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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 (Moghadamtousi *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 aniviral 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). Under the circumstances explained as above, we attempted this review to introduce the mechanism of action of four spices, cinnamon, clove, black pepper and giloy, their main role in treating the SARS-CoV-2 based on earlier investigations and clinical studies.

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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 (Bhowmik *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 tiangiogenic (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

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.

Cloves 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 αcubebene, α-copaene, and γ-and δ-cadinene (Gopalakrishnan, 1984). Crategolic acid, vanillin, gallotannic 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.

Figure 1: Dried mature flower buds of clove.

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

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

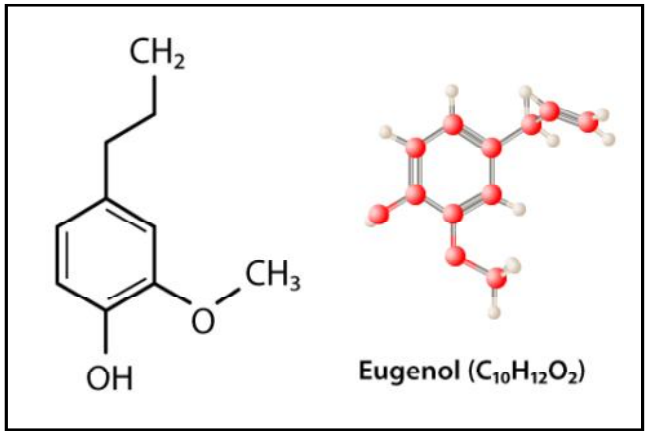

Figure 2: Structure of eugenol.

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. Tragoolpua and Jatisatienr (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, eugeniin 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. Eugeniin 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 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 (Chaieb *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 *Cinnamomum 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.

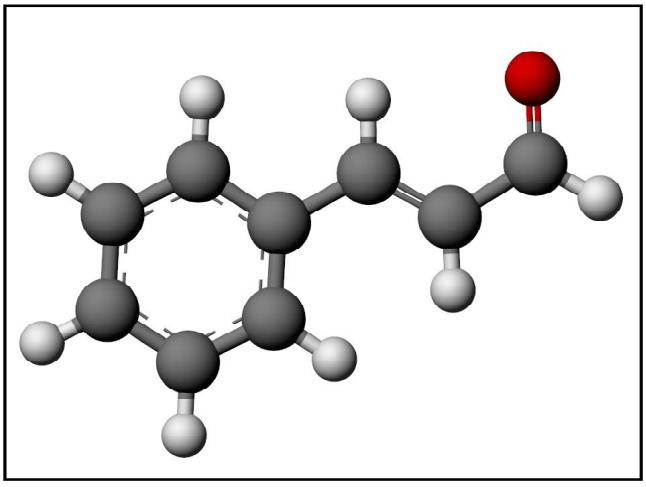

Figure 4: Structure of cinnamaldehyde.

Table 2: Certain functions of cinnamon derivatives for various ailments

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

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-κB is activated and elicited by the extracts of Ceylon cinnamon (Schink *et al.*, 2018b), thereby attributed with disease defense mechanism.

2.3 Black pepper

Balck pepper, *Piper nigrum* L., known as the 'king of spices' and 'black gold', belongs to family piperraceae. 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 physicias 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 3: Certain effects of product of black pepper

Product of black pepper	Activity	References
Piperamides	Inhibition of coxsackie virus type B3	Mair *et al.*, 2016
Aqueous extract	Potent modulator of the macrophages and enhanced splenocyte proliferation	Majdalawieh and Carr, 2010
Isolated alkaloid	Anti-inflammatory effect in RAW 264.7 cells	Pei *et al.*, 2020
Isolated alkaloid	Anti-allergic and anti-asthma activities	Bui *et al.*, 2020

Figure 5: Black pepper.

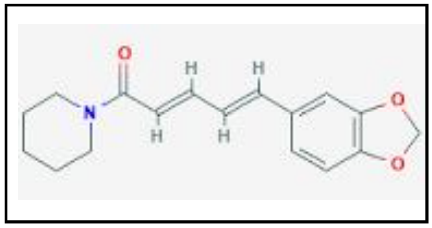

Figure 6: Structure of piperine.

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 piperdardine 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 (2000 times) bioavailability of curcumin (Roshdy *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, vatsaadani, amritavalli, madhuparni,amrita, amritalataa, chinnaruu

-haa, chinnodbhavaa, tantrikaa, guduchi sattva (ayurveda) and giloy (folk). 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). Tinocordioside, 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

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

Figure 7: Giloy leaves.

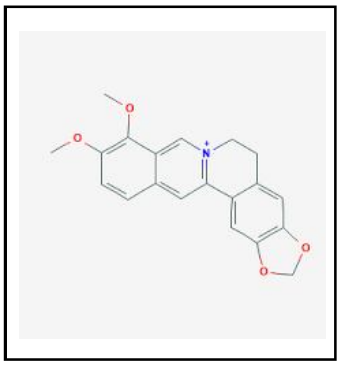

Figure 8: Structure of berberine.

T. cordifolia is a shrub with climbing nature. These plants are avaible 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 effectivess 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 phytocompounds 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.

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Conflicts of interest

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

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