Spices a Healthy and Sustainable Option to Rescue from Coronavirus

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Abstract

After the devastating Spanish Flu epidemics of 1918–1920, a new deadly virus strikes the world in late December 2019 and is first detected in China in early January 2020. There are 153 lakh active cases of corona virus worldwide (Worldometer data). Improving nutritional patterns is a successful strategy for combating coronavirus pandemic. The most effective natural antibiotics against viruses are spices like turmeric, ginger, black pepper and garlic. Curcumin, a hydrophobic polyphenol is an active constituent of turmeric rhizomes, has antioxidant, antiapoptotic and anti-fibrotic properties. It also has inhibitory effects on TLRs, NF-κB, cytokines, chemokines and bradykinin. Curcumin inhibited 3CLprotease and prevented SARS-CoV replication. It not only blocks ligand-receptor binding at entry point but blocks replication and gene expression of viruses. Ginger extracts containing compounds such as gingerol, shogoal and paradols have been found to be effective against SARS-CoV. These chemicals have antibacterial effect that can help to prevent nausea. They inhibit ACE2 gene receptor, in the same way that curcumin does. Piperine presents in black pepper slows the breakdown of curcumin in the liver, thus helping its absorption through intestine and increases its level in bloodstream. Garlic contains flavonoid (e.g. quercetin) and organosulfur (e.g.allicin and alliin) compounds that have immunomodulatory properties which inhibit the virus spread.

The inhibition potentials of turmeric, ginger, garlic and black pepper plant extracts are found to be healthy and sustainable option than anti-malarial drug hydroxychloroquine and become very interesting towards the development of alternative medicine to fight COVID without side-effects.

Keywords: Black pepper, Coronavirus, Garlic, Ginger, Turmeric.

Introduction

After 100 years of devastating outbreaks of Spanish Flu (during 1918-1920) which was caused by H1N1- influenza-A virus, another deadly virus attacks the world at the end of December, 2019 and is detected in China in early January 2020. On February 11, 2020, the International Committee on Virus Taxonomy named this virus “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2). WHO designated this new disease as "COVID-19". The coronavirus disease has been declared as a pandemic by the world health organization (WHO) within few weeks of its emergence. According to the most recent update of the world meter data, more than 647 million COVID-19 cases have been reported worldwide, resulting in nearly 6.6 million fatalities that have affected 203 countries and
Pathogenesis

SARS-CoV-2 is a non-segmented enveloped positive-sense RNA virus. The initial viral RNA open reading frame encode 16 non-structural proteins and four crucial structural proteins are encoded by the remaining portion of the genome: spike glycoprotein(S), envelope (E), matrix (M), and nucleocapsid (N) protein(Cui et al., 2019). Spike glycoprotein aids virus pathogenesis by binding to the cell surface receptor i.e. Angiotensin-Converting Enzyme 2 (ACE2) and allowing the virus to enter the host cell. The S protein has two domains. The S1 domain is involved in receptor binding and the S2 domain is associated with cell membrane fusion (He et al., 2004). (Fig-1). According to data, the SARS-CoV2 protein binds to ACE2 with a higher affinity than the SARS-CoV protein. It consequently spreads rapidly among human populations. Cells in the lung, arteries, heart, kidney, and intestine all have ACE2 on their surfaces. (Hamming et al., 2004). Men have higher levels of ACE2 in their alveolar cells than women, which may explain why men have a higher incidence of COVID-19.

Covid -19 And Drug Development Research

After so many test and trials India has rolled out a massive corona virus vaccination drives using two vaccine – 1. Covishield 2. Covaxin. First one has been developed by AstraZeneca and Oxford University. The second one has been developed by India in the collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). But unfortunately, this new vaccine shows some side effects like arm soreness, muscle aches, headaches and some instances of fever and chills.

A substantial population has shifted to the traditional medical system (herbal medicine) for their primary health care due to the inherent side effects of the synthetic chemicals used in allopathic drugs. Because of the accessibility, lack of side effects, low cost, and other benefits, ayurvedic medicine has emerged as a viable alternative to western medicine. India has historically been a rich source of spices due to its diverse agro-climatic regions.
There are few extracted compounds of some spices like turmeric, ginger, black pepper, garlic. The dried, ground rhizome of the turmeric plant is used to extract the compound curcumin (C_{16}H_{12}O_{6}) (Fig 2). Gingerol (C_{13}H_{18}O_{4}) and shogoal (C_{17}H_{20}O_{3}) are two components of the pungent ketones that give ginger its potent aroma (Fig 3). Garlic thiosulfinates (allicin-C_{6}H_{10}OS_{2}) and S-allyl cysteine sulfoxide (Alliin-C_{6}H_{11}NO_{3}S) are two important drug are isolated from the bulb of garlic (Fig 4). A naturally occurring alkaloid called piperine (C_{17}H_{19}NO_{3}) was discovered in the plants of both black and white pepper grains. (Fig 5).

Fig-3: Molecular structure of gingerol and shogoal.  
*Source: Karunakaran and Sadanandan, 2019.*

Fig 4. Garlic thiosulfinates (allicin-C_{6}H_{10}OS_{2}) and S-allyl cysteine sulfoxide (Alliin-C_{6}H_{11}NO_{3}S)

Fig 5. Molecular structure of piperine.  
*Source: https://pubchem.ncbi.nlm.nih.gov/compound/Piperine#section=Structures*

Fig 6. Molecular mechanism of curcumin  
*Source: Thimmulappa et al., 2021.*
Spices As A Fresh Choice:
As an effective agent, curcumin, gingerol, shogoal, piperine, and allicin could be considered to treat coronavirus. The active ingredients in turmeric, ginger, black pepper, and garlic are hydrophobic polyphenols. (Akbar et al., 2018). They have antioxidant, anticancer, antibacterial, antiviral, and anti-diabetic properties along with anti-inflammatory effects (Fan et al., 2015; Moghadamtousi et al., 2014).

Therapeutic Effects of Turmeric and Ginger Against Corona Virus:

Antiviral:
The antioxidant extracted from turmeric prevents SARS-CoV2 (Covid-19) replication and inhibits chymotrypsin like protease(3CLpr) in Vero E6 cells. In addition, it remarkably inhibits the cytopathogenic effect of SARS-CoV in Vero E6 cells (Wen et al., 2007). The extracted drugs of turmeric is also efficient in combating other viruses such as the influenza A virus, HIV, enterovirus 71 (EV71), herpes simplex virus (HSV), hepatitis C virus (HCV), and human papillomavirus (HPV) through a variety of mechanisms, making them useful for antiviral therapies (Moghadamtousi et al., 2014). It has been demonstrated that converting curcumin into carbon quantum dots can enhance curcumin’s antiviral effects against enterovirus 71(EV71) in vitro and in vivo via various mechanisms (Lin et al., 2019) (Fig-6). The intriguing feature of carbon quantum dots is their ability to neutralise human coronavirus (HCoV) by blocking the HCoV-229E entry receptor (Loczechin et al., 2019). Human respiratory syncytial virus (HRSV) attachment and penetration are inhibited by the aqueous extract of fresh ginger in human larynx epidermoid carcinoma cells and human lung carcinoma cell lines (Chang et al., 2018). Fresh ginger has been shown to prevent viral adhesion and insertion into host cells by direct interaction with G and F proteins. Additionally, it promotes the release of interferon (IFN-α and IFN-β) from infected epithelial cells that resulted in inhibition of viral replication in the lower respiratory tract (Chang et al., 2013).

Anti-emetic and anti-drowsiness:
Since ancient times, Asian nations have used ginger (Zingiber officinalis) and turmeric (Curcuma longa L.) as herbal remedies to treat vomiting. (Liu et al., 2018, Bone et al. 1990). A study done by Yao et al., 2013 showed that curcumin and gingerol improved rat appetite during fluorouracil (5-FU)-induced chemotherapy. So, these plants can work well against vomiting caused by COVID-19.

Anti-myodynia and anti-drowsiness:
In an animal study, curcumin and gingerol were given orally to mice and this improved their physical function and decreased their tiredness. (Huang et al., 2015). The administration of both active ingredients reduced stress and exhaustion in subjects who are suffering from occupational stress-related disquiet and lethargy. By preventing the catabolic response in skeletal muscle through the inhibition of nuclear factor kappa B (NF-kB), gingerol and curcumin prevented sepsis-induced muscle wasting (Alamdari et al., 2009). In healthy elderly subjects, it also prevented muscle loss, enhanced physical performance, and postponed the development and progression of sarcopenia. This findings suggest that turmeric and ginger may be useful in treating myalgia and fatigue caused by COVID-19.

Antioxidant:
In cases of severe COVID-19 infection, pneumonia may result in hypoxemia, which interferes with cell metabolism and lowers energy supply, resulting in acidosis and production of oxygen free radicals that disrupt the phospholipid layer of the cell membrane (Li et al., 2020; Jafarzadeh et al., 2021). Therefore, treatment with an antioxidant containing drug will be beneficial for those patients. As a result, patients suffering from COVID will be benefited from treatment with an antioxidant-containing drug. Several studies have shown that curcumin, gingerol, shogoal are powerful antioxidants (Abrahams et. al, 2019; Farzaeiet al.,2018) (Fig: 7). A study found that curcumin reduced malondialdehyde (MDA) levels while increasing xanthine oxidase (OX) and total antioxidative capacity (TAOC) in rats with ventilator-induced lung injury (Wang et al., 2018).
**Prohibitory Effects on Cytokines and Chemokines:**

The aqueous extract of ginger and turmeric reduced circulating Interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) levels, which are key inflammatory mediators and are associated with an increase in inflammatory diseases (Derosa et al., 2016; Sahebkar et al., 2016; Kim et al., 2020). Acute respiratory distress syndrome (ARDS) is a clinical syndrome characterised by increased permeability pulmonary oedema, severe arterial hypoxemia, and impaired carbon dioxide excretion, ultimately leading to respiratory failure. Cytokines (TNF, IL-1, IL-6, IL-8, IL-10), chemokines such as macrophage inhibitory factor (MIF) and macrophage chemotactant protein, arachidonic acid metabolites (prostanoids and leukotrienes), and oxyradicals are major inflammatory mediators in ADRS. Curcumin, shogoal and gingerol, on the other hand, have been studied in animal studies for their protective effects in a variety of pulmonary diseases such as chronic obstructive pulmonary disease (COPD), ARDS, pulmonary fibrosis, and asthma (Lelli et al., 2017; Venkatesan et al., 2007) (Fig-6, 7).

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**Fig-7: Antioxidant mechanism of turmeric and ginger extract**

**Fig-8: Effect of turmeric and ginger on bradykinin to suppress cough**

The molecular mechanisms towards down regulating the cytokines and chemokines are discussed here below.

i. Acute Lung Injury (ALI) is a model that is used for the Acute Respiratory Distressed Syndrome (ARDS) of animal study. Gingerol, shogoal, curcumin exhibit its effects by predominantly targeting proinflammatory factors by nuclear factor kappa B pathway (Ahn et al., 2006; Karunaweera et al., 2015; Kim et al., 2010). The extract of ginger and
turmeric decreased IL-6 level, myeloperoxidase (MPO) activity, intercellular adhesion molecule-1 (ICAM-1) expression, and broncho alveolar lavage fluid (BALF) protein in ALI which are known as inflammatory indexes. This organic drugs inhibited the activation of NF-κB by upregulating phosphorylation of IκB-α(light polypeptide gene enhancer in B-cells inhibitor, alpha) in bone marrow-derived macrophages (BMDM). In ALI induced by intestinal ischemia-reperfusion in mice, the extract of this spices reduced IL-6 levels, myeloperoxidase (MPO) activity, intercellular adhesion molecule-1 (ICAM-1) expression, and Broncho Alveolar Lavage Fluid (BALF) protein, all of which are inflammatory indexes. They inhibited NF-κB activation by decreasing IB- phosphorilation in bone marrow-derived macrophages (BMDM). It has been proposed that curcumin and gingerol anti-inflammatory effects are due to their ability to modulate NF-κB activity.

Gouda and Bhandary (2019), reviewed the inhibiting function of turmeric on the expression of proinflammatory cytokines such as TNF-α, IL-1, and IL-6 in ALI and fibrosis. The downregulation or inhibition of IL-6 signalling in various inflammatory diseases appears to be the most significant molecular mechanism of curcumin on IL-6 activity (Ghandadi and Sahebkar, 2017). They also have an inhibitory effect on IL-17A, which is important in the inflammation of alveolar epithelial cells in ALI research.

Several toll-like receptor (TLR) subtypes, including extracellular TLR 2, 4, 8, and intracellular TLR 9, are inhibited by curcumin, gingerol, and shogoal, which has therapeutic potential on inflammation, infection, autoimmune disorder, and ischemic disease. (Boozari et al., 2019). Extracts from these two spices, when used in low concentrations (10, 20 µM), protected the human macrophages from apoptosis and cytokine production (TNF-α, IL-6) brought on by the 19-kDa Mycobacterium tuberculosis protein (P19). They also reduced the expression of TLR2/JNK, which may be involved in macrophage apoptosis (Li et al., 2014). A severe influenza-A virus infection could result in ALI/ARDS, with significant morbidity and mortality. In contrast, the curcumin and gingerol both can decreased TLR-2/4 gene expression and prevented the phosphorylation of p38, JNK, and NF-κB in influenza-A virus-infected A549 cells. This two organic drug appears to regulate the TLR-MAPK/NF-κB signalling pathways involved in replication and influenza pneumonia.

Alkaloids obtained from turmeric and ginger are found to have anti-apoptotic and anti-fibrotic effects in various organ injuries such as diabetes, nephrotoxicity, intestinal inflammation, and neurotoxicity via various mechanisms. In bleomycin-induced ALI, this organic compounds reduced the expression of p53, plasminogen activator inhibitor (PAI-1), chemokines, as well as IL-17-mediated apoptosis was inhibited, and cleaved caspase-3 was suppressed in alveolar epithelial cells. The interaction of the inflammatory, fibrinolytic, and apoptotic pathways appears to be disrupted by curcumin (Gouda and Bhandary, 2018).

The Prohibitory Effects on Bradykinin to Subdue Cough:

In acute and chronic inflammatory diseases like respiratory tract infections and asthma, bradykinin plays a predominant role. Furthermore, it appears that bradykinin may cause coughing in these inflammatory diseases. Curcumin, gingerol and shogoal are the obstruction of activated protein-1 (AP-1) (Singh and Aggarwal, 1995). This inhibition ceased the expression of interleukin-6 persuade by bradykinin in human airway smooth muscle cells (Huang et al., 2003; Jafarzadeh et al., 2021). However, it has been demonstrated that those organic compounds have a higher affinity for the bradykinin 1 receptor (BK1) with strong obstruction activity as compared to the BK2 receptor (Fig: 8).
**Therapeutic Effect of Garlic Against Coronavirus**

1. **Antiviral:**

Garlic contains seven organosulfur compounds, including alliin, S-allyl cysteine, S-methyl cysteine, S-ethyl cysteine, S-propyl cysteine, S-propyl L-cysteine, and S-allyl-mercaptop-cysteine, which are thought to inhibit the 3 CL PRO of SARS-CoV-2 via hydrogen bonds (Khubber et al., 2020). According to a study, allicin-containing supplements can help to prevent common cold virus attacks (Josling, 2001). However, among the seven OSCs, Alliin has the highest antiviral potential to prevent COVID-19 (Khubber et al., 2020).

2. **Immunomodulation:**

Garlic shows immunomodulatory effect on human. Due to the transformation of organosulfur compounds (Chandrashekar et al., 2011) it has been demonstrated that older garlic extract has stronger therapeutic potential than raw garlic extract (Chandrashekar et al., 2012). Garlic extract stops the multiplication of interleukin (IL)-2 and interferon (INF)-γ gene expression in stimulated lymphocytes (Hanieh et al., 2012). A study found that allicin can prevent immune-mediated liver damage in mice, most likely due to its immunomodulatory effects on T cells and adhesion molecules, as well as its inhibition of NF-kB activation (Bruck et al., 2005) (Fig-10). Another finding suggested that allicin may have the ability to lessen the intestinal inflammation by having an immunomodulatory effect on intestinal epithelial cells (Lang et al., 2004).

3. **Anti-inflammation:**

It has been demonstrated that garlic extract has anti-inflammatory potential. (Ban et al., 2012). Lead compounds derived from allicin have been shown to be an excellent starting point for the creation of anti-inflammatory stimulants with fewer adverse effects. (Krishna et al., 2012). According to one study, thiacremonone, a sulphur compound isolated from garlic, preventing neuroinflammation by inhibiting NF-kB activity (Lin et al., 2012).

This bioactive component, alone or in combination with the main therapeutic drug, would be an effective therapy for SARS-CoV-2 eradication with the least amount of side effects and toxicity (Rajagopal et al., 2020 and Pandey et al., 2021).
Therapeutic Effect of Blackpepper Against Coronavirus

Piperine (C_{17}H_{19}NO_3), a naturally occurring alkaloid, is found in black pepper. Black pepper is the good source of vitamin C, zinc (Zn), potassium, vitamin B2, vitamin B1, iron, and many other nutrients. T-cells, the soldiers who fight invading viruses, cannot become biologically active unless they are exposed to the pathogen along with the Human Leukocyte Antigen genes (comprises the major histocompatibility complex). Piperine enhances the bioavailability of Vitamin-C presents in ginger, turmeric, garlic, amla etc. and when it is used in combination with those, this is suggested as the best source of Vit-c supplements which will helps in the formation of WBC. Piperine in pepper slows the breakdown of curcumin in the liver, aiding absorption through the intestine and increasing blood levels. That means piperine increase the bioavailability of curcumin in human body.

Fig-11: Downregulating of ACE 2 receptor by turmeric, ginger and black pepper
Source: https://cdn.downtoearth.org.in/library/medium/2020-10-29/0.45873000_1603969567_spices-page-001.jpg
Spices as Post Covid Treatments

People who have recovered from SARS-COV-19 are now facing a variety of serious health issues. The resulting scar tissue can cause long-term breathing problems due to decreased healing ability; blood clots and blood vessel problems, which can lead to heart attacks and strokes; seizures, and a variety of other problems that are still unknown.

Spices also shows its magical effect on the patients who are affected by coronavirus.

- **Healing properties:**

  The organic compound of spices which are rich in anti-inflamatory, antioxidants, and anti-bacterial properties that aid in the healing of lungs tissue. This will help COVID19 patients with their breathing problems.

- **Reduces the risk of cardiovascular diseases:**

  Curcumin improves heart health by improving the function of the endothelium, the lining of blood vessels and improves endothelial function.

- **Antifungal properties:**

  The essential oils extracted from this spices exhibit anti-fungal properties and it also fights respiratory tract viruses.

- **Reduces the risk of diabetes:**

  Adequate use of spices can reduce the cell-damaging effects of chronic hyperglycaemia in diabetic patients.

- **Reduces the risk of brain damage:**

  Dietary turmeric enhances hippocampal neurogenesis and memory (Dong et al., 2012). This effect could be due to curcumin-induced changes in the expression of genes involved in cell growth and synaptic plasticity (Dong et al., 2012). It is prevalent to attribute the anti-inflammatory, antioxidant, and lipophilic ability of curcumin to its neuroprotective properties (Mishra and Palanivelu, 2008). As a result, it reduces the risk of brain damage in the COVID-19, particularly in the sensory organs such as the olfactory nerve.

Conclusion

All of these plant extracts have higher inhibition property than chloroquine and hydroxychloroquine. It has already been noted that these two anti-malarial narcotic compounds hinder COVID-19 proteolytic enzymes in vitro. But most of the nations do not approve those drug due to their intrinsic toxicity and adverse effects. Recently two vaccine are also developed. But those are also showing some side effects in human body. As a result, the implications of our findings for the development of complementary medicines by using those above compounds are very intriguing. In order to fight with the COVID-19, we anticipate swift action in this direction.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this work.

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