Herbs that heal: A scoping review on COVID-19 pandemic

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Abstract
The severe acute respiratory syndrome coronavirus-2 lead to the outbreak of COVID-19, succumbed millions of people across globe and still counting. As demonstrated scientifically, the potent protease enzyme of SARS-CoV-2 binds to angiotensin-converting enzyme2 receptor in cells of infected human beings, leading to health complications, especially respiratory ailments along with cytokine storm. The ancient, traditional medicines treating successfully various antimicrobial and antiviral diseases based on herbs anticipated to emerge as potent therapeutics in treatment of COVID-19. Therefore, this current review is an attempt to discuss mainly on final health complications associated with COVID-19, the overview, major pharmaceutical compounds present, proven earlier therapeutic value, potent use of four widely used spices as inhibitors in respect of SARS-CoV-2 and the underlining mechanisms of pharmaceutical action of cinnamon, clove, black pepper and giloy and their products with the traditional, scientific, molecular docking and clinical studies based reports. The information reviewed may be aiding to discover potent natural alternative medicines in complete treatment of patients suffering from COVID-19.

1. Introduction

“Cytokine storm” is the word that represents the severe case of SARS-CoV-2 infection that leads to hyperinflammatory (reactive oxygen species (ROS) induction and their release along with nitrogen species) syndrome, acute respiratory distress syndrome, failure of kidneys, complications related to nerves system and cardiovascular system (Wang et al., 2020) and inflammation as well (Ye et al., 2020). In COVID patients, the angiocentric inflammation in lungs leads to constant inflammation in certain organs such as the heart, gut, liver, and brain (Wang et al., 2020). Otherwise, any other effective treatment that counters the “cytokine storm,” would interfere with viral replication.

At present, the therapies used in COVID-19 treatment are anti-malarial, antiviral and anti-inflammatory, etc. The similar pharmaceutical values are possessed by certain spices, which have proven their efficacy in various viral treatments, with almost no side effects, readily available in required quantities and with certain other advantages over English medicine (Moghademousi et al., 2015; Srinivasan, 2005). A severe acute respiratory syndrome is an unusual type of contagious pneumonia that is caused by SARS coronavirus. The use of common spices as immunity boosters and antiviral agents is gaining importance. An online survey revealed that 71.8% of people using kadha are combating infection by boosting their immunity with no side effects. Hence, spices have significant role to combat viral infections (Caterina et al., 2021). Even US FDA has approved several spice derived natural products possessing phenolic rich compounds for medical purpose in treating the human diseases (Srinivasan, 2005; Newman and Cragg, 2016), specific inhibitors of protease of SARS-CoV-2 (Umesh et al., 2020).

2. Discussion

2.1 Clove

Syzygium aromaticum L., Merr. and Perry is an evergreen tree from the family Myrtaceae, habituated to tropical climates. Being indigenous to spices island of Indonesia, now cultivated in many countries. The clove of commerce is dried aromatic fully grown unopened flower bud. Cloves are strongly pungent owing to eugenol. Over the years, it is mentioned in Ayurveda, Chinese traditional medicines (Bhownik et al., 2012). With varied potencies, all the three forms, clove (dried bud), oleoresin and clove oil are used in traditional medicine for vivid ailment treatments such as respiratory and digestive disorders (Aisha et al., 2011; Banerjee et al., 2006).

The previous literature studies also evidenced other remarkable properties, such as antiangiogenic (Zheng et al., 1992, Aisha et al., 2011), anticancer (Zheng et al., 1992; Aisha et al., 2011; Banerjee et al., 2006), antioxidant (Ogata et al., 2000), anti-inflammatory (Darshan et al., 2004), and antimutagenic activities (Miyazawa et al., 2001). Clove is the familiar culinary spice in folk medicine. Its ingredients have anti-inflammatory, antithrombotic, antiviral, immunostimulatory and antibacterial properties. Antimicrobial activities of clove, made its wider use in food industry. There is

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positive nod from FDA for safety of using clove buds, derived oil, extracted eugenol, and oleoresins as well for use in food industry (Vijayasteltar et al., 2016). Ogunwande et al. (2005) informed that WHO confirmed the dosage of daily maximum clove uptake (2.5 mg) per kg body weight.

Clove are originally whole dried buds and also used in the form of ground spice, and essential oil as well. Dried clove buds contain ~20% essential oil, which is rich in eugenol, accounting for 70-90%. The other main phytochemicals isolated from clove essential oil include eugenyl acetate, β-caryophyllene, and several sesquiterpenes (Zheng et al., 1992; Mittal et al., 2014), including acubebene, α-copaene, and γ-and δ-cadinene (Gopalakrishnan, 1984). Crategolic acid, vanillin, galotannic acid, etc., are present in lesser amounts (Mittal et al., 2014). Eugenol and other constituents (methyl salicylate and methyl amyl ketone) are representing for aroma of cloves. Yield of the oil varies with the raw material, from 1% in stem and leaf to 17.46% in bud.

Table 1: Anti-inflammatory, immunostimulatory, and antithrombotic properties of clove and their products

<table>
<thead>
<tr>
<th>Product of clove</th>
<th>Medicinal property</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clove essential oil</td>
<td>Anti-inflammatory effects in animal models</td>
<td>Öztürk and Ozbek, 2005</td>
</tr>
<tr>
<td>Clove bud ethanol extracts</td>
<td>Anti-inflammatory effects in animals</td>
<td>Öztürk and Ozbek, 2005</td>
</tr>
<tr>
<td>Eugenol</td>
<td>Anti-inflammatory activity - reduces pleural exudates in animals</td>
<td>Daniel et al., 2009</td>
</tr>
<tr>
<td>Eugenol</td>
<td>Regulate the cellular inflammatory cascade pathways</td>
<td>Bahramsoltani et al., 2020</td>
</tr>
<tr>
<td>Whole clove aqueous extract</td>
<td>Relieves lipopolysaccharide induced lung inflammation</td>
<td>Magalhães et al., 2010</td>
</tr>
<tr>
<td>and eugenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clove aqueous extract</td>
<td>Protective effects pyelonephritis in animal models</td>
<td>Nassan et al., 2015</td>
</tr>
<tr>
<td>and eugenol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clove aqueous extract</td>
<td>Curative action on kidney inflammation in COVID-19 patients</td>
<td>Su et al., 2020</td>
</tr>
<tr>
<td>Clove essential oil</td>
<td>The immunostimulatory activity</td>
<td>Carrasco et al., 2009</td>
</tr>
<tr>
<td>Clove buds</td>
<td>Improve the blood supply to both the brain and the heart and tonic for the cardiovascular system</td>
<td>Bahramsoltani et al., 2020</td>
</tr>
<tr>
<td>Clove oil</td>
<td>Human platelets enhancement</td>
<td>Saeed et al., 1994</td>
</tr>
<tr>
<td>Clove extracts</td>
<td>Inhibit the thrombin-induced platelet aggregation</td>
<td>Yang et al., 2011</td>
</tr>
<tr>
<td>Eugenol</td>
<td>Platelet inhibitor and preventing blood clots</td>
<td>Garcia-Mediavilla et al., 2007</td>
</tr>
<tr>
<td>Eugenol</td>
<td>Clove anti-atherosclerotic potential</td>
<td>Yang et al., 2011</td>
</tr>
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</table>

Traditional medicine uses cloves as respiratory aids, and in particular, the spice is one of the ingredients of teas used in tropical Asia to facilitate coughing (Bhowmik et al., 2012). Moreover, an aromatherapy procedure consisting of breathing in the aroma released from hot clove tea is another common way to use cloves for respiratory disorders like coughs, colds, asthma, bronchitis, and sinusitis (Bhowmik et al., 2012). Moreover, it is customary in Asia to chew cloves for treating soreness of throat and inflammation of the pharynx (Bhowmik et al., 2012).

The eugeniin inhibits DNA polymerase, the selective inhibitor of the HSV 1 (Kurokawa et al., 1998), thereby interfere in viral DNA synthesis and eugenol interfere with viral replication leading to reduced infection (Reichling et al., 2009).

**Antiviral properties of clove:** The whole clove antiviral activity was tested by Tragoolpua and Jatisatienr (2007), the ethanol extract of buds directly inactivated the standard HSV strains (Hussein et
al., 2000) reported that clove methanol extracts inhibited the HCV protease.

Among the products with antiviral properties, eugenol, 4-allyl-2-methoxyphenol is the major constituent one. Tragooolpuad and Jatisatien (2007) used pure eugenol as the reference compound in their anti-HSV studies and found higher antiviral activity. Benencia and Courreges (2000) reported the eugenol inhibition of HSV-1 and HSV-2 replication. The study exhibited the eugenol as virucidal and no other element associated cytotoxicity was reported. Eugenol also showed antiviral activity against the influenza A virus (IAV) (Dai et al., 2013), inhibitor of the Ebola virus in vitro (Lane et al., 2019). While, eugenin isolated from the herbal extracts of cloves showed anti-HSV activity (Kurokawa et al., 1998), which was due to the inhibition of the viral DNA synthesis. Eugenin is the inhibitor of the protease of Dengue virus (DENV), and established as promising drug for DENV therapeutics (Saleem et al., 2019). Cloves are used in India and Morocco by herbalists for treatment and prevention of COVID-19 (Chaachouay et al., 2021). Kaempferol, a phytochemical compound in silico binds to the main protease, via, substrate binding pocket of SARS-CoV-2 with high affinity and interacting with Cys145 and His41, which are the active site residues. This demonstrates that clove flavonoids can be potential SARS-CoV-2 inhibitors (Rehman et al., 2020). As revealed by the molecular docking, the intense affinities of clove extracts, i.e., bicornin applied at ‘9.2 kcal/mol and biflorin (‘8.5 kcal/mol) for Mpro, leads to potential inhibitory activity (Rehman et al., 2020).

Clove is currently employed to prevent and control the SARS-CoV-2-associated disease along with other herbs (Kanyinda, 2020). described the clove based protocol for COVID-19 treatment, especially when used at early stages of the viral infection.

Protocol: first cloves are put to boiling with water in mix with other herbs/material for 15 min, administered to patients after its volative, active principle compounds are dissolved in water and same applies for drinkable clove decoction.

The therapeutic use of cloves in traditional medicine to treat respiratory ailments various viruses, in addition to anti-inflammatory, immunostimulatory, and antithrombotic properties established clove potential with its phytochemical constituents against the COVID-19. There is the note of antibacterial effects exhibited by clove derived essential oils reducing the infections of immunosuppressed patients (Chaib et al., 2007) and preventing secondary bacterial infections in COVID-19 patients (Bahramsoltani et al., 2020).

2.2 Cinnamon

Among the genuses, Cinnamomum those belongs to the family Lauraceae, the Ceylon cinnamon: Cinnamomum verum or C. zeylanicum has therapeutic values unlike Chinese cinnamon, Cinnamomum cassia or Cinnamonum aromaticum, which is used a culinary spice for foods (Oketch-Rabah et al., 2018). Presence of various compounds gives an idea about, of which cinnamaldehyde and eugenol are crucial. Leaves contain cinnamaldehyde of 1 - 5% and eugenol- 7to 95%, while cinnamaldehyde is reported to 65 to 80%, eugenol varies from 5 to 10% in stem bark, root bark contains 60% of camphor and eugenol content in leaf oil and bark oil ranges from 77.3-90.5% and 4-10%, respectively (Sangal, 2011; Vangalapati et al., 2012).

Its ethanolic extracts had anti-inflammatory activity which has antagonistic effect on the activation of TLR2 and TLR4 and has no effects on cell viability during culturing (Schink et al., 2018b). Trans-cinnamaldehyde, cinnamic acid, cinnamyl alcohol, cinnamyl methyl ether, p-cymene, methyl salicylate, 1-tetradecanol and benzoic acid are the active compounds in the extracts. Schink et al. (2018a) reported synergy with the anti-inflammatory properties in various compounds. The mixtures have good efficacy compared with pure active compounds. Cinnamaldehyde of cinnamon detoxifies ROS/RNS by activation of NRF2 inducer (Long et al., 2015; Wondrak et al., 2010), while, another compound, cinnamaldehyde mitigates the PI3K/Akt pathway, thereby inhibit metastasis, angiogenesis (Patra et al., 2019). Lu et al. (2010) reported that the water based Ceylon cinnamon extracts inhibits VEGFR2 kinase. Ranasinghe et al. (2017) conducted the clinical safety of cinnamon in the form of toxicity and any associated side effects with respect to dosage applied and found no risks.

Figure 3: Cinnamon bark.

Figure 4: Structure of cinnamaldehyde.
Ceylon cinnamon extracts would helpful in treating COVID-19 patients in combination with other medications. Dexamethasone use leads to atherosclerosis, which can be rectified with Ceylon cinnamon extract usage (Nayak et al., 2017). The bacterial pneumonia can be cured with the antibacterial effects of C. zeylanicum (Ranasinghe et al., 2013; Doyle and Stephens, 2019) and safe as well. Inflammatory complications are very common in covid patients (Portincasa et al., 2020; Heneka et al., 2020). Treating COVID-19 patients with cinnamon extracts could alleviate such complications, available at cheaper cost and easy to meet the required quantities. Individual compounds from cinnamon that have positive effect are provided in the list. The crucial regulator for pro-inflammatory cytokines cum transcription factor called NF-kB is activated and elicited by the extracts of Ceylon cinnamon (Schink et al., 2018b), thereby attributed with disease defense mechanism.

2.3 Black pepper

Black pepper, *Piper nigrum* L., known as the ‘king of spices’ and ‘black gold’, belongs to family piperaceae. It’s the most widely used and important spice of the world. The dried, mature fruits are used as spice. Charaka and Susrutha, the ancient physicians referred its medicinal values. The Greek physicians described the medical values of black pepper in Materia Medica. Around 135 compounds are reported in pepper essential oil. Black pepper contains phenolics such as phenolic acid, glycosides and flavonol glycosides. Black pepper is one of the important drugs in Indian systems of medicines. The alkaloid, piperine chemically 1 peperoyl piperidine is the major constituent, which is pungent in nature and possessing pharmacological values such as anti-inflammatory, antioxidant, antiplatelets, antihypertensive, anti-Alzheimer’s, antidepressant, antimicrobial, germicide, carminative, anthelmentic, etc. (Jafri et al., 2019; Tiwari, et al., 2020; Yoo et al., 2019). It is used in Ayurveda, Siddha, Unani, and Tibetan, traditional medicine systems.

### Table 2: Certain functions of cinnamon derivatives for various ailments

<table>
<thead>
<tr>
<th>Function of cinnamon product</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory functions</td>
<td>Schink et al., 2018a,b</td>
</tr>
<tr>
<td>Dampens pro-inflammatory cytokines release</td>
<td>Liu et al., 2019; Weber et al., 2019</td>
</tr>
<tr>
<td>Angiogenesis, thrombosis, and vascular endothelialitis are inhibited</td>
<td>Xin et al., 2017; Patra et al., 2019</td>
</tr>
<tr>
<td>Activates NRF2, mitigating ROS/RNS production leading to inflammation</td>
<td>Yao et al., 2015</td>
</tr>
</tbody>
</table>

The daily limited consumption of black pepper along with ginger helps in preventing coronavirus (Rajagopal et al., 2020). As per the report of Pathak and Khandelwal (2007), the use of pepper gives relaxation from COVID-19 symptoms. Yao et al. (2015) reported that quercetin, flavonoid of Black pepper are having antiviral properties and helps in boosting body immunity power. The antiviral activity of Balck pepper against vesicular stomatitis virus, human para-influenza virus on human cell lines with higher alkaloid content was more in chloroform extract (Priya and Saravana, 2017). According to molecular docking investigations, piperine inhibits methyltransferase of Dengue virus and effective against Ebola virus compared to Ribavirin (Nag and Chowdhury, 2020) and against COVID-19 due to piperardine plus piperanine (Rajagopal et al., 2020). In molecular docking study against SARS-CoV-2, piperine showed high binding affinity (−7.0 kCal/mol) for RNA-binding pocket, the simulation confirmed the piperine as potential inhibitor of the RNA-binding site. Therefore, piperine seems to be potential candidate to inhibit the packaging of RNA and inhibiting the viral proliferation (Choudhary et al., 2020). Piperine is an inhibitor of hepatic and intestinal glucuronidatio, leading to enhanced (200 times) bioavailability of curcumin (Rosdhy et al., 2020).

### 2.4 Tinospora cordifolia (Giloy and Guduchi)

The medicinal plant, *Tinospora cordifolia* (Thunb). Miers from the family Meni-spermaceae. The other names are: giloy, guduchi, vatsadani, amritavalli, madhuparni,amrita, amritalataa, chinnaruu
Tinospora is also mentioned in herbal ingredient of “soma” or “heavenly elixir” meaning food for immortals, as per Rigveda (Khare, 2007; Mishra and Kaur, 2013; Leonti and Casu, 2014). T. cordifolia is also known as “nectar of life”, as it strengthens the body immune system. It is distributed in Asian counties, almost all parts (stem, leaves, seed, root, flower) of the giloy have pharmaceutical values and are used in traditional medicine to cure diseases such as, urinary infections, skin allergies, jaundice, diabetes, inflammation, allergies, anemia, etc. (Kumar, 2020). Giloy is very unique boosting the body immunity and resistance against infections, hence, used as ayurvedic medicines since 1000s of years (Panchabhai et al., 2008). Recently, there is spike in direct use of herbal based formulations in treatment of ailments. WHO is also been encouraging to converge herbal medicine with modern medicine to have effective combat with ailments (WHO, 2019). Tinocordiside, magnoflorine, syringin, cordifolioside are the phytonutrients present in tinospora equipped with immunomodulatory pharmaceutical values (Sharma et al., 2019). Phytochemistry of all parts of guduchi is robustly documented in early writings (Sharma et al., 2019).

### Table 4: Antiviral properties of certain reports of products of giloy

<table>
<thead>
<tr>
<th>Product of giloy</th>
<th>Activity of product</th>
<th>Target/organism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. cordifolia silver nanoparticles</td>
<td>Antiviral potential</td>
<td>Chikungunya virus cell</td>
<td>Sharma et al., 2019</td>
</tr>
<tr>
<td>Alcoholic leaves extract of T. cordifolia</td>
<td>Decreases intracellular reactive oxygen species (ROS)</td>
<td>Chikungunya patients with high levels of intracellular ROS</td>
<td>Banerjee et al., 2018</td>
</tr>
<tr>
<td>Crude stem extract of T. cordifolia</td>
<td>Antiviral potential</td>
<td>Against HSV in Vero cell lines by inhibiting the growth of HSV</td>
<td>Pruthvish and Gopinatha, 2018</td>
</tr>
<tr>
<td>Aqueous extract of T. cordifolia stem</td>
<td>Immunomodulatory potential and increase INFγ and IL levels (IL-1, IL-2, IL-4)</td>
<td>Infectious bursal disease virus</td>
<td>Sachan et al., 2019</td>
</tr>
<tr>
<td>Hydro-alcoholic extract of T. cordifolia stem</td>
<td>Cellular immunity as well as humoral immunity</td>
<td>Broiler chicks</td>
<td>Nety et al., 2017</td>
</tr>
<tr>
<td>Chloroform extract</td>
<td>prevented pro-inflammatory biomarkers</td>
<td>RAW264.7 macrophages</td>
<td>Philip et al., 2018</td>
</tr>
</tbody>
</table>

**Figure 7:** Giloy leaves.

**Figure 8:** Structure of berberine.

T. cordifolia is a shrub with climbing nature. These plants are available in distribution in sub-tropical and tropical regions of the world. No much work is attempted in this shrub but the members of family have exhibited anti-inflammatory activity, antidiabetic, immune-stimulatory, antioxidant, phagocytosis due to steroids, terpenes, alkaloids and polysaccharides (Sharma et al., 2012; Kapil and Sharma, 1997; Tiwari et al., 2014; Sharma et al., 2013; Imtiyaj Khan et al., 2011; Panchabhai et al., 2008). The stem of guduchi forms a strong base for treating leprosy, helminthiasis, rheumatoid arthritis, heart ailments. It improves immune system and supports production of regular white blood cells along with its levels, structure and function (Sharma et al., 2019). T. cordifolia is used in ayurveda to treat sporadic fever, urinary, skin, and eye ailments (Chi et al., 2016). In chicks, the stem aqueous extract of giloy has developed immunity against bursal disease (Sachan et al., 2019). The Patanjali Ayurveda Limited, India has commercialized the giloy aqueous extracts and manufacturing the tablets, branded as giloy ghanvati. Rastogi et al. (2020) recommended the use of T. cordifolia as it is loaded with compounds with antiviral properties. The giloy dry stem crude extract exhibited antiviral activity on HSV (Herpes Simplex Virus) (Pruthvish and Gopinatha, 2018). Berberine can regulate 3CLpro protein’s function, thereby controls viral replication (Chowdhury, 2020). Tinocordiside from giloy inhibits protease in respect of SARS-CoV-2 (Shree et al., 2020). Berberine, isocolumbin, tinocordiside, and magnoflorine are the active compounds of giloy, which are with high binding affinity against the key glycoproteins, which are crucial for attachment and replication of SARS-CoV-2 virus particles (Sagar and Kumar, 2020). The aqueous extracts of T. cordifolia as giloy ghanvati reported as phenotype amelioration of COVID-19 virus, when used with humanized zebrafish model. It also reversed the spiked protein in...
respect of SARS-CoV-2 which demonstrates the positive correlation of its effectiveness with the phytochemical present in giloy ghanvati and their importance in virus elimination (Balkrishna et al., 2021). Molecular docking revealed that tinocordiside at the dose of 8.10 kcal per mol from T. cordifolia is the anticipated inhibitors of main protease working against SARS-CoV-2 M(pro) and are safe with drug like mechanism based on prediction of ADMET profile of phytochemical and stable based on MD stimulation investigation. This study also suggested the medicinal plants potentially alleviate Mpro of SARS-CoV-2 (Shree et al., 2020). The in silico and molecular docking revealed that phytochemical, berberine from guduchi can restrict the virus as it has potent to inhibit functions of 3CL(pro) protein and which may the reason for its wide use in treating jaundice and rheumatism, etc. (Chowdhury, 2020). In silico based docking of the ligands (secondary metabolites from guduchi) to inhibit main protease of SARS-CoV-2 confirms that ten metabolites including tinosporide and tinocordifolin are effective key molecules (Sampark et al., 2021).

3. Conclusion

From the review, we conclude that spices have a significant play against viral infections. Traditional systems of medicine have proved to be effective in treating various ailments without side effects as refereed in various earlier literatures. The cinnamon, clove, black pepper and giloy play a vital role in inhibition of main protein of SARS-CoV-2, thereby effective in controlling COVID-19 virus and other viral infections as well. The phytochemicals present in the above spices are crucial for their antiviral activity. However, further attention is required to explore the mode of action against lethal viruses and their effectiveness. And also conduct of extract based experiments with in cell cultures, encapsulated powder formulations and water extracts are ray of hope to exact administer of these spices to patients, while standardizing the treatment doses for COVID-19 patients. The molecular insights on the specific phytochemical interactions with SARS-CoV-2 protein targets will act as a platform to design drugs with optimized characteristics.

Funding

The present research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors’ thanks various front line workers and doctors for their service rendered and investigators who worked on and working on herbal medicines to find better alternative therapeutics.

Conflicts of interest

The authors declare that there are no conflicts of interest relevant to this article.

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