenium with ginseng leaf saponins could induce immune response to a live bivalent infectious bronchitis coronavirus vaccine in chickens. This means that ingestion of selenium from lemon or as supplement could be of help in managing COVID-19 infections.

**Vitamin C:** Lemons are a rich source of vitamin C, one squeezed lemon can provide up to 21% of a person's daily

need. Being an antioxidant, vitamin C helps maintain strong immunity against oxidative damage caused by free radicals (Zhang and Liu, 2020). It also acts as enzyme co-factor for hormone production, collagen synthesis and immune potentiation (Zhang and Liu, 2020). With respect to the respiratory tract illnesses such as COVID-19, vitamin C can provide protection against viral diseases through its function in the synthesis and activity of interferon- $\alpha/\beta$  at the initial stage of coronavirus infection (Hemila and Chalker, 2020). According to Hemila and Chalker, (2020), the high amount of vitamin C given to an emergency COVID-19 patient daily, shortens the time on ventilation by about 25% for people who required ventilation for over 10 hours. Although, high amount of vitamin C given intravenously, are currently being tested in COVID-19 patients who have developed pneumonia in China (Cheng, 2020). An earlier study by Atherton *et al.* (1978), reported that vitamin C increased the resistance of chick embryo tracheal organ cultures to avian coronavirus infection. During a cold and flu season, vitamin C is the first recommended medicine for flu-like symptoms, such as sneezing, running or stuffy nose and swollen sinuses (Field *et al.*, 2002). Vitamin C deficiency can lead to impaired immunity and higher susceptibility to viral infections. In addition to the vitamins and mineral elements in lemon, it also contains other potent phenolic compounds including limonene, limonin and hesperidin, Fig 3.

**Limonene:** Limonene occupies the outermost yellow part of the rind (skin) of lemon. This part of lemon contains 300 mg of limonene and it represents 98% of lemon healing power (Bacanli *et al.*, 2015). Limonene has shown to increase the activity of macrophages (white blood cells that engulf foreign particles) in the lungs of rats (Hamada *et al.*, 2002). Excessive stomach acid is the major cause of heartburn and gastroesophageal reflux disease (GERD). Limonene helps neutralize stomach acid, assist in pushing contents downward to reduce GERD (Jing *et al.*, 2013). Limonene has significantly decreased the prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) production, transformed the growth factor- $\beta$  (TGF- $\beta$ ) gene expression and increased the phosphorylated-extracellular signal regulated kinase (EPK)1/2 expression levels in ulcerative colitis rat (Ye *et al.*, 2017). Limonene may lower the risk of heart by metabolizing certain risk factors, such as elevated cholesterol, blood sugar and triglyceride levels (Mitropoulou *et al.*, 2017; Klimek-Szczykutowicz *et al.*, 2020). Limonene has shown to exhibit high anti-HSV-1 activity by direct interaction with the free virus particles (Astani and Schnitzler, 2014). In addition, the compound also showed a significant effect against yellow fever virus and tobacco mosaic virus (Gomez *et al.*, 2013).

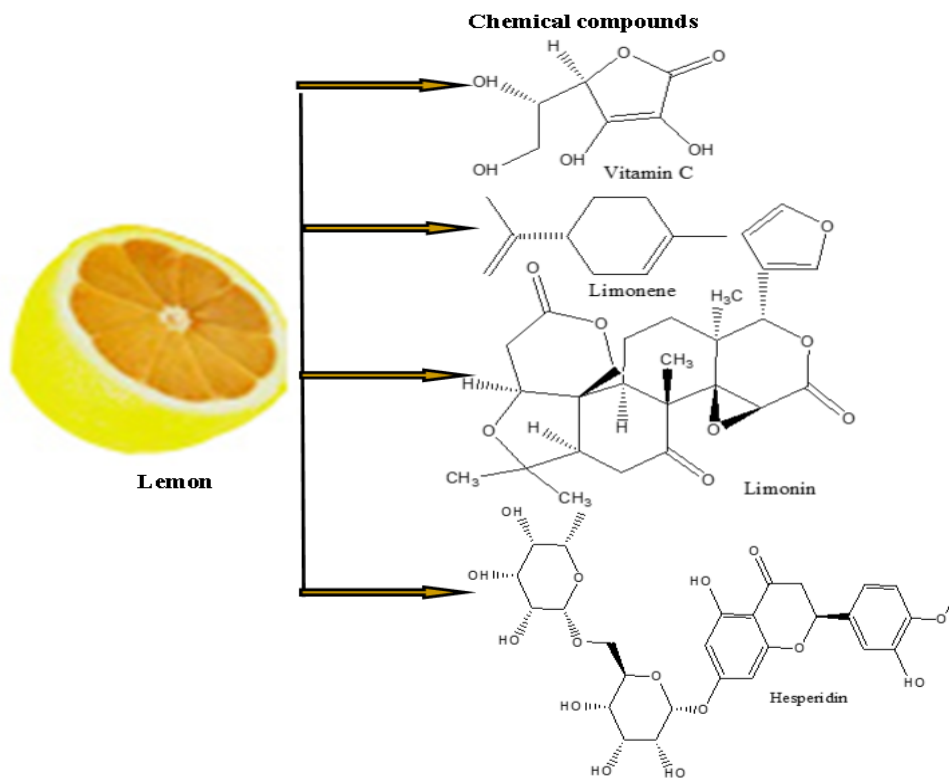
**Limonin:** Limonin (lemonade) is another excellent compound found mostly in lemon pulp (Russo *et al.*, 2014). Limonin represents the total lemon's bitter taste with an exceptional health benefits in both humans and animals (Fabroni *et al.*, 2020). Limonin extract added to animal feeds in large quantities, was observed to boost their immune systems against diseases (Bampidis and Robinson, 2006). The compound can remain in the blood for up to 24hrs to easily flush toxins from the liver, promote bile flow and stimulate

gall bladder (Bampidis and Robinson, 2006). In addition, limonin has been found to cure sore throat and flu virus permanently (Jayaprakasha and Patil, 2007). Kidney stones which form small lumps when waste products crystallize and build up in the kidneys, has been subsided by limonin juice (Zerwekh *et al.*, 2007). The low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) are prone to damage by free radicals in a process known as oxidation, and they can become harmful as they clogged the arteries, causing heart attacks, stroke and kidney failure in COVID-19 patient (Huang *et al.*, 2019). Lemonin helps controls LDL, by promoting high-density lipoprotein (HDL) which carries unused cholesterol back to the liver, preventing clogged arteries and other types of heart disease (Chaturvedi *et al.*, 2016).

**Hesperidin :** Hesperidin is yet another natural compound that occupies the membrane peel of lemon. It forms the highest concentration of crystals which appear as white flakes when lemon juice is extracted (Xiong *et al.*, 2019). Hesperidin in lemon, helps in maintaining the healthy thin walls of the small capillary blood vessels (Xiong *et al.*, 2019). The compound does this by protecting the endothelium against hypoxia via the stimulation of mitochondrial enzymes. Hesperidin was recently shown to bind to COVID-19-spike protein (Spro) and interfered with the re-folding of spike and then inhibits the viral infection process (Adem *et al.*, 2020). The researchers

concluded that the compound could become a meaningful medicine for the treatment of SARS-CoV-2 infections.

Another research revealed that hesperidin antiviral activity also exhibited a high binding affinity to COVID-19-3CLpro, indicating that the compound should be used as 3CLpro inhibitor (Wu *et al.*, 2020). According to Jia *et al.* (2019), SARS-NsP13 sequence is a conserved multi-functional protein, which include N-terminal metal binding domain (MBD) and helicase domain (Hel) necessary for the replication of coronavirus. Based on structure modeling or helicase protein, hesperidin showed high binding affinity to the SARS-NsP13 target Jia *et al.* (2019). As the ACE2 remains the host specific target receptor in which COVID-19 gain access to the body, it has also been considered as the major target for the treatment of coronavirus infection to block SARS-CoV-2 from entering host cells. According to Wu *et al.* (2020), the only compound that could target the interface between spike and ACE2 was hesperidin. The compound was found to lie on the middle shallow pit of the surface of RBD of spike, its dihydro-flavone part went parallel with theb-6 sheet of RBD, and its sugar part inserted into the shallow pit in the direction away from ACE2, where a few hydrophobic amino acids, including Tyr436, Try440, Leu442, Phe443, Phe475, Try475, Try481 and Tyr49 form a hydrophobic shallow pocket to contain hesperidin compound (Wu *et al.*, 2020).



**Figure 3:** Major phytochemical compounds found in lemon



## Conclusion

A virus is able to strike the body when the immune system is weakened or compromised due to unhealthy lifestyle, which includes poor nutrition, vitamins and minerals deficiencies, lack of probiotic, chronic stress, depression and anxiety, cigarette smoking, regular use of alcohols, illegal drugs, a diet high on sugar and lack of sleep. She mentioned that a strong immune system can easily render any virus powerless, including coronavirus. In order to strengthen the body immunity and protect against coronavirus or other viral infections, then B, C, D vitamins, zinc, selenium, magnesium and supplements should be considered.

Garlic, ginger and lemon contain several natural vitamins, minerals and phenolic-compounds including, vitamin A, B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub>, B<sub>5</sub>, B<sub>6</sub>, C, E, potassium, quercetin, omega-3s, iron, zinc, magnesium, selenium, allicin, ajoene, S-allylmercaptol-cysteine, gingerol, shogaol, paradol, limonene, limonins and hesperidin. All these compounds contain anti-inflammatory, antiviral and anti-coagulant (blood thinner) properties. Potassium present in garlic can subside hypokalemia which was a major problem associated with COVID-19. On the other hand, quercetin in garlic could form H-bonds that will interact with 6LU7 amino acids in the COVID-19 Mpro active. The zinc content in ginger can penetrate the mucous secretions of the respiratory system to strengthen the immune system and can prevent COVID-19 from replicating. The high content of other vitamins and minerals, together with the various phytochemicals are potent antiviral agents that kill all kinds of flu viruses, including rhinovirus, influenza A and B, parainfluenza virus (PFV), herpes virus (HSV), cytomegalovirus, etc. Therefore, the combination of garlic, ginger and lemon can block all the different pathways of COVID-19 infections. Although the suggestion of this article originated from an experience, however, several literatures have shown the enormous benefits embedded in garlic, ginger and lemon. According to the University of Maryland Medical Center, natural products have save many lives from stuffiness, bronchial congestion, severe cough and tightness of the lungs to ease breathing from viral attacks.

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