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GINGER (*Zingiber officinale)* AS AN AIRWAY SMOOTH MUSCLE RELAXANT: A Potential Benefit for Covid-19 Patients

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ABSTRACT

Covid-19 is an infectious disease caused by SARS-CoV-2 virus. Lungs is the extremely affected organ that Covid-19 targets causing it to be inflamed and irritated. This review aims to substantiate that Ginger;s active constituents have the potential to promote anti-inflammatory properties specifically on the lungs and to provide sufficient data showing that ginger has effects on relaxing airway smooth muscle due to its antiviral and immunomodulatory effects. Ginger contains active compounds like gingerol, shogaol, terpenes and phenolic compounds which are responsible for its medicinal properties. Ginger acts on the lungs by reducing narrowing of airway by converting [Ca2+] regulation. A form of decoction, suspension or infusion can be concocted in order to suffice the potential properties of Ginger to prevent, manage and aid Covid-19 symptoms.

Introduction

According to the World Health Organization, over 262 Million confirmed Covid-19 cases as of December 2021. Also, Covid-19 has reached over 5.2 Million worldwide deaths [1]. COVID-19 is a respiratory disease which mostly affects upper respiratory system including lungs. COVID-19 causes a variety of respiratory issues, reaching from mild to severe cases. Elderly individuals and those who have heart disease, cancer, or diabetes may develop severe symptoms. It is possible for the lining to become irritated and inflamed. Resulting in shortness of breath, chest pain and cough. COVID-19 causes mild to moderate symptoms in about 80% of patients. Some people develop Pneumonia, a lung infection that causes the alveoli to become inflamed [2].

The entry point of beta-coronaviridae is through respiratory tract epithelium. Inflammatory mediators such as CXCL10 and interferons are generated by infected epithelial cells and create an inflammatory response which manifests symptoms like cough, shortness of breath in Covid-19 patients. [3] Progression of these symptoms to Covid-19 patients lead to Pneumonia. Due to a shortage of surfactant in the alveoli caused by viral pneumocyte death, the lungs struggle maintaining the opening of alveoli when the section of lung collapses. The immune response of the body will release white blood cells and will directly target the alveoli. Concurrently, inflammatory substances released by white blood cells cause blood vessels around the air sacs to leak leading to difficulty in breathing or breathlessness. [4] In severe cases, when the virus keeps on duplicating in the lungs, this leads to persistent injury damaging the alveolar resulting in acute respiratory syndrome. [5] This is the critical phase or outcome of Covid-19 to patients. [6]

According to the study of Townsend, *et. alGinger's* bioactive constituents have effects in relaxing airway smooth muscle. It's mechanism of action is by reducing narrowing of airway by converting [Ca2+] regulation.[7] Diverse plants like the family of Zingiberaceae have isolated products with antiviral properties such Terpenes, Beta-Sesquiphellandrene and Phenolic compounds. These chemicals' antiviral characteristics and immunomodulatory effects can be used to prevent, treat, and manage COVID-19. However, an effective, safe, affordable, and accessible therapeutic alternative still awaits (Attah, *et. al.*,).[8] In addition, a study by Jafarzadeh A., Jafarzadeh S., & Nemati M., supported these claims about antiviral, anti-inflammatory and immunomodulatory effects of ginger.[9]

The main intention of this review is to establish possible antiviral, antiinflammatory and vasodilator effects of Ginger and its bioactive constituents that can probably prevent constriction of the vascular regions of the lungs which can aid in COVID-19 patients' pulmonary system.

Methods

This article review is based on retrieved research and peer-reviewed publications from various Pubmed and ResearchGate journals. The article search started on November 17 to November 29, 2021. Topics searched focused on ginger and its active constituents and the COVID-19 virus' and its effect on our lungs. All evaluated journals were methodically filed in a single folder to ease access and avoid any documented contradictions. All articles were reviewed and arranged. Articles that mention ginger for possible treatment of Covid-19 were prioritized. The review was done comprehensively to establish ginger's possible effectiveness against the COVID-19 Virus.

Based on one study, raw ginger eases the airway. T[1]racheas were floating in an organ bath with epithelia removed, constricted with acetylcholine (ACh). After establishing steady force, increasing quantities of fresh produce ginger powder dispersed in 1ml of water were added to the Krebs-Henseleit buffer, with water. The relaxation was dose-dependent, with the peak lightening arising between 50 and 100 mg/ml. 30 minutes later, the ginger-treated ASM strips were approximately 70% relaxed. [10]

Covid-19: The Statistical Situation

According to the World Health Organization, over 262 Million cases of COVID-19 are confirmed globally as of December 2021. This includes 5 million deaths as reported to WHO. America has the highest confirmed cases (97 million), followed by Europe (87 million), South-East Asia (44 million cases), Africa which is the lowest has more than 6 million confirmed cases.[11] In the Philippines, there are more than 2 million confirmed cases, 2.7 million recovered, 15 thousand active cases, and 48 thousand died. [12]

Covid-19 virus and its effect on the lungs

Covid-19 has a variety of symptoms. There is a lot to learn about the virus, but one thing is certain it is extremely transmissible and spreads quickly. It has symptoms that are comparable to the flu. Its severe manifestations, on the other hand, can range from respiratory issues to kidney issues.

What is the virus's mode of transmission? It appears to be transmitted mostly by droplets infection, which occurs when individuals cough or when you contact someone who is infected and then touch your face. As a stowaway, the virus begins in the mouth or nose and spreads deeper into the body. Its final destinations are the intestines, spleen, or lungs, which are where it has the most effect. Corona viruses may cause havoc with even a small number of hosts.[13]

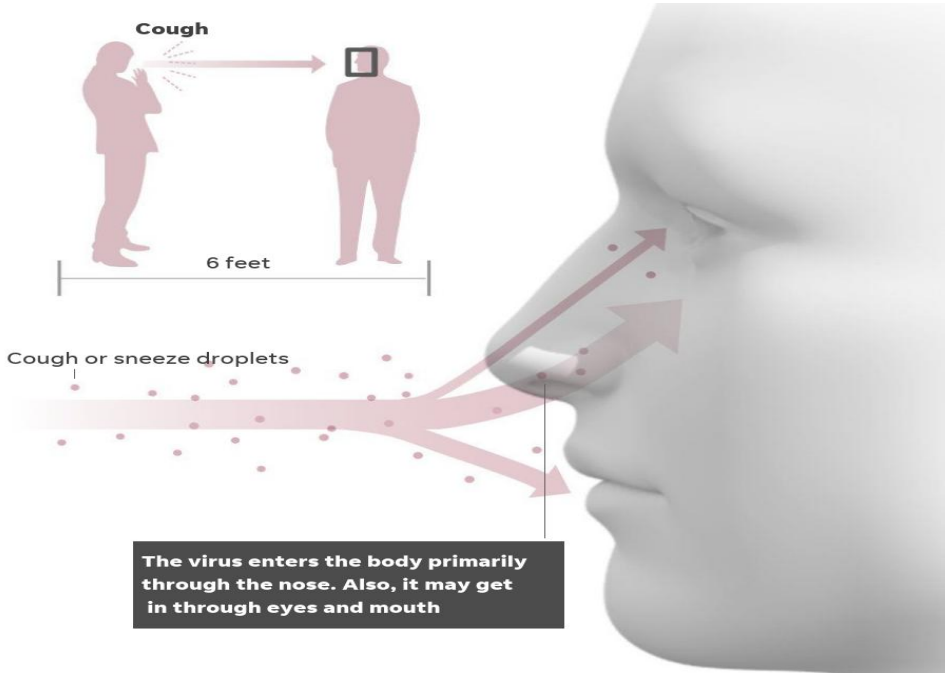
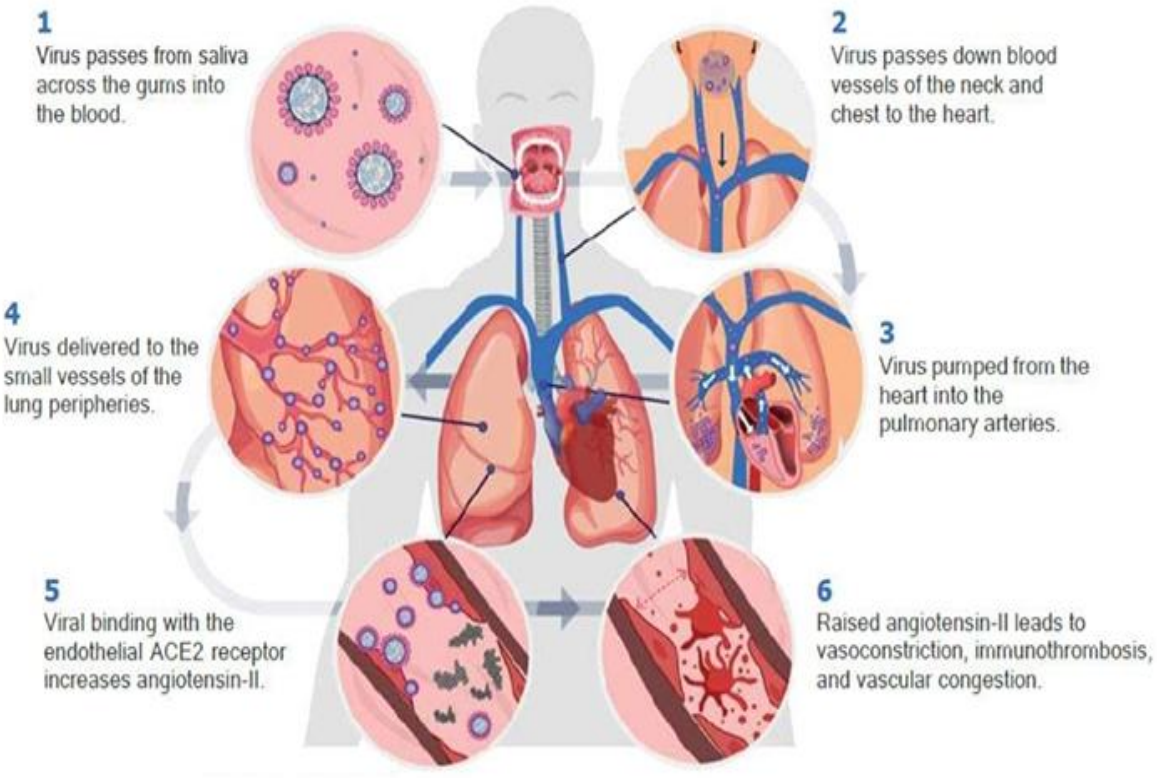


Illustration on how the covid virus spreads and enters our body

[1] After establishing steady force, increasing quantities of fresh produce

The coronavirus injects its genetic material into its victims' membranes via a specific receptor. Unaware of what's going on, the cell follows easy and straightforward instructions: copy and rebuild. It replicates more copies of the original virus until reaching a breaking point and is given one last order which is to self-destruct. Cell disintegrates and unleashes fresh corona particles that are poised to attack other cells. The number of infected cells increases at an exponential rate. Approximately ten days later, millions of body cells have been infected, and billions of viruses have infested the lungs.[14] Once inside the body, it infects Epithelial cells in the lung. Virus's receptor protein attaches to the host, allowing the virus to enter. Virus starts to reproduce inside host cell before killing it.[15] The upper respiratory system is the first to be compromised. Moderate flu-like symptoms develop. [16]



The lungs are the first organs of the body to be impacted by CoronaVirus. It quickly captures cells in the respiratory system. CoronaVirus is thought to assault epithelial cells' airway linings, which filter pollen and viruses, causing debris and fluids to fill our airways. [17] The virus infects both lower and upper respiratory tracts. The lungs will enlarge and become irritated as it passes through the airways. When a person contracts CoViD-19, the lungs are the most impacted, and it might have serious consequences. When the virus attacks the cells in the lungs, the body replaces the damaged tissue with thick, strong scar tissue. This can result in pulmonary fibrosis, a chronic and progressive disease that makes it harder for the lungs to function normally. As the patient's condition worsens, he or she will have severe breathing difficulties and shortness of breath. [18]

The lung is not the only organ that is affected in our body. The SARS-CoV-2 virus attaches to ACE2 receptors found throughout the body, causing harm to our system. It can result in a cytokine storm, which may lead to death. Different organs may be damaged, with a temporal course independent of viral load. Complications are caused by inflammation, platelet activation, hypercoagulability, endothelial dysfunction, blood vessel constriction, stasis, hypoxia, and muscle immobility.[19]

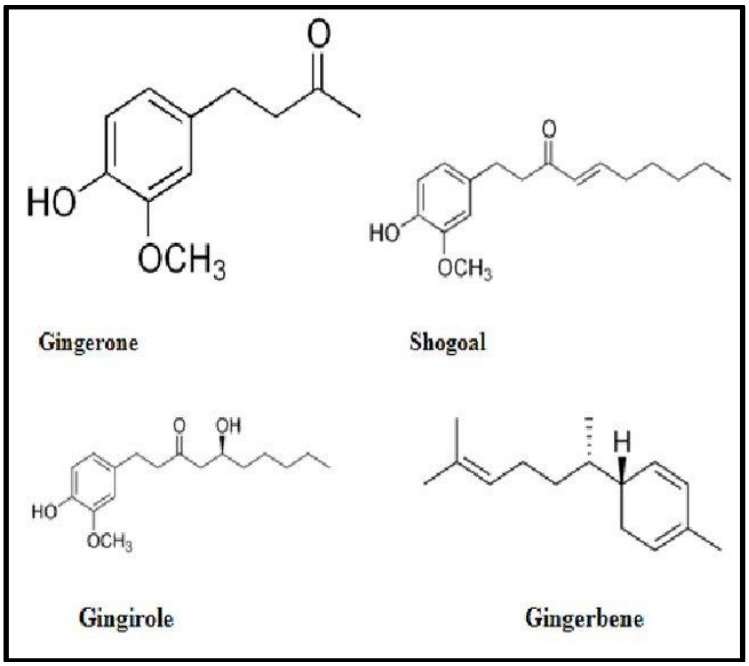
Ginger Plant: Its Structure and Function

Structure of the Ginger plant

Zingiber officinale, commonly regarded as ginger, is a perennial herbaceous plant Zingiberaceae family cultivated for its edible rhizome, a widely used spice. A corky top layer and an aromatic pale-yellow center characterize the brown rhizome. Furthermore, the above-ground shoot is upright and reed-like, with alternating, linear leaflets on the stem. Branches develop from various bases and wrap around each other simultaneously. The leaves can

grow 7 cm (2.75 in) long and 1.9 cm wide (0.7 in). Flower heads are borne on shorter stalks, and the plant produces pale yellow flowers in the form of cones. Ginger is a yearly plant that grows to 0.6–1.2 m (2–4 ft) in height. Southeast Asia is regarded to be the origin of ginger. [20]

All gingers are perennials with rhizomes, generally underground, leafless stems. Roots grow from the base of the stem. [21] Ginger rhizome is a form of underground stem modification that develops horizontally underground that gives aerial stems. [22] Ginger's leafy stems may reach a height of one meter. Every bract protects a single little yellow-green and purple blossom. [23]



Chemical structure of important phytochemicals present in ginger.
This figure was uploaded by Mostafa I Waly

Phenols	Volatile oils	
	Sesquiterpenes	Others
Gingerols and shogoals	bisapolene, zingiberene, zingiberol, sesquiphellandrene, curcurmene	6-dehydrogingerdione, galanolactone, gingesulfonic acid, zingerone, geraniol, neral, monoacyldigalactosylglycerols, gingerglycolipids

Kathi, J Kemper, 1999.

Active Chemical Constituents of ginger
This figure was uploaded by Mostafa I Waly

The spice ginger is a well-known and popular spice. Where phenolic compounds, polysaccharides, terpenes, organic acids, lipids, and raw fibers, among other chemical components, are abundant. The phenolic compounds of ginger are accountable for ginger's diverse bioactivities.Phenolic constituents of ginger are primarily responsible for its health benefits. Ginger was found to have antioxidant, antibacterial, respiratory protecting, antiemetic effects.[24]

Ginger's Antiviral Property

Other than anti-inflammatory, anti-nausea, and anticarcinogenic properties, *Z. officinale* is high in metabolites with antiviral potential. [25] A study on prevalent respiratory infections found that ginger, remarkably fresh ginger, can induce cells to fight the virus by preventing it from linking itself to the host's cells, noting its potential use in the treatment of airway virus infection. [26] Fresh ginger has been proposed to inhibit penetration to host by interconnecting proteins. [26] Fresh Ginger increases production of interferon by infected epithelial cells. As a result, fresh ginger has antiviral activity averse to HRSV. It can impede viral duplication in lower respiratory tract. [26] Besides that, certain ginger compounds, such as zingerone and gingerols, are said to impede viral duplication and preclude viruses from undertaking host cells. [27]

In addition to its direct antiviral effects, it has been found that ginger can boost innate antiviral immunity. Interferons, first-line defense against viral infections, and an in vitro study found that gingerols promote IFN-g secretion from activated T cells. [28] Furthermore, fresh ginger extract stimulates interferon secretion. [26] Ginger inhibits influenza virus duplication by inducing tumor necrosis factor production by macrophages. [28] Also, in vitro studies show that ginger extract has antiviral properties averse to Avian Influenza and Feline Calicivirus, which are similar to human norovirus. [29, 30, 31]

Regarding SARS-CoV-2, Researchers used drug repurposing and computational techniques in this part. This helps the researchers find the SARS-CoV-2 and its high-affinity inhibitors. Some proteins needed for the replication and viral survival in several sites yield that the SARS-CoV-2 associated with a PLpro cleaves polyprotein a/b. Additionally, type 1 interferon is obstructed by the SARS-CoV-2-related to the PLpro against the infection reaction. [32] As a result, to precede infection replication and survival, the PLpro consciously built an appropriate target against SARS-CoV-2 medications. [33] The bioactive components and another family of ginger compounds inhibit PLpro on the report of the molecular docking methods. [34] Moreover, the 6-gingerol shows a high restricting partiality with various infection proteins which is fundamental for SARS-CoV-2 duplication was reported by molecular docking investigations. [35] In vitro and in vivo findings in these docking computational investigations should be supported.

Currently, no solid scientific proof that ginger can stop or help treat COVID-19 or kill this specific coronavirus. However, there is little speculation that the compounds in ginger can inhibit the replication of the virus.

Ginger and its Vasodilating property

Aside from its anti-inflammatory effects, traditional healers in South Asia recommend ginger as a treatment for heart conditions like cardiomyopathy and hypertension as well as for symptoms like palpitations and poor circulation. Vasodilators are drugs that relax blood vessels and lower blood pressure. Researchers have found that ginger can have a variety of beneficial benefits on the immune system, as well as on the inflammatory response, anti apoptosis and blood sugar control. In addition to this, research has demonstrated that ginger has antiemetic and antiepileptic qualities [36].

Ginger lowers blood pressure in hypertensive rats, however the impact is dose-dependent; however, transitory atrioventricular dissociation has been reported shortly after ginger administration [37]. In addition, ginger was found to have CCB activity similar to verapamil in rats and rabbits after constriction of airways. Ginger and nifedipine were found to act together to lower blood pressure in the sole human trial that addressed the condition [38]. Results of the study showed that ginger crude extract improved vasoprotective effect on porcine arteries through repression of Cyclooxygenase and Nitric Oxide Synthase. The tested effects of homocysteine induced endothelial cell damage together with the levels of proteins.These findings proposed that ginger crude extract may have a potent vasoprotective effect [39].

Ginger, rhizome of the biennial herb *Zingiber officinale* Roscoe, which grows throughout South Asia. Ginger is used as a medication according to traditional medicine [40]. Ginger (Zingiberaceae) is popular for its therapeutic properties and is found all over the tropicals, especially in Southeastern Asia. As a painkiller, hypoglycemic, antiemetic, antibacterial, and antimycotic, ginger helps to treat inflammatory illnesses such as gout, osteoarthritis, and rheumatoid arthritis. Antidiabetic, anti dyslipidemia, hypotensive, vasodilator, antiobesity, and anticancer agents are some of the other uses [41].

The palpitating effect of ginger could be attributed to vasodilation caused by increased nitric oxide production. Ginger may increase Acetylcholine, which may contribute to its cardiovascular effects. In-vitro tests it was demonstrated that ginger at a dose of 5 mg/ml, is a partial vasorelaxant, as it relaxed the rabbit's aortic strip that had been procontracted with phenylephrine. Ginger's vasodilator effect is partially mediated by nitric oxide production. L-NAME is used to inhibit nitric oxide synthase and is a non-selective NO synthase inhibitor [42].

Ginger is mostly used to treat nausea, but this herb can also be used for other things. It is a stimulant for the digestive system, has been used to treat headaches, is warming because of its vasodilating and heart-stimulating effects, and is used to improve or mix with other botanical formulas. People in China use it in recipes to make low-dose plants less toxic, like Aconitum spp. root and Pinellia ternata (pinellia, ban xia) root and root. Cooking aconite with ginger makes lipo alkaloids that are less harmful. One study found that raw Pinella caused rats to have more gastrointestinal (GI) activity, which caused some damage in the process. Pinellia mixed with ginger juice, on the other hand, didn't cause any damage [43].

According to the findings of a study, Serum nitric oxide levels rose significantly. There is an increase in cytokine production related to nitric oxide production by neutrophils and macrophages, which is caused by signaling changes and cell injury. [44]. In addition to causing vasodilation by relaxing vascular smooth muscle cells, it also aids in the activation of macrophages through the IFN-y mediated effector pathways, which is beneficial [45]. In mice, ginger reduces allergic airway inflammation by increasing the Th1 response and alleviating the Th2 response caused by ovalbumin. In conclusion, ginger has an antiallergic impact in an asthmatic mouse model through modulating Th1/Th2 cytokines [46] [47] [48]. Ginger root has been shown in the scientific literature to have anti-inflammatory, antiemetic, and gastroprotective properties [49].

According to a randomized controlled study, Cyclooxygenase (COX) is an enzyme that has a role in the promotion of inflammation. COX is responsible for the conversion of arachidonic acid and prostaglandins. The transformed prostaglandins have different effects on the body. Some cause vasodilation while others release the enzyme thromboxane A4, which acts as an aggregating agent. In this case, the vasodilation is beneficial because it permits the larger white blood cell to penetrate the injured location. The increased blood flow is what causes the damaged area to become more red and warm in color as a result of the increased blood flow. However, more research is required to prove that ginger root has a direct vasodilator effect. The cellular and molecular mechanisms underlying ginger root's blood pressure-lowering properties have not yet been fully understood [50].

Discussion

CoronaVirus is an infectious disease that has a variety of symptoms. Receptor protein can bind to the receptors of a host cell, allowing virus to enter the cell. The virus starts to reproduce within the host cell and eventually kills it [15]. The uppermost respiratory system, that consists of nose, mouth, larynx, and bronchi, is the first to be affected. The patient starts to experience mild flu-like signs or symptoms such as a dry cough, fever, gasping for breath, headache, exhaustion, and muscle soreness [16]. COVID-19 first affects the lungs [17]. When a virus infects lung cells, the body repairs the damaged tissue with thick, robust scar tissue that results in pulmonary fibrosis, a chronic and progressive condition that makes it difficult for the lungs to function correctly. The patient will experience severe breathing difficulties and shortness of breath as his or her condition worsens. [18]

As stated in the statistics, CoronaVirus outbreaks have impacted our lives. Based on the findings of the study of Chang JS, et. al. Ginger has antiviral activity against the human respiratory syncytial virus (Figure 1) [26]. As a result, fresh ginger has been shown to have antiviral activity against HRSV and suppress viral reproduction in the lower respiratory tract [26]. Aside from that, ginger compounds like 6-gingerols and zingerone have shown inhibition of viral replication [27]. Ginger has been discovered to improve innate antiviral immunity. Interferons defend against infections, and gingerols enhance IFN-g release from activated T cells, according to an in vitro study [28].

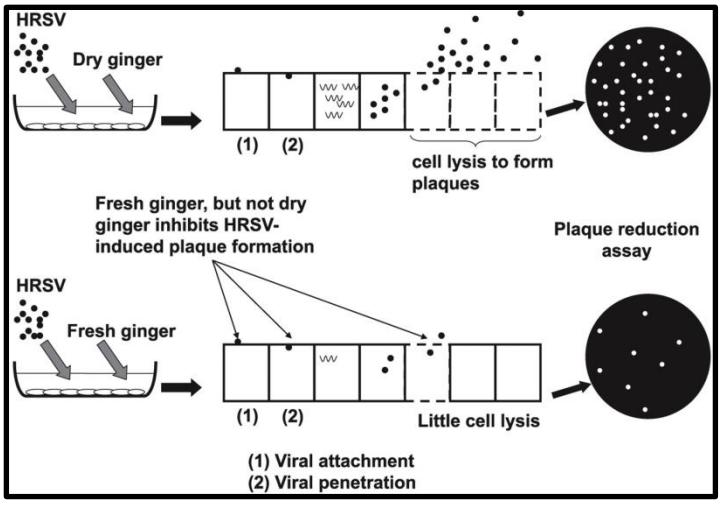


Figure 1

Ginger is advised by traditional healers in South Asia for the usage in cardiomyopathy, high blood pressure, palpitations, and to improve circulation due to its vasodilator properties. According to several studies ginger possesses antihyperglycemic effects. [36]. Results of the study showed that ginger crude extract improved vasoprotective effect on arteries. In the existence of homocysteine (Hcy), Hcy enhanced iNOS, eNOS and COX-2 expression while ginger significantly reduced eNOS. These findings indicated ginger crude extract may have a potent vasoprotective effect [39].

Ginger's hypotensive and bradycardic effects could be attributed to vasodilation caused by increased nitric oxide release or synthesis, as well as a calcium channel blocking properties. Ginger's vasodilator effect is partially mediated by nitric oxide production. L-NAME is used to inhibit nitric oxide synthase and is a non-selective NO synthase inhibitor [42]. Ginger is a digestive stimulant, has been used to treat headaches, is warming due to its vasodilating and heart-stimulating properties, and is used to enhance or mix with other botanical formulas [43].

After establishing a steady force, increasing amounts of fresh produce ginger powder dispersed in 1ml of water were added to the Krebs-Henseleit buffer. The relaxation was dose-dependent, with the maximum relaxation taking place between 50 and 100 mg/ml. The ginger-treated ASM strips were approximately 70% relaxed after 30 minutes. [10].

5. Delimitations

The general intent of this peer review article is to provide insight into potential antiviral treatment of Ginger (Zingiber officinale) against the Covid-19 virus as Ginger as gingerol and shogaol, relax precontracted human airway smooth muscle depending on the dose. It delimits the study may not be generalizable to other product forms of ginger as it mainly focuses on its action as a powder in a glass of warm water for oral intake. Other lung conditions aside from the Covid-19 virus will also not be focused on in this article.

6. Conclusion

According to the different studies presented and expounded, it is likely that ginger and its bioactive constituents have promising effects in vasodilating constricted and inflamed lungs. In the case of Covid-19 infection, Ginger has the potential to help patients' pulmonary system circulation by attenuating their clinical symptoms such as shortness of breath, coughing and muscular or chest pain. In course of time, more bioactive constituents in ginger can be isolated and investigated to be used for medicinal purposes. Above all, more clinical trials of ginger may be carried out in order to prove its effectiveness on human beings.

7. Acknowledgements

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