

Food spices as potential therapeutic agents in targeting inflammatory cytokine storm: A review on underlying mechanisms and therapeutic targeting strategies for SARS-CoV2

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Since ancient times, spices such as black pepper, cinnamon, ginger, turmeric, garlic, black cumin, clove, ocimum, saffron, and nutmeg constitute an important part of foods and beverages in India. Besides, adding aroma and flavour to the food, they are also known for multiple medicinal benefits. During the COVID-19 pandemic, an interesting pattern of disease prevalence and severity was observed especially in the countries where spices are consumed regularly. It has attracted researchers worldwide to explore the therapeutic potential of spices in COVID-19 management. Various *in silico* studies have reported good binding affinities of spices and derived components towards structural druggable targets of SARS-CoV2. There are several compelling pieces of evidence for the role of spices in the attenuation of inflammatory cytokine storm which is the crux in the pathogenesis of COVID-19. Therefore, this review is written to provide deep insights into the role of food spices and their underlying mechanism in targeting SARS-CoV2. Based on experimentally verified data from different *in-vitro*, *in-vivo*, *in-silico*, and clinical studies, the information presented will certainly help in the development of promising drug therapeutics or preventive strategies to deal with SARS-CoV2. Further studies geared towards the development of drugs based on spices and derived compounds are suggested.

Keywords: COVID19, Cytokine storm, Natural products, SARS-CoV2, Spices, Structural targets

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Introduction

Coronaviruses are known to humans for a long time. In the last decades, coronaviruses have attracted wide interest with the emergence of SARS-CoV (Severe Acute Respiratory Syndrome) in 2003 and MERS (Middle East Respiratory Syndrome) in 2012¹. On 31 December 2019, the WHO reported the first case of novel SARS-CoV2-caused illness² and declared the outbreak of SARS-CoV-2, a worldwide public health emergency on 30 January 2020³. Later on 11 February 2020, WHO officially named this outbreak as coronavirus disease 2019 abbreviated as COVID-19⁴. COVID-19 imposed a huge burden on socioeconomic and psychological features along with the tremendous rise in morbidity and mortality globally. As the identified SARS CoV2 was novel, the unavailability of specific scientific literature and treatment options was the challenge. A lot of research

was carried out during this period to gain the information on pathogenesis of COVID-19 and possible therapeutic options for treatment.

In the process of understanding disease pathogenesis, past knowledge of human coronaviruses- SARS-CoV and MERS-CoV proved very useful to help hypothesize possible chain of events of SARS-CoV-2 pathobiology⁵ to restrain the outbreak of SARS-CoV2⁶. In a study, upon comparing genome sequences of SARS-CoV2 with SARS-CoV and MERS-CoV, more sequence homology was found between SARS-CoV and SARS-CoV2⁷. The result showed COVID-19 shares about 79% genomic sequence similarity with SARS-CoV and similar receptor binding domain structure along with some amino acid variation at some key residues⁸. Some approved and preclinical anti-SARS drugs were also tested against SARS CoV2 for antiviral activity due to the high genomic similarity between SARS and SARS-CoV2⁹. It was observed that as part of disease pathogenesis, SARS-CoV2 enters the host cell by the

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interaction of its receptor binding domain (RBD domain) of spike protein, which shows a strong affinity for human angiotensin-converting enzyme 2 (ACE2) which is a metallopeptidase and works as functional receptor for SARS-CoV2. RBD domain is critical for the fusion of the SARS-CoV 2 (Wuhan CoV) with the host cell membrane and the S-protein-ACE2 binding pathway represents a risk factor for human transmission of SARS-CoV2⁷. After binding, the spike protein undergoes conformational changes and mediates membrane fusion after proteolytic activation¹⁰. A study was also carried out to find out the possible route of infection. For this, the localization of ACE2 protein in different human organs was investigated as ACE2 also represents the receptor of SARS-CoV. The findings showed an abundant presence of ACE2 proteins in lung alveolar epithelial cells and enterocytes of the small intestine along with oral and nasal mucosa, nasopharynx, skin, lymph nodes, thymus, bone marrow, liver, kidney, brain¹¹, pancreas¹², cardiovascular system³ and may represent the potential site of damage. Cloning and expression of SARS-CoV-2 proteins were also done to identify those proteins that interact with human proteins. A total of 332 high-confidence SARS-CoV-2 protein-human protein interactions were reported. The proteins involved represent components of epigenetic and gene expression regulators, signalling, vesicle trafficking, ubiquitin ligases etc¹³. The knowledge of damages caused at different levels and mechanisms involved in pathogenesis helped the identification of potent therapeutic targets and further insight into the construction of new efficient therapeutic strategies.

A wide variety of therapeutic approaches were proposed for the management of COVID-19 like hydroxychloroquine therapy, anticoagulant therapy, antiviral therapy, convalescent plasma¹⁴, anti-TNF (tumour necrosis factor) therapy¹⁵, nucleotide analogs, protease inhibitors etc. that have shown varying levels of success¹⁶. Many vaccine candidates were also developed, but still several questions open about the long-term effectiveness and efficacy of these vaccines. On the other side, the use of herbal medicine and dietary therapy gained interest as well during this pandemic and contributed significantly to contract the disease threat. Even during the period of SARS, herbal remedies were used as adjuvant to standard treatment. In a clinical trial in China, the use of herbal remedies showed prevention from

contraction of influenza-like symptoms in at-risk hospital workers¹⁷. Chinese herbs along with Western medicines were found to improve the symptoms of SARS in terms of absorption of pulmonary infiltration, and it also lowered the dose of corticosteroid¹⁸. In this direction, anecdotal data also supports the therapeutic potential of ayurvedic and homeopathic systems in the management of COVID-19¹⁹. Medicines based on natural products and their derivatives useful to fight COVID-19 are classified into antivirals like ribavirin, lopinavir, arbidol, anti-malarial drugs like chloroquine and hydroxychloroquine, anti-protozoal drugs like emetine, antibiotics like azithromycin, anti-cancer drugs like homoharringtonine etc²⁰. Bioactive components present in some foods and herbs due to their antioxidant, immunomodulatory and antimicrobial activities are able to pre-and post-exposure prophylaxis by raising both the activity and number of natural killer cells, lymphocytes, cytokine suppressors and macrophages²¹. Therefore, herbal medicines may prove a potential approach to managing the challenges concomitant with COVID-19. In this review article, we aimed to provide deeper insights into the potential of natural products and herbal medicines with special emphasis on spices as therapeutics in human coronavirus infectious disease which can further show direction to deal with SARS CoV2. This review article also discusses several available therapeutic strategies for existing inflammation-based clinical symptoms that may find potential implications in COVID-19 therapeutics.

“Inflammatory cytokine storm” factor in COVID-19

Dysregulation of the immune system was found to play a crucial role in the development of severe COVID19²². Changes in both innate and adaptive immune responses were observed in COVID-19 patients²³. Over-activation of the immune system leads to an outburst of inflammatory cytokines giving rise to a condition called “inflammatory cytokine storm”, which is an important factor for the progression of COVID-19 pathogenesis and may lead to the generation of a devastating condition called acute respiratory distress syndrome (ARDS) or extrapulmonary multiple organ failure and may even cause death^{24,25}. The pattern was similar to other pathogenic human coronaviruses like SARS-CoV and MERS-CoV known to cause severe pneumonia causing acute lung injury (ALI) and ARDS due to

speedy virus replication, increase of both inflammatory cell infiltration and pro-inflammatory cytokine responses. This boost in cytokine and chemokine responses and excess viral load during early and late stages of infection majorly contributes to high morbidity and mortality rate during pathogenic HCoV infections²⁶.

In a study, 41 confirmed COVID-19 patients were studied. All 41 were pneumonic along with common symptoms such as fever, cough, and fatigue. They noted patients infected with the 2019-nCoV had more plasma concentrations of IL-1B, IFN γ , IP10, and monocyte chemoattractant protein-1(MCP1) which probably act as an activator for T-helper-1 (Th1) cell responses whereas patients under ICU had more concentrations of GCSF, IP10, MCP1, macrophage inflammatory protein 1-alpha (MIP1A), and TNF α . Cytokine storm was found as a factor related to COVID-19 disease severity²⁷. Further, critically ill adult patients with SARS-CoV-2 pneumonia and older patients (>65 years) with ARDS and comorbidities were found more prone to death²⁸. Henceforth, it was concluded that the resolution of cytokine storms at an early stage could halt the progression and severity of the disease. In a study to measure the correlation between inflammation-related cytokines in COVID-19 patients and disease severity, levels of IL-2R and IL-6 were found positively correlated with the severity of the disease. The more the disease severity, the higher the expression level of these cytokines. The authors noted the involvement of IL-2R and IL-6 in the occurrence and development of COVID-19 pneumonia and suggested the use of these as reference indicators for disease diagnosis and as therapeutic targets²⁹. Thus, the development of therapeutic strategies targeting cytokine storm for the amelioration of exacerbated inflammatory response shows significance in human CoV-caused infections²⁵ including COVID-19³⁰.

Therapeutic strategies to counter “Inflammatory cytokine storm”

Based on the literature, early check upon cytokine storm by administration of immunomodulators and cytokine antagonists and lowering of lung inflammatory cell infiltration may enhance the treatment and decline the mortality rate of patients with COVID-19²⁵. Initial results of immunomodulatory therapy were found promising and therefore show potential avenues of research for COVID-19 treatment^{31,32}. Moreover, therapy

involving suppression of cytokines has been used in other disease treatments too like rheumatoid arthritis, and juvenile idiopathic arthritis³³. Such available conceptual knowledge should be extended further to target cytokine storms in COVID-19. This review has highlighted a few immunomodulatory approaches to counterbalance the exaggerated immune response-cytokine storm which may give future indications for clinical diagnosis and management of COVID-19. Fig. 1 represents different therapeutic strategies for COVID-19 treatment. Some of them are mentioned below.

Inhibition of IL-6

IL-6 plays a significant role in driving cytokine storm³⁴. Since the overproduction of IL-6 in covid19 patients is associated with the inflammatory storm, the suppression strategy of IL-6 pathways may ameliorate the inflammatory storm. Blocking IL-6 receptors with tocilizumab (TCZ) showed promising clinical results with the betterment of respiratory function³⁵. Reduced mortality in patients administered with anti-IL-6 agents and standard of care (SOC) compared to SOC alone. It has also been found to prevent the increase of secondary infections³⁴. TCZ is the first humanized anti-IL-6 receptor (anti-IL-6R) monoclonal antibody approved for rheumatoid arthritis. By inhibiting the cis- and trans-signaling cascades including the Janus kinase-signaling pathway along with the activator of the transcription pathway, TCZ efficiently modulates inflammation³⁶. In this line, the use of IL-6 inhibitors may also find potential application in the treatment of COVID-19. Therefore, TCZ is suggested as a promising drug to manage inflammatory/cytokine storm associated with COVID-19 and subsequent mortality³⁵. Phase III clinical trial to evaluate the safety and efficacy of TCZ in COVID-19 patients along with SOC is

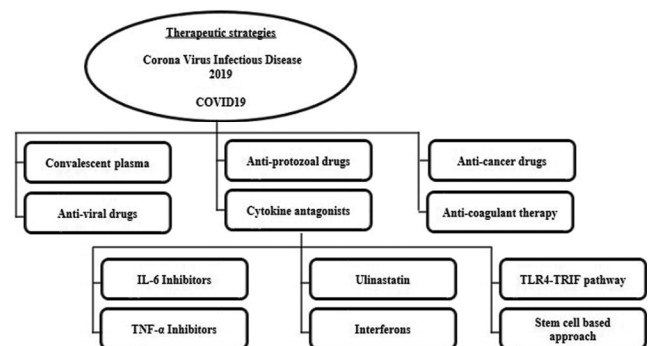


Fig. 1 — Different therapeutic strategies for COVID-19 treatment.

underway³⁷. Similarly, a clinical phase 2/3 trial of one more IL-6 inhibitor Sarilumab (Kevzara) was initiated by Sanofi and Regeneron pharmaceutical companies³⁸. In line with the evidence, IL-6 inhibition was found promising in the management of cytokine storm and needs further attempts to explore as Covid19 therapeutics.

TNF- α inhibitors

Tumor Necrosis Factor (TNF) being a product of inflammation is a valid therapeutic target in many inflammatory and autoimmune diseases^{15,33}. TNF inhibitors may lower the severity of COVID-19³⁹. In a large comparative cohort study, COVID-19 patients with recent TNF inhibitor exposure for other disease conditions showed a lowered rate of hospitalization and mortality compared to COVID-19 patients who were not exposed⁴⁰. Similar results were found in another study where COVID-19 patients with prior anti-TNF exposure for pre-existing conditions required no ventilator support or ICU and none of them died⁴¹. Likewise, a COVID-19 patient with spondyloarthritis was reported to get recovered after treatment with etanercept, a TNF- α inhibitor and methotrexate⁴². At present, TNF- α inhibitor is not much explored for targeting human coronaviruses induced pathogenesis. Both biological plausibility and observational clinical data support exploring anti-TNF therapy in COVID-19 treatment³³. Earlier, TNF- α inhibitors were also suggested as potential therapeutics for ameliorating SARS CoV infection⁴³. TNF α - receptors aggravates SARS CoV pathogenesis through inflammatory activity. In a knock-out mouse strain, the removal of TNF α R lowered tissue damage by interfering with components of inflammatory response. Based on the evidence, blockade of TNF- α signaling may show promising future strategies in the development of human coronavirus therapeutics⁴⁴. A clinical trial of TNF- α inhibitor, adalimumab registered by China is also undergoing evaluation⁴². Besides the multiple benefits, TNF- α inhibitors are associated with many adverse effects recognized by different clinical trials involving infections, neutropenia, injection site reactions etc. In people with weak immune systems, they can also cause viral, bacterial, and fungal infections and may develop diseases like hepatitis B, histoplasmosis, candidiasis etc⁴⁵. In view of the huge therapeutic potential of TNF- α inhibitors in COVID-19 treatment, more clinical trials and strategies are needed to evaluate the safety of usage and to lower the risk of associated adverse effects, respectively.

Ulinastatin

Ulinastatin is a glycoprotein molecule naturally present in the human body known to have anti-inflammatory activities. It interferes with the cytokine storm initiated by inflammation by maintaining the balance between proinflammatory and anti-inflammatory responses²⁵. Ulinastatin has shown ameliorative effects on ARDS patients by lowering mortality and reducing the length of mechanical ventilation and ICU stay. Additionally, it has improved the oxygenation index and lowered respiratory rate and levels of serum inflammatory markers like TNF- α , IL-6, IL-8 etc⁴⁶. In fact, the Shanghai COVID-19 expert group also mentioned the use of a high dose of ulinastatin to improve the oxygenation index. It also improved the pulmonary interstitial lesions and subsequent lung functioning⁴⁷. Further, the anti-inflammatory potential of ulinastatin has been also explored in the treatment of other inflammatory diseases like acute pancreatitis⁴⁸ and severe decompression sickness⁴⁹. In the severe acute pancreatitis (SAP) rat model, ulinastatin alleviates inflammation by increasing the expression of IL-10 and promoting the fraction of Tregs in the population of CD4+ T cells whereas suppresses the production of TNF- α and IL-1 β leading to the amelioration of acute inflammatory response and subsequently lowering the mortality rate of SAP rats⁵⁰. Recently, a phase III clinical trial of ulinastatin was approved for COVID-19 patients with mild to moderate ARDS⁵¹. Evidence strongly suggests the use of ulinastatin as a promising anti-inflammatory agent. Targeting of cytokine storm by ulinastatin thus represents a significant approach for the management of COVID-19.

Interferons

Interferons are demonstrated as a significant and potential candidate in COVID-19 treatment⁵². IFN- λ by inhibiting neutrophil infiltration and IL-1 β production ameliorates inflammation⁵³. Type 1 INF's possess antiviral, immunomodulatory and anti-inflammatory activities. They intervene inhibition of proinflammatory gene products by stimulating immunosuppressive cytokine interleukin-10 (IL-10). They are also able to restore immune homeostasis by stimulating an array of immunosuppressive mediators like suppressors of cytokine signaling-1 (SOCS-1) and tristetrapolin (TTP) etc. They have shown significant anti-inflammatory and protective effects in several autoimmune diseases⁵⁴. IFN- α 2b administration during the early stages of COVID-19

was associated with lowered rate of in-hospital mortality and improved clinical outcomes whereas delayed administration increased mortality⁵⁵. Phase II double-blind placebo-controlled trial of IFN- β reported positive outcomes in hospitalized COVID-19 patients⁵⁶. A combination involving IFN- γ and a type I IFN might work synergistically to improve the clinical conditions⁵².

IFN- $\alpha\beta$ and IFN- λ also show antiviral activity along with immunomodulatory potential. IFN therapy has been also used for the treatment of other human coronavirus infections, which may form the rationale to explore it for COVID-19 treatment as well due to the high genomic similarity between these strains. In a study, SARS-CoV infected mice showed improvement in lung immunopathological conditions upon early administration of IFN-I whereas delayed IFN-I signaling showed increased aggregation of inflammatory monocyte-macrophages (IMMs), production of cytokines/chemokines and dysregulated virus-induced T-cell reactions. Removal of the IFN- $\alpha\beta$ receptor or lowering of IMM showed protection against lethal infection. The study revealed the role of IFN-I and IMM in progressing lethal SARS-CoV infection and suggested their targeting as a therapeutic strategy for the control of coronaviruses and also other respiratory viruses⁵⁷. Thus, IFN therapy represents a potential therapeutic option for the management of COVID-19⁵⁸. However, further studies are needed to clarify the standard timing and appropriate dosage to circumvent the unintended results⁵².

TLR4-TRIF pathway and inhibition of oxidized phospholipids

TLR's are pattern recognition receptors (PRRs) that are significant components constituting the first line of the host defense system. Oxidized phospholipids (OxPL) are endogenous danger-associated molecular patterns (DAMPs) that recognize PRRs⁵⁹ and are produced after damage and inflammation⁶⁰. Since inflammation is associated with COVID-19, oxidized phospholipids are also present in the lungs of COVID-19 patients. Further, inflammation also aggravates oxidative stress and generates more oxidized phospholipids⁶¹. Accelerated generation of OxPL is associated with the pathogenesis of ALI and inflammation⁶². OxPL was found to mediate the TLR4-TRIF pathway causing the release of cytokine by activation of lung macrophages and also initiating lung injury. TLR4-TRIF-TRAF6 signaling is highlighted as an important factor for the regulation of the severity of ALI which is evidenced

by the development of H5N1-induced ALI resistance in TLR4 mutant mice. Even in the case of SARS-CoV, oxidized phospholipids were found in the lungs of patients⁶³ and OxPL-induced ALI might be the major reason behind the death of SARS-CoV patients⁶⁴. Therefore, blocking TLR signaling or inhibition of oxidized phospholipids may show a significant therapeutic strategy to alleviate inflammation and damage linked with COVID-19 and SARS-CoV pathogenesis. Furthermore, the administration of TLR4 antagonist, eritoran obstructed the production of cytokine and oxidized phospholipids along with lowering influenza-induced mortality in mice and reduced viral load. Eritoran-based blockage of TLR signaling was reported as a significant strategy to target inflammation that occurred in influenza, and possibly other infections⁶⁵. Therapy based on TLR4 antagonists and oxidized phospholipids represents a potential realm for the development of COVID-19 therapeutics as they may serve as an effective tool to obstruct the cascade triggered by TLR4 binding³⁰. Still, there is a scarcity of research and needs more attention as the development of TLR4 antagonists may find potential applications in the management of human coronaviruses-induced symptoms and can also lower the chances of death associated with ALI.

Stem cell-based approach

Mesenchymal stem cell (MSC's) based treatment has proven its potential in the treatment of inflammatory diseases and can also be explored for the management of cytokine storm associated with COVID-19⁶⁶. MSC's are capable of managing ARDS by regenerating lung tissues and also repairing them by secreting paracrine soluble factors⁶⁷. Management of ARDS by MSCs strengthens their candidature as therapeutics in Covid-19 treatment. Interestingly, MSC upon administration in positive COVID-19 patients showed improvement in pulmonary function and disease symptoms. Inflammation was also lowered as marked by a reduction in the concentration of C-reactive protein and serum TNF- α whereas accelerated the serum anti-inflammatory interleukin-10 levels. The recovery seen in critically ill COVID-19 patients occurred probably due to improvement of inflammatory response and stimulating tissue repair and regeneration⁶⁸. Additionally, the human umbilical cord mesenchymal stem cells (hUCMSCs) upon transplanting into critically ill COVID-19 patients, showed significant immunomodulatory activities and

also repair the injured tissues. It also improved clinical parameters and CT images and reduced inflammatory symptoms⁶⁹. In fact, results of a clinical trial of MSC reported that COVID-19 do not infect therapeutic MSC observed by their undifferentiated state and absence of ACE receptor during follow-up. Evenmore, recovered MSC showed long-term and actively maintained immunomodulatory activities due to continuous and increased production of high levels of anti-inflammatory and trophic factors⁷⁰. A number of clinical trials of MSCs have been registered for the treatment of COVID-19 highlighting its effectiveness⁶⁶. MSC-based therapy may prove a major breakthrough in COVID-19 therapeutics which is highly potent, safe and able to treat severe critical disease^{68,70}.

Significance of natural products and herbal medicine-Alternative strategy for Covid-19 treatment

The role of natural products and herbal medicines as a significant reservoir for drug discovery is undebatable. Since historical times, they served as a source of new molecular entities (NMEs). Natural products and their derivatives constitute over one-third of all FDA-approved NMEs⁷¹. Natural products and herbal medicines are used to treat acute respiratory infections in the past time. Due to their promising antiviral activities against human coronaviruses, they have become potential candidates for novel antiviral prophylactics too⁹. A lot of clinical trials have also been registered to analyze the effectiveness of natural products against SARS CoV2^{9,72}. Compared to other prophylactics and antibodies, the bioavailability of natural products is less affected by low gastric pH, gut microbiota and different digestive enzymes making natural products more stable drug candidates in both the human gastrointestinal tract and for oral consumption. Thus, factors like tolerable toxicity, increased stability for oral formulation and simple scale processing of herbal components make it an aspiring drug candidate for COVID-19 prophylactic⁹. Of interest is that, polar compounds like silvestrol, myricetin, caffeic acid, and quercetin have shown good inhibitory effects on human coronavirus. Polyphenolic compounds found as most potent coronavirus inhibitors⁷³.

In an integrated network analysis of 9 herbal medicines for the treatment of COVID-19, eighteen lead compounds with the highest drug-like potential were identified. Out of 18, ten compounds were found as flavonoid derivatives with either flavones or flavanone core. They further found COX-2 and

MAPK-mediated inflammatory pathways as drug targets of these 18 herb-derived compounds⁷⁴. Even, most of the herbal medicine-based treatments of coronavirus including SARS and MERS focused on the use of polar compounds⁷³. COVID-19 treatment by traditional Chinese medicines is based on the use of natural molecules like quercetin, luteolin, naringenin, kaempferol, etc. which are found as their components and likely use different potential therapeutic targets like ACE2 and 3CL protein, COX-2, MAPK1, IL-6, MAPK14, MAPK8, NF-kB, Ras, TNF, suppresses inflammatory mediators and controls immunity to inhibit COVID-19⁷⁴. Some flavonoids like EGCG, quercetin, and luteolin may target TBK1 kinase to further control TRIF-dependent TLR pathways⁵⁹ which is a crucial therapeutic target for COVID-19.

Furthermore, some natural products found to obstruct the membrane receptors of the human coronavirus along with obstruction of enzyme function too⁹. In an *in silico* study, compounds from rhizome *Alpinia officinarum* were docked into the solvent-accessible S3-S4 pocket of SARS-CoV-2 papain-like protease (PLpro). Due to the presence of the protease domain, it is considered a potential druggable target as it is involved in the cleavage of viral polyproteins required for the survival and replication of SARS-CoV2. Compounds from *Alpinia officinarum* showed high *in silico* binding affinity to closed PLpro conformer and were found as potential SARS-CoV-2 PLpro inhibitors⁷⁵. Fig. 2 represents different therapeutic targets used by natural products and herbal medicines efficient in COVID-19 management.

A systematic review was conducted to evaluate the influence of herbal intervention on COVID-19 patients. The study included 3177 COVID-19 patients' data from 32 randomized controlled studies. They observed

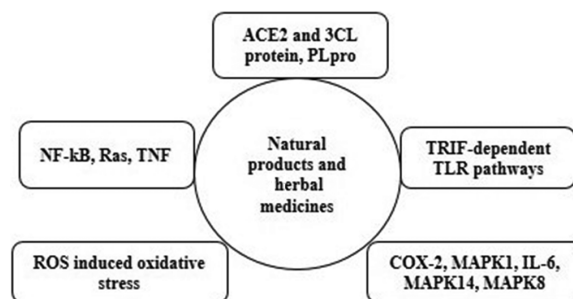


Fig. 2 — Therapeutic targets used by natural products and herbal medicines efficient in COVID-19 management. Where ACE2: angiotensin-converting enzyme 2, 3CL protein: 3C-like protease, PLpro: SARS-CoV-2 papain-like protease, TRIF dependent TLR pathways: TIR-domain containing adaptor protein inducing interferon- β dependent Toll-like receptor pathway.

significant improvement in basic disease symptoms like fever, cough, chest CT and parameters like WBC, lymphocyte percentage, and C-reactive protein level in patients with the herbal intervention group in comparison to patients with Western medicine alone⁷⁶. Based on the reported evidence, natural products and herbal medicines offers an unignorable source of drug leads with a strong potential to manage COVID-19. Therefore, worldwide awareness is required for exploring natural products and herbal medicines as promising prophylactics against COVID-19. As the discovery and development of any new drug candidate may take years and seem unempirical, exploring already existing drugs represent a practical and promising approach to managing COVID-19. With known safety data and standardized processing operations, repurposing herbal drugs as prophylactics could accelerate treatment options for COVID-19⁹.

Potential of spices as COVID-19 therapeutic candidate

Since ancient times, spices are in use as flavouring agents in the kitchen. Besides, the aroma and flavour produced by spices, they are also known for various health benefits and being part of a dietary component can be considered safe for consumption as a drug as well. The medicinal benefits of spices were also

observed during COVID-19 due to a huge disparity seen in the mortality rates of different countries with different dietary habits⁷⁷. The countries with low mortality rates were found to consume spices and fermented vegetables. Basically, these food items are agonist of the antioxidant transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) whereas spices are transient receptor potential ankyrin 1 and vanillin 1 (TRPA1/V1) agonists and seems to work in a synergistic manner. Spices desensitize TRP channels (transient receptor potential channels) and lower the disease severity and act together with exogenous antioxidants to stimulate the Nrf2 pathway which further potentiates the action period of spices. Thus, higher consumption of spices and fermented vegetables could lower the severity and mortality of COVID-19⁷⁸. Moreover, the consumption of spices prevents the generation of oxidized phospholipids due to their antioxidant activity. This decrease in OxPL may subsequently avoid activation of TLR4 pathway-induced cytokine release and lung injury⁶³. As the inflammatory cytokine storm is an important factor for the progression of COVID-19 pathogenesis, so consumption of spices with anti-inflammatory activity will be of significant value to prevent and control COVID-19. Fig. 3 represents some spices and their pharmacological activities significant in the

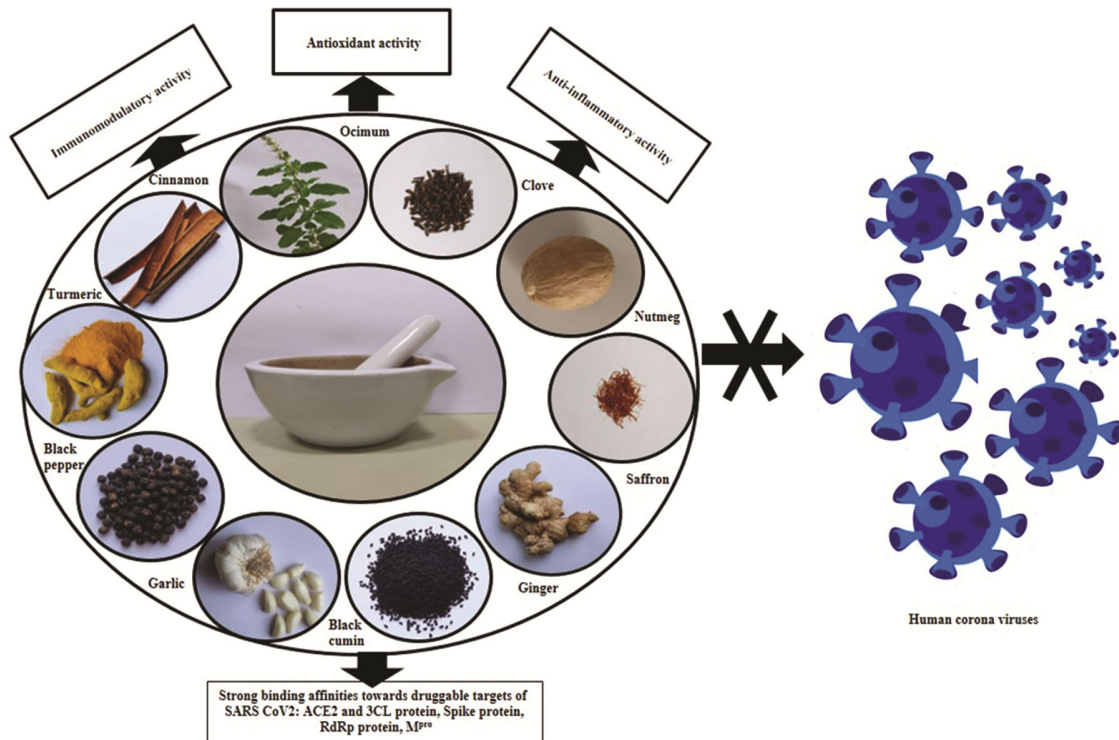


Fig. 3 — Representation of spices and their pharmacological activities significant in therapeutic targeting of SARS-CoV2 in the management of COVID-19.

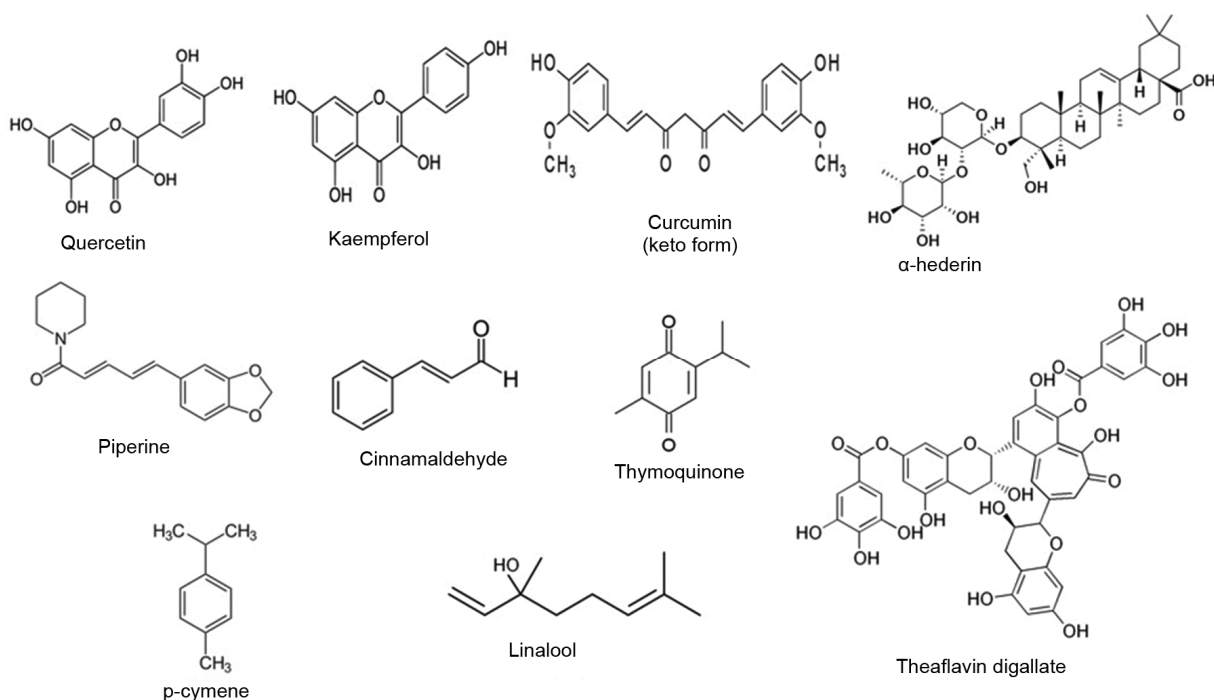


Fig. 4 — Skeletal formula of some natural product molecules with significant potential as COVID-19 therapeutics.

therapeutic targeting of SARS-CoV2 in the management of COVID-19. Hence, this review article has suggested many of the kitchen spices used as food ingredients and also potent for the management of COVID-19 pathogenesis. Fig. 4 shows the skeletal formula of some natural product molecules with significant potential as COVID-19 therapeutics.

Black Pepper

Black pepper (*Piper nigrum*; Family: Piperaceae) has been explored for many pharmacological activities such as antioxidant, antimicrobial, anti-inflammatory etc. The major component found in black pepper is the alkaloid piperine⁷⁹. As per a docking study, piperine showed good binding affinity towards the RNA-dependent RNA-polymerase (RdRp) protein of SARS-CoV2, resulting in direct inhibition of replication of SARS-CoV2. On the basis of the docking energy score, it was found as a novel inhibitor of SARS-CoV2⁸⁰. It was also found to suppress ATP-induced pyroptosis of macrophages by inhibition of AMPK signaling. Serum levels of IL-1 β were also found diminished suggesting anti-inflammatory activity of piperine⁸¹. Interestingly, based on many animal studies, black pepper and piperine both were found safe as food additive⁸². In a rat model of radiation-induced acute lung damage, administration of piperine significantly ameliorated the lung-damaging effects produced by γ -rays. It

efficiently suppresses the serum inflammatory cytokine levels such as TNF- α , IL-1 β and IL-6⁸³. In a study to evaluate the immunopharmacological activity of piperine, human peripheral blood mononuclear cells (PBMCs) exposed to piperine showed significant immunomodulatory activity for immune system suppression. On observing the RT-PCR profile, piperine effectively inhibited expression of IL-2 and IFN- γ mRNA expression from stimulated PBMCs⁸⁴.

Immunosuppression as part of immunomodulation is very critical as overstimulation of the immune system or immune functioning even after the complete resolution of infection may result in host damage⁸⁵. Piperine being able to suppress the immune system is found a potent immunomodulator. Besides, the direct antioxidant activity of piperine against a wide range of free radicals makes it useful for targeting oxidative stress⁸⁶ also associated with COVID-19. Although black pepper is not been much explored for the management of cytokine storm/ARDS, due to its strong anti-inflammatory and antioxidant action, it shows strong potential as therapeutic for human coronavirus infection. As therapeutic strategies for hCoV infections involve suppression of inflammatory responses²⁶, black pepper may serve as a significant candidate for improving inflammation during COVID-19 and intervening replication of SARS-CoV2.

Cinnamon

Cinnamon (*Cinnamomum Sp.*; Family: Lauraceae) mainly contains cinnamaldehyde, cinnamate and cinnamic acid. It is known for an array of diverse pharmacological activities like antioxidant, anti-inflammatory, anticancer, antimicrobial, antidiabetic etc⁸⁷. Tenufolin and Pavetannin C1 compounds present in cinnamon were found as potential inhibitors of COVID-19 in an *in silico* study. These compounds showed good binding affinities for the main protease and spike protein of COVID-19 which is an essential part of COVID-19 propagation⁸⁸. Further, cinnamaldehyde and linalool inhibit endotoxin-induced expression of TNF- α , IFN- γ , IL-1 β , IL-18, TLR4, NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) etc. They also suppress the NF- κ B signaling and caspase-1 activity. They are suggested for prophylactic use, especially in inflammatory conditions driven by the over-activation of TLR4 signaling pathway⁸⁹.

Cinnamon is known for its strong anti-inflammatory effects. Trans-cinnamaldehyde and p-cymene were identified as the active components present in cinnamon extract adding up to its anti-inflammatory property. Cinnamon extract, trans-cinnamaldehyde and p-cymene influence early TLR2 and TLR4 pro-inflammatory pathways by interfering with pathways like NF- κ B/AP-1 signaling⁹⁰. In fact, cinnamon showed significant therapeutic potential in various respiratory virus-infected diseases including SARS⁹¹ and influenza A/PR-8 virus⁹². Basically, it interferes with clathrin-dependent endocytosis in order to inhibit SARS CoV⁹¹. Likewise, it intervenes with the protein synthesis, inhibiting *in vitro* influenza A/PR-8 virus growth while reducing the viral yield and mortality rate in infected mice model⁹².

Furthermore, cinnamon possesses strong immunomodulatory properties. It upregulates the production of immunoregulatory cytokines such as IL-10 and TGF- β whereas downregulates secretion of pro-inflammatory cytokines such as IFN- γ , TNF- α , IL-6, IL-1 β etc by stimulating regulatory DCs (rDCs). The reason for the anti-inflammatory activity of cinnamon lies in balancing the levels of proinflammatory and immunoregulatory cytokines, upregulating levels of IL-10, and suppressing the maturation of antigen-presenting cells⁹³. Several pieces of evidence support the strong therapeutic potential of cinnamon in inflammation-induced symptoms. Despite, its strong potential it is less explored as a drug candidate in human coronavirus

therapeutics including COVID-19. Thus, in view of the intrinsic activities of cinnamon, comprehensive preclinical and clinical studies are needed for its further development as a drug.

Ginger

Ginger (*Zingiber officinale*; Family Zingiberaceae) is known for the control of chronic inflammatory diseases. A clinical study to measure alleged anti-inflammatory activity, it showed a noteworthy decrease in levels of inflammatory biomarkers such as IL-6, CRP and TNF- α ⁹⁴. It is also potent in targeting ARDS. Ginger supplementation remarkably reduces serum levels of IL-1, IL-6, TNF- α and leukotriene B-4 and enhances oxygenation and static compliance in ARDS patients. The result obtained bolster ginger supplementation is useful for gas exchange and it could also lower the period of stay in the intensive care unit and mechanical ventilation⁹⁵. 6-Shogaol and 10-gingerol present in ginger is a potent antioxidant and anti-inflammatory compounds due to the presence of α,β -unsaturated ketone moiety and length of the carbon chain, respectively⁹⁶.

In structure-based molecular docking experimentation, compounds present in ginger were docked into S3-S4 pocket of PLpro of SARS-CoV-2 which is one of the drug targets of SARS-CoV-2. The results revealed high *in silico* binding affinity between closed PLpro confirmation and studied compound and suggested ginger for potent SARS-CoV-2 PLpro inhibitory activity. The potential compounds are generally present in abundant amounts in the rhizomes of ginger. Thus, exploration of various structure-based modifications or formulations of ginger in the treatment of SARS-CoV-2 infections is also suggested⁷⁵. Furthermore, in another docking screening study, 169 compounds were screened against two drug antiviral target ACE2 receptor and viral main protease of SARS-CoV-2. Interestingly, theaflavin 3,3'-digallate, a component found in ginger showed significant binding affinities for both targets. Being a phenolic compound, anti-SARS-CoV2 activity of this compound is also found associated with its antioxidant property. The result supported the anti-SARS-CoV-2 activity of the studied ginger compound⁹⁷. Apart from this, gingerol also showed strong inhibition towards RdRp protein of SARS-CoV2 reflecting direct blocking of viral replication⁹⁸. In line with the reviewed data, ginger shows strong therapeutic potential against inflammation-based symptoms including COVID-19. The anti-

inflammatory activity and active components present in the ginger with strong binding affinity for druggable targets of SARS CoV2 indeed open promising therapeutic targets for SARS CoV2.

Turmeric

Turmeric (*Curcuma longa* L.; Family: *Zingiberaceae*) is generally found in South and Southeast tropical Asia. The rhizome part of this plant is consumed as a dietary spice. Curcumin is the most active component present in turmeric⁹⁹. Curcumin is known for its various pharmacological actions. Curcumin and demethoxycurcumin showed specific interaction for the RdRp protein of SARS-CoV2. The minimum binding energy between these two molecules and the target protein indicates significant binding affinity and suggests the molecules as a potential inhibitor of SARS-CoV2 replication⁸⁰. Moreover, the anti-inflammatory property of curcumin has been explored in the management of different chronic inflammation-induced diseases such as obesity, diabetes, dementia etc¹⁰⁰. Curcumin blocks the release of proinflammatory cytokines like IL-6, IL-1 and TNF- α ¹⁰¹, balances the levels of pro- and anti-inflammatory factors, progresses the cell death pathway of polymorphonuclear cells and diminishes ROS activity that subsequently improves the survival rates in animal models of lethal pneumonia¹⁰². The pathways responsible for the anti-inflammatory action of curcumin involve NF-kB, TLR-4 signaling pathway and PPAR- γ pathway¹⁰⁰. In a study, the prophylactic potential of curcumin was observed as curcumin composite blocked the attachment of respiratory syncytial virus (RSV), which is known to infect the lower respiratory tract of infants¹⁰³. However, the limitation of curcumin lies in its slow bioavailability in the human body but intravenous administration of curcumin may reach the therapeutic requirement of curcumin levels in the blood¹⁰¹. Besides, in order to improve its bioavailability, curcumin has been delivered by different drug delivery systems as well¹⁰⁰. In this line, curcumin nanomicelle supplementation also confirmed the anti-inflammation and antioxidant activities of curcumin probably due to improvement in levels of malondialdehyde, C-reactive protein, TNF- α , and total antioxidant capacity¹⁰⁴. Different clinical trials have been conducted and supported ameliorating effects of curcumin in inflammation-related diseases¹⁰⁰.

Curcumin specifically offers a significant advantage in the disease conditions where cytokine storm is associated with mortality¹⁰¹. Altogether,

curcumin possesses strong anti-inflammatory, antioxidant, and antiviral activity, shows low toxicity and could be explored for the management of various inflammation-associated diseases including viral pneumonia and ARDS/ALI associated with coronavirus pathogenesis¹⁰². The data reviewed suggested the strong therapeutic potential of curcumin for COVID-19. Despite the limitations associated with the use of curcumin, different drug delivery techniques may be employed to resolve the issue.

Garlic

Garlic (*Allium sativum*; Family: Liliaceae) is known for potential antibiotic activity covering a wide spectrum of bacteria and viruses. The immunomodulatory properties of this spice are largely due to the presence of organosulphur and flavonoid compounds. Reactive sulfur species allicin represents a significant inhibitor of SARS-CoV-2 main protease (Mpro). By dual S-thioallylation of Cys-145 and Cys-85/ Cys-156 residues of SARSCoV-2Mpro, allicin blocks replication of SARS-CoV2¹⁰⁵. Garlic also showed an inhibitory effect on the influenza bronchitis virus which is also a coronavirus and model for other coronaviruses like SARS and MERS¹⁰⁶. Different studies support the antiviral activity of garlic against a wide range of pathogenic viruses. The organosulphur compounds of garlic target viruses at different levels including viral entry into the host, suppressing enzyme activities like viral RNA polymerase and reverse transcriptase, and modulation of gene expression and signaling pathways¹⁰⁷. Garlic compounds lower the expression of proinflammatory cytokines and also improve immunological abnormalities. They also lower the secretion of adipose tissue-derived hormone leptin which stimulates the release of proinflammatory cytokines¹⁰⁸.

In an *in silico* study, inhibitory activities of 17 organosulfur compounds from garlic essential oil towards ACE2 and main protease protein PDB6LU7 of SARS-CoV-2 were measured using molecular docking experiments. The compounds which constitute about 99.4% of garlic essential oil interacted strongly with both proteins. Allyl disulfide and allyl trisulfide which constitute 51.3% of oil showed the strongest anticorona virus activity. Results reported synergistic action of these 17 compounds inhibits ACE2 and PDB6LU7 proteins. Thus, garlic blocks the invasion of coronavirus into the human body and shows preventive ability towards COVID-

19¹⁰⁹. Thus, garlic can be used prophylactically in order to control virus-caused diseases¹⁰⁷. Garlic and derivatives should be regularly consumed as an adjuvant to the main therapeutic which may lower side effects and toxicity by lowering the used dose²¹.

Black Cumin

Black cumin (*Nigella sativa*; Family: Ranunculaceae) possesses many pharmacological activities like anti-inflammatory, immunomodulatory, antioxidant, bronchodilator, antimicrobial etc. The components present are nigellidine, thymoquinone, thymohydroquinone, nigellimine, dithymoquinone¹¹⁰, α -hederin, Stigmasterol glucoside etc and is known as prophetic medicine that has been used in a different system of medicine such as Ayurveda and Siddha, Unani and Tibb¹¹¹. In addition to this, the anti-inflammatory and immunomodulatory properties of *N. sativa* also nominate this spice as a potential therapeutic candidate against COVID-19 as dysregulation of cytokine response and ARDS is a significant factor in influencing severity and mortality during COVID-19¹¹². A review strategy was also proposed to target SARS CoV2 using a combination of Zn salt supplement and *N.sativa*. The bioactive components were supposed to work as ionophores which could lead Zn²⁺ to enter host target cells - pneumocytes. As Zn is reported to improve innate and adaptive immunity, this combination could prove useful for COVID-19 treatment¹¹³.

N. sativa potentially targets SARS CoV2 main protease (Mpro). The results of a study reported some components of *N. sativa* showed good binding affinity to Mpro and represent Mpro inhibitory potential of *N. sativa*¹¹¹. Further, a randomized controlled phase II clinical trial was registered to evaluate the potency of *N. sativa* oil in treating mild COVID-19¹¹⁴. It may mitigate inflammation and oxidative stress-related symptoms. The anti-inflammatory and antioxidant activity of *N. sativa* oil was measured in a clinical trial where it was found to significantly increase the serum levels of IL-10 and significantly lowered the serum malondialdehyde and nitric oxide levels in patients of rheumatoid arthritis, an inflammatory disease¹¹⁵. Thymoquinone, α -hederin, and nigellidine present in *N. sativa* seed, represent great potential as therapeutic candidates against COVID-19¹¹⁶. α -hederin showed regulation of IL-13 secretion pathway by inhibiting miRNA-126 expression¹¹². As, IL-13 represent an important cytokine in chronic airway inflammation, inhibition of IL-13 might constitute a

significant approach for improving lung functions¹¹⁷. Moreover, thymoquinone lowered the markers of allergic airway inflammation in a mouse model of allergic lung inflammation and also lowered eosinophilic infiltration into the airways, suppressing Th2 cytokines^{118,119}. The effect on airway inflammation might be observed due to the suppression of prostaglandin D2 production, Th2 cytokine and also by lowering COX-2 protein expression¹¹⁸. Based on the literature, these components showed superiority over FDA-approved drugs during molecular docking studies¹¹² and offer great pharmacological potential to get explored as COVID-19 therapeutics. Although, more clinical studies are needed to further explore the data and experimentally validate the safety and efficacy.

Clove

Clove (*Syzygium aromaticum*; Family-Myrtaceae) is a widely used culinary spice with several pharmacological activities¹²⁰. It has been reported for antioxidant, anti-inflammatory, antibacterial, antiviral, antifungal, analgesic and anticancer activities¹²¹. It has been explored for different microorganisms including pathogenic bacteria, Babesia, Plasmodium, Theileria parasites, viruses like herpes simplex, and hepatitis C. Some important phytochemicals present in clove oil are- eugenyl acetate, eugenol, and β -caryophyllene¹²². It also inhibits respiratory syncytial virus (RSV) and enveloped viruses. The phytochemicals such as betulinic acid and savinin present in clove also inhibit post-binding entry of SARS coronavirus into cells and act on the envelope of coronaviruses (COVID-19)¹²¹. In another computational study, 53 phytochemicals from clove were used for targeting the main protease (M^{Pro}) of SARS-CoV-2. Eugenol, syzyginin B and eugenol showed strong interaction with the target as measured by binding energies and molecular dynamics simulation. The compounds were found as druggable obeying ADMET profiling parameters and were suggested as potential candidates against SARS-CoV-2. In fact, eugenol is one of the components of the Siddha formulation used for COVID-19 treatment¹²³. Hence, data supported clove as a promising source of molecules for therapeutic targeting of SARS CoV2.

Ocimum

Ocimum tenuiflorum (or *Ocimum sanctum* Linn; Family-Lamiaceae) is considered as "Queen of Herbs" with a huge range of medicinal activities.

Different parts of this plant have been used since ancient times in Ayurveda and Siddha practices for the treatment of several disease symptoms. It has been reported with immunomodulatory, anti-inflammatory, antitoxic, antimalarial, antimicrobial, antitussive and antidiabetic activities. The antimicrobial activities cover protection against gram-positive and gram-negative bacteria, viral and fungal infections. Antiviral activity has been explored for herpes simplex, HIV, H9N2, and new castle disease virus¹²⁴. A molecular docking and molecular dynamics (MD) simulation study was performed to identify potential inhibitors from *O. sanctum* against SARS-CoV-2M^{Pro} (main protease). Out of 46 active phytochemicals, vicenin, isorientin-4'-O-glucoside 2''-O-p-hydroxybenzoate and ursolic acid showed significant binding interaction. The MD simulation analysis also showed the molecular complex as structurally stable. The result of the study showed compounds as druggable following more than two parameters of Lipinski rule of five and also came under the standard scale of water solubility (LogS), Caco-2 permeability and human intestinal absorption, with no carcinogenic effects. The study considered the compounds as potent anti-COVID-19 therapeutics¹²⁵. Another *in silico* analysis showed a significant affinity of flavonoids and polyphenolic compounds extracted from *O. sanctum* towards SARS-CoV-2M^{Pro}. The compounds covalently bonded to catalytic residue Cys-145 of the structural target and also irreversibly interacted with the viral enzyme. Luteolin-7-O-glucuronide present in it also showed optimum activity- low toxicity, high druggability and active site binding free energy¹²⁶. The data mentioned above shows *O. sanctum* as a significant source of molecules for the targeting of SARS-CoV-2.

Saffron

Saffron (*Crocus sativus*; Family- Iridaceae) is a medicinal plant used for centuries in the alleviation of disease symptoms such as fever and cold, bronchitis, immune respiratory symptoms¹²⁷, hypertension, stomach disorders etc¹²⁸. The anti-inflammatory, antioxidant, antitussive cytotoxic, and antigenotoxic activities of saffron may help in the therapeutics and management of COVID-19. Due to anti-depressant activity, it has also been reported to relax post-hospitalization symptoms like anxiety, depression and also boosts immunity in general¹²⁷. Crocetin esters, picrocrocin, and safranal, the active phytochemicals show strong antioxidant and anti-inflammatory

activities. Crocin is reported to lower cytokine storm associated with COVID-19 and also lowers the expression of ACE2. Besides, *in silico* data suggest inhibitory interaction of crocin and astragaloside with SARS-CoV-2 spike protein and protease, respectively. The review findings suggest saffron and its components promising to develop as a therapeutic drug for COVID-19. However, clinical studies are needed to evaluate the efficacy and use of saffron as a treatment regimen¹²⁹.

Nutmeg

Nutmeg (*Myristica fragrans* (Houtt.); Family- Myristicaceae) is a commonly used spice. Owing to immunomodulatory, anti-inflammatory and antioxidant activity, its extract and isolated components have been used in various disease treatments. Macelignan, a phytochemical present, shows an inhibitory effect against neuroinflammation and oxidative toxicity. Treatment with macelignan showed lowered levels of IL-6, TNF- α , IFN- γ , MDA and increased levels of SOD and GSH activities¹³⁰. An *in silico* investigation was performed to evaluate the therapeutic potential of components present in nutmeg using the significant therapeutic targets of SARS-CoV-2 -main protease (M^{pro}) and spike-ACE2 protein. The results of the docking study showed higher affinity of the contained compounds- Licarins A, B, and C and malabaricones B and C. ACE2 was inhibited by licarin A and licarin B whereas M^{pro} was inhibited by licarin A, licarin B, licarin C, malabaricone B and malabaricone C. These compounds also obeyed the criteria of Lipinski, Veber, and Egan. The oral bioavailability predictions of the study also suggested the oral use of these compounds except malabaricone C for the treatment of COVID-19¹³¹. Data confirmed nutmeg as a probable source of COVID-19 therapeutics.

Conclusion

Spices represent great imperative both in food and pharmaceuticals. Several inherent properties of spices such as anti-inflammatory, immunomodulatory, antioxidant, and antiviral have proven effective against hCoV infections including SARS-CoV2. Targeting the main protease and spike protein of SARS CoV2, inhibiting the production of inflammatory markers, stimulating the production of anti-inflammatory markers, and suppressing cytokine storm and subsequent ARDS are some potential therapeutic targets reported in different studies that

are employed by different spices to fight against hCoV caused infections. Thus, available intriguing evidence bolsters the development of spices as a therapeutic lead against human coronavirus infections including COVID-19. As yet, only a few clinical trials are underway to check the potency of spices as COVID-19 therapeutics, but more clinical studies are required for further experimental validation and evaluation of the safety and efficacy of the drug.

Conflict of interest

The authors declare that there are no conflicts of interest.

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