Chapter 20
Spices and Biomarkers of COVID-19: A Mechanistic and Therapeutic Perspective

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Abstract In the face of the COVID-19 pandemic, many people around the world have increased their healthy behaviors to prevent transmission of the virus and potentially improve their immune systems. Therefore, the role of diet and food compounds such as spices with bioactive and antiviral properties may be important in

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these efforts. In this chapter, we review the efficacy of spices such as turmeric (curcumin), cinnamon, ginger, black pepper, saffron, capsaicin, and cumin by investigating the effects of these compounds of COVID-19 disease severity biomarkers.

Keywords Spices · Curcumin · Ginger · Cinnamon · Turmeric · COVID-19

1 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus which has caused and perpetuated the COVID-19 pandemic [1, 2]. The results of a study conducted in early 2021 showed that the disease originated from a single strain of the virus, which infected wild bats and appeared to spread to humans via an intermediate host [3]. The latency period of the disease varies between 1 and 14 days, and most people experience symptoms such as fever, cough, headache, and fatigue within the first 7 days of exposure to the virus [4]. Among the people who show significant symptoms, about 81% have mild to moderate symptoms, 14% have severe symptoms such as shortness of breath and hypoxia, and 5% may show life-threatening symptoms such as respiratory failure or multi-organ dysfunction [5]. In the case of the Omicron variant which erupted around the world at the end of 2021 and the beginning of 2022, the severity of symptoms appeared less than in the other variants of concern [6]. Recently, new strains of SARS-CoV-2, including XBB and BF7, have been identified. The BF7 strain is increasing in the United States and XBB has appeared in Singapore, Bangladesh, and India. Some experts believe that by identifying these sub-strains, the virus may turn into SARS-COVID type 1 or 3. According to forecasts, there is a possibility of spreading new strains, such as BQ1, BQ1.1, BQ1.3, and XBB, which mutate quickly, especially in the cold season and wintertime. These strains have high infectivity but low mortality. One of the characteristics of these sub-strains is that despite low level symptoms, cardiovascular, digestive, bone or muscle complications, and even diabetes may occur after infection. Although these new strains of the virus have become more similar to the common cold in terms of symptoms and mortality, long-term and different complications may occur [7].

2 Immunopathology

Although this virus has the highest affinity for angiotensin-converting enzyme 2 (ACE2)-expressing epithelial cells in the lungs, people with COVID-19 infection have systemic inflammation. This can lead to vasodilation and allow infiltration of lymphocytes and inflamed monocytes into the lungs and heart [8]. In addition, clinical laboratory findings indicate increased levels of interleukin (IL)-2, IL-7, IL-6, interferon-gamma-induced protein 10 (IP-10), tumor necrosis factor alpha (TNF-α) and cytokine release syndrome (CRS), which represent a type of underlying immune system pathology in COVID-19 infections [9]. Preventive actions to diminish the chance of infection include observing healthcare principles and other preventive methods such as getting vaccinated, wearing a mask, ventilating indoor spaces, managing the duration of exposure to infected people, and washing hands [10].

3 Herbal Remedies

Although many medications have been found to improve COVID-19 symptoms, people in all countries cannot access them. As most COVID-19 patients experience a mild form of the disease, supportive care in these cases includes medications such as non-steroidal anti-inflammatory drugs (NSAIDs) to relieve symptoms, adequate fluid intake, rest, observance of personal hygiene, and a healthy diet. Some severe cases may be caused by excessive systemic inflammation known as a cytokine storm [11].

Plants with medicinal properties have always been effective treatments against many disorders, including infectious diseases. According to a study conducted between 1940 and 2014, about half of the micromolecules approved by the United States Food and Drug Administration (FDA), originated from natural products or their derivatives [12]. This is not surprising as foods such as spices contain many bioactive substances, including phenolic compounds, flavonoids, tannins, sulfur-containing compounds, and alkaloids [13, 14]. However, since there are still no completely effective treatments for COVID-19 to date, India's Ministry of Ayush has released guidelines on promoting traditional Ayurveda methods for self-care, including the use of seasonings such as cumin, turmeric, garlic, and ginger in cooking [15].

4 Spices

Spices are obtained from dried parts of a plant and used to add taste, flavor, and color to foods and preserve them. In addition to their application as a condiment of foods, several health benefits have been traditionally linked to spices. Spices can be considered an inexpensive and available therapy to combat various diseases, including diabetes, neurological conditions, renal disorders, prostate diseases, osteoarthritis, rheumatoid arthritis, asthma, and cancer [16–20]. As inflammation plays a significant role in the pathogenesis of all of these diseases, the major effects of spices on these diseases have been attributed to the anti-inflammatory and antioxidant effects of the active ingredients. Furthermore, considering the cytokine storm that can occur in severe COVID-19 cases, spices might have added beneficial effects. The potential effects of some of these spices against COVID-19 disease are reviewed below.

4.1 *Turmeric (***Curcuma longa** *L.)*

Turmeric belongs to the ginger plant group (Zingiberaceae), which has been used in traditional medicines for thousands of years. This plant grows naturally in India but is now grown and used worldwide, including in Southeast Asia [16]. Turmeric rhizomes contain several metabolites as major bioactive substances, such as sesquiterpenes, curcuminoids, steroids, and polyphenols [21]. Curcumin, a polyphenolic product and the main bioactive compound in turmeric rhizomes, is also known as diferuloylmethane [22]. Several mechanisms have been proposed for curcumin‘s protective action against many diseases due to its biological properties, including inhibition of inflammatory mediators and cytokines, preventing the creation of reactive oxygen species (ROS) in macrophages, and regulating the pro-inflammatory cytokine secretion and adhesion molecules [23, 24]. In line with this, this spice has been found to have multiple pharmacological effects, including antioxidant, anticancer, anti-diabetic, lipid-lowering, antiviral, antiseptic, and anti-pneumonia properties [25–43].

Recently, curcumin–piperine co-supplementation was shown to cause a significant reduction in weakness and prevent muscle wasting by inhibiting NF-κB in outpatients with COVID-19 [44, 45]. Despite several unique properties of curcumin, its low absorption and bio-availability have challenged its applicability in different diseases. Recently, new formulations of curcumin, such as phospholipid-modified curcumin and nano-curcumin, or combinations with other herbs, such as piperine, were introduced to circumvent this limitation [34]. As shown in Table 20.1, several clinical trials were undertaken using nano-curcumin or curcumin piperine in COVID-19 patients. Nano-curcumin was used at a dosage of 80 to 160 mg/day for 14 to 21 days [25, 46–49]. In almost all of these studies, nano-curcumin had beneficial effects on clinical outcomes and COVID-19-related biomarkers, such as inflammatory molecules. Compared to the control group, nano-curcumin significantly reduced inflammatory biomarkers such as IL-17, interferon-gamma (IFN-γ), T cell helper (Th)-1 and Th-17 responses and clinical symptoms, including weakness, tiredness, cough, chills, myalgia, olfactory and taste disturbances, duration of fever, and recovery time. In addition, it increased anti-inflammatory cytokines and T-cell regulatory (Treg) responses, transforming growth factor-beta (TGF-β), lymphocyte counts, and oxygen saturation (SpO_2) levels [25, 46–49]. Similarly, curcumin piperine had beneficial effects on diverse symptoms of patients with COVID-19, such as reduction in weakness and tiredness, fever, cough, sore throat, dyspnea, deterioration, duration of hospitalization, and mortality rate. Likewise, maintenance of oxygen saturation levels above 94%, reduction of the need for mechanical ventilation and lower D-dimer levels were observed in the curcumin piperine group compared with controls [44, 50]. Several potential mechanisms have been attributed to curcumin as a natural agent for the treatment of COVID-19 (Fig. 20.1). First, curcumin may directly inhibit viral adhesion and entry via blocking the binding of the SARS-CoV-2 spike protein to ACE2 receptors on host cell membranes. Second, viral RNA transcription and replication may also be disrupted by curcumin. In this action,

Table 20.1 Randomized clinical trials regarding effects of curcumin and ginger against COVID-19

First author (publication year), Reference No.	Sample number	COVID-19 Patients	Age/mean age	Intervention	Control/ placebo	Duration (days)	Main results↑↓↔
Askari, 2022, [44]	46	Outpatients	18–65 years	1000 mg curcumin + 10 mg piperine/ day	Placebo capsule	14	Clinical symptoms: ↓weakness and tiredness Biochemical items: Complete blood count, liver enzymes, blood glucose levels, lipid parameters, kidney function ↔Inflammatory indices: CRP ↔
Pawar, 2021 [50]	140	Inpatients	18–85 years	1050 mg Curcumin with 5 mg bioperine/day	Placebo capsule	14	Clinical symptoms: fever, cough, sore throat, breathlessness, deterioration, duration of hospitalization, mortality rate ↓ Clinical manifestation: SpO2 levels ↑ Mechanical ventilation ↓ D-Dimer levels↓ Neutrophil/lymphocyte ratio↔

(continued)

Table 20.1 (continued)

First author (publication year), Reference No.	Sample number	COVID-19 Patients	Age/mean age	Intervention	Control/ placebo	Duration (days)	Main results↑↓↔
Hassaniazad, 2021 [47]	40	Inpatients	18–75 years	160 mg of nano-curcumin/day	Placebo capsule	14	Inflammatory indices: Expression TBX1 gene of Th1 responses ↓ Expression FOXP3 gene of regulatory T cells↑ Expression RORC gene of Th17 response ↓ Serum level of IL-17 and IFN-γ ↓ Serum level of TGF-β and IL-4↑ Up regulation of FOXP3 and GATA3 genes ↑
Valizadeh, 2020 [25]	80	Inpatients	19–69 years	160 mg of nano-curcumin/day	Placebo capsule	14	Inflammatory indices: Expression level of IL-1β, IL-6↓ Expression level of IL-18 and TNF-α↔ Serum levels of IL-1β, IL-6, IL-18 and TNF-α↓ Clinical manifestation: Mortality rate↓ Fever, cough and dyspnea ↓

Ahmadi, 2021 [46]	60	Outpatient	18–65 years	160 mg nano-curcumin/day	Placebo capsule	14 days	Clinical symptoms: Cough, chills, myalgia, olfactory and taste disturbances ↓ Fever, headache, sore throat, weakness, dyspnea, GI disturbances, dermatological disturbances ↔ Inflammatory indices: Serum level of CRP ↔ Biochemical Indices: Lymphocyte count↑
Tahmasebi, 2021 [49]	120	Inpatients	21–73 years	160 mg nano-curcumin/day	Placebo capsule	21	Inflammatory indices: Serum level of IL-35, IL-10, TGF-β↑ FoxP3, IL-35, IL-10,TGF-β expression levels ↑ Mortality rate↓
Saber-Moghaddam, 2021 [48]	41	Inpatients	18–75 years	160 mg nano-curcumin/day	Placebo capsule	14	Clinical symptoms: Fever, chills, tachypnea, myalgia, cough↓ Recovery time ↓ SpO2 levels↑ Biochemical Indices: Lymphocytes count↑ Serum level of ALT, AST, CRP↔

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Table 20.1 (continued)

First author (publication year), Reference No.	Sample number	COVID-19 Patients	Age/mean age	Intervention	Control/placebo	Duration (days)	Main results↑↓↔
Hellou, 2021 [116]	50	Inpatients	38–66 years	1 ml artemiC (12 mg artemisinin, 40 mg curcumin, 30 mg frankincense and 120 mg vitamin C)/day	Placebo capsule	15	Clinical symptoms: Duration of fever ↓ Biochemical Indices: SpO2 levels↑
Li, 2022 [67]	109	Inpatients	Mean age: 52.7 years	First group:1500 mg ginger/daySecond group: 3000 mg ginger/day	Third group as control	14	Clinical symptoms: SpO2 levels↑ Consciousness frequency of patients↑

Abbreviations: ↑ significant increase in the parameter in comparison to control group, ↓ significant decrease in the parameter in comparison to control group, ↔ no significant change. *M* male, *F* female, *Spo2* oxygen saturation profiles, *Th1* T hehper1, *Th17* T helper 17, *IL-17* interleukin 17, *IFN-γ* interferon γ, *TGF-β* tumor necrosis factor-β, *IL-4* interleukin 4

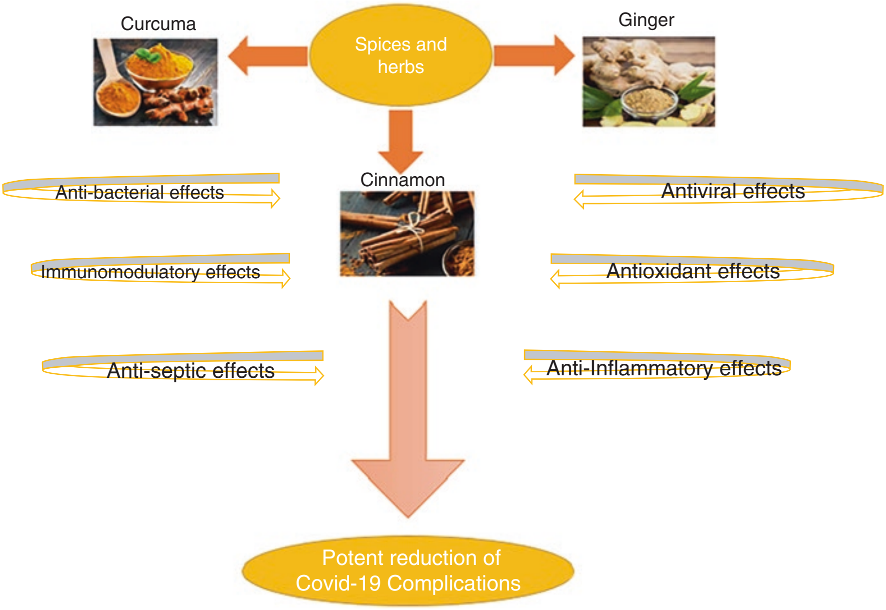

Fig. 20.1 Potential mechanisms of turmeric (curcumin), cinnamon, and ginger against COIVD-19 infection

curcumin suppresses the formation of the replicas–transcriptase complex by binding to the main protease of SARS-CoV-2. Next, the host antiviral response can be increased by curcumin by induction of IFN-stimulated genes at the mRNA level [51, 52]. In addition, curcumin can prevent secondary bacterial infections in COVID-19 patients [37, 53, 54].

4.1.1 Safety of Curcumin

Curcumin is regarded as a safe phytochemical as clinical studies have found that up to 12 g of curcumin per day did not result in any serious side effects [55]. Furthermore, a study by Srivastava showed that the consumption of curcumin at a dose of 2.5 to 8 g per day for 3 months was not associated with any toxic effects [56]. Curcumin has also been shown to be safe and well tolerated in the pediatric population [57].

*4.2 Ginger (*Zingiber officinale*)*

Ginger is one of the important medicinal plants that naturally exist in different countries. It belongs to the ginger family (*Zingiber officinale*) and is a well-known herbal remedy in the traditional Unani system of medicine [58]. Ginger is a rich source of bioactive molecules such as phenolic compounds, alkaloids, and steroids. Moreover, ginger contains sub-compounds such as 4-gingerol, 6-gingerol, 8-gingerol, 10-gingerol and 6-shugaol, and also 14-shogaolsm. Various studies have shown the anti-vomiting, anti-fever, anti-pain, anti-arthritic, and anti-inflammatory effects of ginger (Table 20.2). Recently some studies have shown the antiviral activity and anti-influenza effects of ginger and its bioactive compounds [59, 60]. The antiviral activity of lyophilized extract from *Zingiber officinale* on hepatitis C virus has been investigated at different concentrations from 5 to 200 μg/mL. The results showed that the 100 μg/mL dose effectively inhibited the amplification of viral RNA segments and prevented virus replication [61]. The potential of several ginger bioactive compounds, namely, gingeranone A, geraniol, zingiberene, zingibernol, and zingerone, as anti-SARSCoV-2 compounds has also been investigated. In a molecular binding study, researchers found that the bioactive compounds of ginger inhibited the binding of the SARS-CoV-2 spike protein to the ACE2 receptor and acted as an inhibitor for the main protease protein (MPro) [62, 63]. Mpro is responsible for processing the poly-proteins pp1a and pp1ab during viral replication [64]. Mpro plays a central role in mediating the replication and transcription of SARS-CoV-2 mRNA. Based on molecular binding modeling, two potential candidates from ginger (zingiberenol and zingiberol) act as Mpro receptor inhibitors against the virus [65]. Also, in a study by Jeena et al. on a ginger essential oil, it was shown that this substance has antioxidant effects and increases blood levels of antioxidant enzymes such as catalase, superoxide dismutase, glutathione, and glutathione reductase [66]. Furthermore, a recent study showed that the consumption of ginger in COVID-19 patients resulted in increased SpO_2 levels and consciousness frequency of patients [67].

4.2.1 Safety of Ginger

According to survey results, 71.8% of the people of India were consuming the kadha (traditional Indian drink containing cinnamon, basil, ginger, black pepper, and raisins) prescribed by the Ministry of Ayush. About 52.4% of them used these compounds once daily, and 24.1% used them twice daily. In addition, 68.8% of people used ginger, cloves, dill, black pepper, and tulsi in their kadha. Most of these people (86.1%) did not report any side effects after consuming kadha, while 13.9%, especially the elderly, experienced side effects such as heartburn, constipation, diarrhea, mouth ulcers, and hypertension. Therefore, according to Ayurveda, consuming these spices in large quantities might have some complications (Table 20.1) [68].

4.3 *Cinnamon (*Cinnamomum cassia*)*

Cinnamomum cassia is an aromatic plant belonging to the Lauraceae family. It has been a popular spice in Chinese, Indian, Iranian, and Greek medicine since ancient times. This plant is extracted from the bark of young branches and used as a daily

Table 20.2 Potential mechanisms of turmeric (curcumin), cinnamon, and ginger against COIVD-19 infection

First author (publication year) Reference No.	Plant parts, extracts, and compounds	Possible mechanisms
Zhang, 2019 [117]	Curcumin	1.Reduction of IL-1β, IL-6, TNF-α, NF-κB activation, 2.Reduction of stressed-induced P2X7R/NLRP3 inflammasome axis activation
Peng, 2021 [118]	Curcumin	1. Regulating Janus kinase/signal transducer and activator of transcription (JAK/STAT) inflammatory signaling way 2. Inhibition of the accumulation of NLRP3 inflammasome, or inhibition the NF-κB pathway
Zhang, 2019 [119]	Curcumin	1.Reduction of NO, IL-1β, IL-6, iNOS levels 2. Increased level of IL-4, IL-10, Arg-1 promoted microglial polarization to the M2 phenotype
Li, 2019 [120]	Curcumin	Reduction in IL-1β, TNF-α, NLRP3, caspase 1
Zhang, 2018 [121]	Curcumin	Reduction of TLR4, IL-1β, TNF-α, VCAM-1, ICAM-1, NF-κB
Atabaki, 2020 [122]	Curcumin	Reduction of CRP, CD4+ and CD8+ T cells, Th17 cells and B cell frequency
Dai, 2018 [123]	Curcumin	Inhibition of virus uptake, proliferation, and particle production
Ahkam, 2020 [62]	Ginger	Inhibition of the spike protein combination to ACE2 receptor or inhibition of main protease
Zhuanga, 2009 [124]	Procyanidins and butanol extract of ginger	Disruption of the clathrin-dependent endocytosis pathway
Jeena, 2013 [66]	Ginger essential oil	1. Increased blood level of antioxidant enzymes including catalase, super oxide dismutase, glutathione, glutathione reductase 2. Increased level of superoxide dismutase, glutathione peroxidase and glutathione-s-transferase in liver
Rabie, 2022 [65]	Ginger compounds (zingiberenol and zingiberol)	Inhibition of main protease activity
Al-Sanea, 2021 [125]	Strawberry and methanolic extract of ginger	Neohesperidin is of particular interest as a potential dual inhibitory compound with its binding potential to human AAK1 protein and SARS-CoV-2 NSP16 protein
Zareie, 2021 [73]	Eugenol Extracted oil of cinnamon	Disturbance of ERK, (p38MAPK) and IKK/ NF-kB signaling pathways
Raina, 2015 [126]	Aqueous extracts and methanolic extracts of cinnamon	Inhibition of NO, PGE2, LTB4, and MMP production

(continued)

Table 20.2 (continued)

First author (publication year) Reference No.	Plant parts, extracts, and compounds	Possible mechanisms
Gunawardena, 2015 [127]	Water extract/ cinnzeylanine	1. Blocking LPS + IFN-γ induced NO, and TNF-α production 2. Strong activity related to inhibition of TNF-α production
Rathi, 2013 [128]	Polyphenol fraction of cinnamon	1.Reduction of Serum TNF-α density 2. Inhibition of cytokine (IL-2, IL-4, and IFN-γ) release 3. Inhibition of prostaglandin
Vetal, 2013 [129]	Type-A procyanidin polyphenols	1. Reduction of serum CRP level 2. Reduction of serum turbidity
Hagenlocher, 2015 [130]	Cinnamaldehyde	1. Inhibition of degranulation and mRNA expression 2. Reduction of mediator release 3. Reduction of cytokine expression 4. Reduction of pro-inflammatory mast cell mediators release and expression
Han, 2017 [131]	Essential oil blends of cinnamon	1. Dramatic impacts on levels of protein biomarkers involved in inflammation, immune modulation, and tissue remodeling 2. Effects on signaling pathways such as mitotic roles of the polo-like kinase canonical pathway

Abbreviations: *ACE2* angiotensin-converting enzyme 2, *ERK* extracellular signal-regulated kinase, *NO* nitric oxide, *PGE2* prostaglandin E2, *LTB4* leukotriene B4, *LPS* lipopolysaccharide, *IFN-γ* interferon γ, *TNF-α* tumor necrosis factor-α, *TGF-β* transforming growth factor-β, *IL* interleukin 4, *CRP* C-reactive protein

seasoning worldwide. The main uses of cinnamon include the treatment of flatulence, diarrhea, toothache, fever, leucorrhoea, and headache [69]. Additionally, reports indicate the effectiveness of regular consumption of cinnamon in preventing throat infections. Previous studies have shown that cinnamon contains 21 bioactive molecules, including two well-known compounds, cinnamaldehyde (60.41%) and eugenol (3.19%), which have antibacterial effects. In addition, antimicrobial, antiviral, antifungal, antioxidant, anti-hypertensive, anti-diabetic, anti-tumor, and immune-modulating effects of cinnamon have been reported in recent studies [70–74]. According to one study, a higher dose of cinnamon (100 mg/kg) strongly enhanced serum phagocytic index, immunoglobulin levels, and antibody titers. A lower dose (10 mg/kg) only improved serum immunoglobulin levels [75]. The higher dose promoted cellular and humoral immunity, while the lower dose only affected humoral immunity [75, 76]. Cinnamon, like other herbs, has shown immunomodulatory, antiseptic, and antiviral properties, which can be a complementary treatment in inhibiting inflammation-related diseases, such as COVID-19 [77]. In addition to cinnamaldehyde and eugenol, other important bioactive substances of cinnamon include trans-cinnamaldehyde, cinnamic acid, p-cymene, and essential oils [78, 79]. The promising activity of eugenol in the treatment of influenza A and Ebola virus, and reports of the antimicrobial, antifungal, and anti-inflammatory properties of this substance are available. Evidence suggests that eugenol inhibits autophagy and replication of influenza A virus by interfering with extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (p38-MAPK), and inhibitor of nuclear factor-κB (IκB) kinase (IKK) signaling pathways [80–82]. It has also been demonstrated that the active substances in cinnamon suppress expression of cyco-oxygenase-2 (COX-2) and the inducible nitric oxide synthase (iNOS) pathways and therefore diminish the production of inflammatory cytokines such as IL6, IL-1β, and TNF-α [83, 84]. These properties explain the anti-inflammatory and analgesic effects of cinnamon in inflammatory illnesses such as rheumatoid arthritis, diabetes, heart disease, cancer, and neurological disorders such as Alzheimer disease [85, 86]. This suggests that cinnamon may be able to suppress inflammation and disrupt COVID-19 disease complications. Cinnamon extract (CE) and cinnamaldehyde are used as anti-allergic agents by reducing the release and expression of specific mediators of mast cells [87]. CE, p-cymene, and cinnamaldehyde have been shown to potentiate mature monocyte-derived dendritic cells (DCs) and, subsequently, allergen-specific immune responses in the co-generation of human DC-T cells in vitro. Furthermore, these treatments were shown to reduce expression of mast cell-specific proteases, total IgE production, and histamine levels. These results could be due to the suppression of the production of nitric oxide (NO), TNF-α, IL-1β, and IL-6, and blocking MAPK and nuclear factor κB (NF-κB) pathways [88, 89]. Another study showed that nine cinnamon phytochemicals likely have suppressive effects against the SARS-CoV-2 MPro enzyme. Using the available strategies, these naturally derived plant compounds may create a potential reliable drug [90].

4.3.1 Safety of Cinnamon

The FDA stated that cinnamon is well tolerated in amounts commonly found in food. Additionally, the cinnamon extract is secure and exempt from toxicity data requirements by the US Environmental Protection Agency (EPA) [91].

4.4 Other Spices

4.4.1 Black Pepper

Black pepper is another spice with several potential health advantages. Previously, ethanol fractions of *Piper nigrum* have been used in mouse models with ovalbumin-induced asthma, in which IL-1β, IL-4, IL-6, IL-17A, and TNF-α were found to be reduced, and IL-10 and INF-γ increased by the extracts [92]. Inflammatory cell infiltration and the state of fibrosis were also decreased. In addition, other studies have indicated that piperine was effective in blocking bacterial sepsis mediated by prevention of pyroptosis through reduced levels of IL-1β and AMP-activated protein kinase (AMPK) [93]. Piperine also attenuated acute pancreatitis by diminishing the levels of IL-1β, IL-6, and TNF-α [94].

4.4.2 Saffron

Previous studies have shown that saffron can have favorable effects against a wide range of human diseases, including metabolic syndrome, diabetes, psychological conditions, cancer, neurological disorders, gastrointestinal disorders, and cardiovascular diseases [95–108]. These effects could be mediated through its actions as an immuno-modulatory, antioxidant, anti-inflammatory, anticonvulsant, anti-mutagenic, antidepressant, anti-carcinogenic, and anti-diabetic agent. As an example, crocin, a major component of saffron, was shown to be effective against bacterial lipopolysaccharide (LPS)-induced sepsis and cardiotoxicity in H9c2 cells. In line with this, the biomarkers TNF-α, prostaglandin E2 (PGE2), IL-1β, and IL-6 were significantly downregulated, and NO, COX-2, and iNOS mRNA expression was significantly reduced by this treatment [109]. Also, the efficacy of saffron, particularly crocin and picrocrocin, against infection by herpes simplex virus 1 (HSV-1) and human immunodeficiency virus 1 (HIV-1) has been documented. Crocin and picrocrocin inhibited virus entry and replication [110, 111]. Moreover, the efficacy of saffron in asthmatic patients has been shown [112].

4.4.3 Capsaicin

Capsaicin is one the most important constituents of capsicum, which is useful against diabetes, asthma, cancer, and other diseases [113]. Inflammatory biomarkers such as IL-6, IL-1β, and TNF-α were found to be reduced in response to capsaicin [114]. In addition, this molecule reduced inflammation of the salivary glands by reducing mRNA and protein expression of TNF-α and IL-6 in the human salivary gland (HSG) cell line [115].

4.4.4 Cumin

Cumin is another common spice widely used in food preparation and which has anti-oxidant and anti-inflammatory properties. Cumin has been applied to treat some diseases such as cancer, diabetes, hyperlipidemia, among others [92]. Cumin contains phenols and flavonoids which give it antibacterial, antifungal, and antiviral properties, which may be useful against COVID-19 disease [92].

5 Conclusion and Future Perspectives

In this study, we reviewed the potential mechanisms of spices, including turmeric (curcumin), ginger, and cinnamon, as well as some other spices, such as black pepper, saffron, capsaicin, and cumin, with emphasis on their bioactive properties against different aspects of the SARS-CoV-2 life cycle. The beneficial effects of curcumin on several biomarkers and clinical symptoms of patients with COVID-19 have been shown in multiple clinical studies. However, these studies have been limited such that a definitive conclusion cannot be reached. Also, clinical trials on the actions of ginger, cinnamon, black pepper, saffron, capsaicin, and cumin are scarce. Considering the results of preclinical studies, it is clear that these spices contain a diverse array of bioactive compounds known to decrease oxidative stress and inflammation, modulate the immune system, and prevent viral, bacterial, and fungal infections in COVID-19 patients. In the future, more clinical studies consisting of biomarker-stratified patients and employing biomarker readouts of therapeutic or toxicity-related responses are urgently needed. This will help us to prepare for the next pandemic, which may be on the horizon sooner than we think.

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