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# Are Indian Culinary Spices Acting as an Immunomodulatory Factor Against Covid-19?

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**Abstract**

Coronavirus disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus- 2 (SARS-CoV-2) due to its rapid community transmission and absence of an effective antiviral drug has caused a high morbidity and mortality in human lives world over. According to the WHO Situation Report No. 102 as on January 12, 2022, India recorded 35.87 million confirmed cases of COVID 19 with a death rate of 1.34 %, the total death being 0.48 million, in comparison to the global death rate of 1.78%. The host-pathogen interactions are important to understand an infectious disease and to follow specific treatment for cure and measures for prevention. Various factors involved in disease emergence with interplay between pathogens, hosts and environment changes the disease ecology creating novel transmission patterns and severity. Indian conventional foods and culinary spices contain a number of active principles, including polysaccharides, terpenoids, alkaloids, flavonoids, glycosides, and essential oils, which act as immunomodulators and have tremendous capability to maintain and/or stimulate the immune system primarily through the modulation of nonspecific immune responses. This review highlights the bioactive components of some of the most commonly used Indian culinary spices grounding a new dimension of research on these natural phytoproducts to bring out their functional and medicinal values vis-à-vis improvement of human health. In conclusion, the structure of bioactive molecules present in the Indian dietary spices may pave way for the development of anti-SARS-CoV-2 drugs for the prevention and treatment of COVID-19.

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## Introduction

Since 1918 to the present day, emerging infectious diseases caused by newly evolving viruses like Influenza virus, Ebola virus, Nipah virus, Hanta virus, Zika virus and Coronavirus have imposed serious threat to the public health sector and has burdened the economic growth across the globe. Towards the end of 2019, a new virus identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was reported from Wuhan city, People's Republic of China, and the World Health Organization (WHO) on 11 February, 2020, declared the disease as Coronavirus disease 2019 (COVID-19). On March 2020, COVID-19 was announced as a global pandemic by WHO, due to its rapid spread across the globe. Fever, dry cough, lethargy, headache, sore throat has been recognized as the most common symptoms associated with COVID-19 along with serious symptoms like shortness of breath, pain in the chest and/or loss of taste, smell, speech or movement.

John Hopkins University and Medicine reported mortality data due to COVID-19, comparing twenty most affected countries worldwide, in which India showed 4.98 percent mortality per 1 lakh population while Peru, Chile, Brazil and US secured the top most ranks with mortality percentage of 90.87, 60.57, 59.09, 56.77 respectively.[1] As per the WHO Situation Report No. 102 as on January 12, 2022 on COVID 19, India had 35.87 million confirmed cases with a death rate of 1.34 %, the total death being 0.48 million in comparison to the global death rate of 1.74% with 5.49 million deaths out of the 308.45 million confirmed cases of COVID 19.[2]

The question in this context is, how a country like India with 1.3 billion population is battling against COVID-19 pandemic with a striking difference in the mortality percentage with that of the developed nations. It has been opined that the host pathogen interaction and the tropical environment played a significant role in reducing the susceptibility of a large section of Indian population to COVID-19 along with enhancement of their innate immunity and immune responses against the virus under the hot humid environmental conditions.[3] One probable answer to the low fatality rate of Indians against COVID 19 hither to not very seriously thought of might be the Indian diet and food habits which is providing some degree of resistance to infection by immunity boosting agents contained in their natural diet as goes the Ayurvedic proverb "When diet is wrong, medicine is of no use; when diet is correct, medicine is of no need". The Indian dietsare however, incomplete without the indulgence of spices and since ages, India is regarded as the "Spice Bowl of the World". Spices in India are not only used as culinary enhancers with regard to its aroma, color and taste but also, used to cure various ailments and as immunity boosters since time immemorial.

It has been reported that, in countries where there is meagre consumption of dietary spices, occurrence of COVID-19 cases per million population is higher.[4] Further, a recent study based on molecular docking analysis revealed that spice bioactives have high affinity for binding with the specific targets involved in SARS-CoV-2 infection and transmission.[5] Thus, this review provides an overview of some recent scientific findings of the most commonly used spices in the regular Indian diet which has the potential bioactive components possessing immunomodulatory effects for boosting up the immune system against the COVID-19 battle.

## Innate and Adaptive Immune Response Elicited Against Covid-19 Infection

The host immune system comes into force immediately on account of an acute viral infection by destroying the virus invaded cells or with the action of cellular pro-inflammatory cytokines.[6] The elimination of the virus infected cells is achieved through an initial innate immune response via macrophages, natural killer (NK) cells or dendritic cells which is followed by antigen specific adaptive immunity of the host via T and B cells with the release of inflammatory cytokines to inhibit viral replication.[6,7]

A recent report helps in understanding the interaction between coronavirus and the host immune system with the secretion of chemokines and cytokines (IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1) in large quantities in the SARS-CoV-2 infected cells leading to inflammation in the lung tissue.[8] Moreover, the host immune response induced against COVID-19 infection is biphasic with initial incubation and non-severe stage followed by a severe stage characterized by inflammation-driven damaging phase.[9] Incorporation of immune boosters as a strategy to enhance immune responses during the non-severe defense-based protective phase of infection could prevent the disease progression into the severe stage (Fig. 1). However, a patient with acute COVID-19 infection has high levels of interleukin-1 (IL-1) and tumor necrosis factor (TNF) in the lungs which are strong stimulators of HA-synthase-2 (HAS2) in $CD31^+$ endothelium, $EpCAM^+$ lung alveolar epithelial cells, and fibro blasts[10] leading to transparent gel like deposition in lungs as revealed by recent autopsies[11] and characteristic "ground glass" CT images of the lungs.[12] As such, it is essential to suppress the hyper inflammatory immune response in the severe stage of infection.

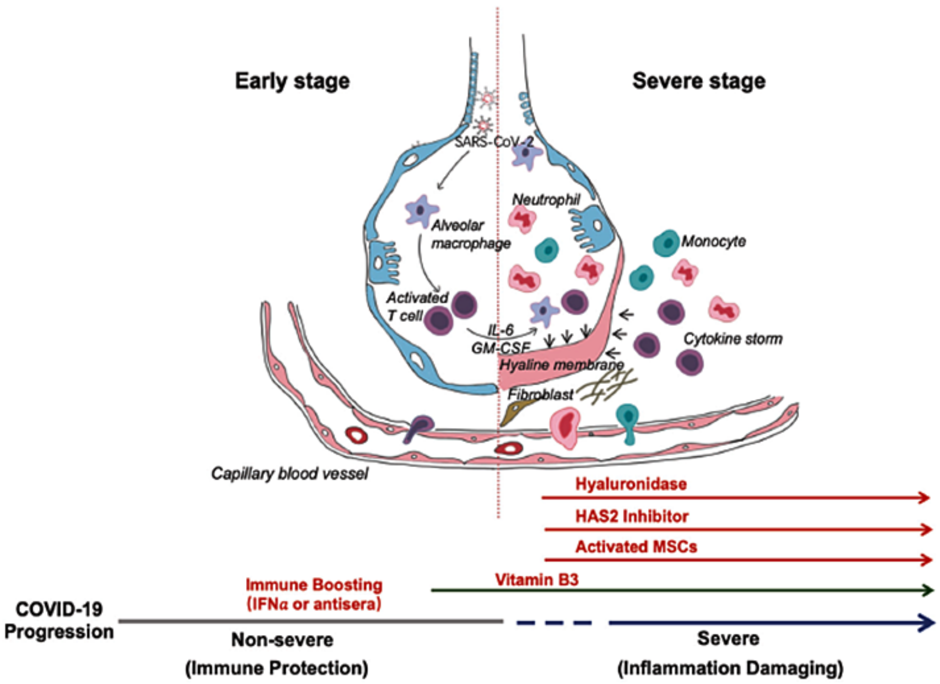


**Figure 1: Diagrammatic representation of non-severe and severe stages of COVID-19 infection and potential supportive therapy.[9]**

**Indian Dietary Spices as Immunomodulators**

Indian traditional foods being a rich source of several functional and medicinal ingredients are often regarded as functional foods. The functional molecules present in Indian foods play a significant role in management of healthy body weight, maintenance of normal blood sugar level and a strong immune system of the body. Moreover, different processing techniques in Indian traditional practices like sprouting, malting and fermentation further enhance the functional properties of such foods.[13]

In respect of the immune response triggered by COVID-19 infection, some of the spices from the regular Indian diet comprise of several bioactive phytochemicals which seems to boost up the immune system of the Indian population in an effective way and there by, maintaining the fatality percentage at a much lower end in comparison to the other most infected countries of the world. The effectiveness of few such commonly used spices with anti-inflammatory, anti-viral and immunomodulating properties are discussed below:

**Turmeric**

Turmeric (*Curcuma longa*) also known as the "Golden Spice" hails from the ginger family, *Zingiber*aceae, and its use as an inevitable culinary spice dates back to the Vedic culture in India (approximately 4000 years ago).[14] The bright yellow color of turmeric is due to the presence of turmerone and curcuminoids. Curcuminoids is a mixture of three components (demethoxycurcumin, 5'-methoxycurcumin and dihydrocurcumin) with antioxidant properties.[15,16] In addition to curcuminoids, turmeric possesses other bioactive chemical compounds like sesquiterpenes, diterpenes and triterpenoids.[17]

Curcumin, a polyphenolic compound, is the key ingredient of turmeric and its immunomodulatory properties arise from several interactions not only with the immune cells (dendritic cells, macrophages and B and T lymphocytes) but also, with those molecules (cytokines) associated with inflammation.[18] Various studies on curcumin showing immunomodulatory and anti-inflammatory properties are listed in Table 1. Besides, curcumin is reported to have antiviral activity against human immunodeficiency virus, influenza virus, herpes simplex virus, hepatitis B virus and Japanese encephalitis virus through different molecular pathways.[34-40] The potential of curcumin to be developed as a treatment of choice against COVID-19 has also been assessed using molecular docking approach against Main Protease (Mpro) and spike (S) glycoprotein receptor binding domain (RBD) of SARS-CoV-2.[41] The study revealed that curcumin possessed all the optimum physicochemical and pharma cokinetic properties to inhibit Mpro covalently. Furthermore, Ayurvedic medication indicates, intake of turmeric has beenused towards treatment for numerous respiration distress like asthma, bronchial hyperactivity and hypersensitivity as well as for runny nostril, cough and sinusitis.[42] In India, turmeric mixed with milk is often taken as a remedy against sore throat, fever and cold.

**Table 1: Studies associated with curcumin- mediated immunomodulatory and anti-inflammatory effects.[33]**

| Study type | Decrease effect | Increase effect | Reference |
|---|---|---|---|
| *in- vitro* | Dendritic cell maturation, CD80, CD86, IL-12, NF-κB, IL-6, TNF- α, PTGS-2, p38MAPK, HDAC8, NF-κB, iNOS, IL-1β, COX-2, HO-1, NF-κB, PGE-2, TLR4, caspase 3 | STAT 3, SOCS1,SOCS3, PBMC proliferation | 18-26 |
| *in- vivo* | MPO, IL-1β, TNF- α, IL-6, TLR4, NF-κB, leucocyte infiltration, TNF- α | serum IgG, IgM, concanavalin A | 27-32 |

**Ginger**

Ginger belonging to the family *Zingiber*aceae is a key spice in Indian cuisines which not only acts as a culinary enhancer but possess several nutritional and ethno medicinal properties. Traditionally, the use of ginger as a medicinal plant against several diseases dates back to more than 2500 years ago. Fresh and dried ginger primarily comprise of gingerols and shogaols as the chief phytochemical components which are responsible for exhibiting a wide range of biological activities like anticancer, antimicrobial, anti-inflammatory, anti-oxidant and anti- allergic activities.[43] Moreover, the presence of several active phyto-ingredients in ginger (gingerol, shogaol, paradol, zerumbone) aids in enhancing activity of enzymes as well as its circulation and assimilation throughout the body.[44] Various studies pertaining to anti- inflammatory properties of ginger are listed in Table 2. Apart from its anti-inflammatory abilities, rhizomes of ginger are rich in metabolites with anti- viral properties.[49-55] An *in-vitro* study reported that hot water extract of fresh ginger stimulated the secretion of IFN-β in mucosal cells which has anti-viral property against human respiratory syncytial virus (HRSV) by inhibiting viral attachment with the host cell receptors.52 This anti-viral property is therefore comparable in the management of fever, cough and respiratory trouble associated with COVID-19 infection. Further, allicin is another active component of ginger which is reported to contain anti- influenza cytokines against H1N1 virus.[56] These properties contribute towards enhancing innate immunity and in this COVID-19 pandemic situation, ginger is an important spice to be included in regular diet in disease prevention and enhancing immunity and strengthening the various biological functions of the body.

**Table 2: Studies associated with anti-inflammatory properties of ginger.[50]**

| Study type | Active Component | Biological Activity | Reference |
|---|---|---|---|
| *in vitro* | 6- shogaol, 6-gingerol, 6-dehydroshogaol | Blocks activation of NF- κB pathways and production of NO and PGE2 | 45-46 |
| *in vivo* | Ginger extract | Blocks activation of NF- κB pathways, TNF- α, IL-1 β production. Enhance myeloperoxidase enzyme levels | 47-49 |

**Garlic**

Garlic (*Allium sativum*) is a bulbous spice belonging to the family Amaryllidaceae with characteristic pungent and spicy flavour. Garlic has been considered as an important

medicinal plant since earliest of time through since 6th century BC.[57] The major bioactive component of fresh or crushedgarlic is allicin (allyl 2-propenethio sulfinate or diallyl thiosulfinate), a sulfur containing natural compound. In addition to allicin, other sulfur containing phytochemicals of garlic are ajoene, diallyl polysulfides, vinyldithiins, S-allylcysteine, along with non- sulfur containing compounds like saponins, flavonoids, lectins, polysaccharides (fructan), different enzymes, vitamin A, B and C, minerals and amino-acids.[58] The interaction of allicin with cellular biomolecules like glutathione and L-cysteine results in the formation of S-allyl-mercapto-glutathione (SAMG) and S-allyl-mercaptocysteine (SAMC) respectively.[59,60]

Allicin has a direct impact on pathogens by bringing about unfavorable structural changes in the pathogen’s proteins.[61] Besides, there exists a plethora of pre-clinical investigations which revealed thatgarlic and its sulfur containing components possess anti-viral properties against virus associated respiratory infections.[62-65] In most of these studies, the proposed mechanism of antiviral action with aqueous garlic extract was found to be by: direct inhibition of viral infection by blocking entry of virus particles through disintegration of viral envelope and cell membrane, enhancing host immune response, inhibiting viral replication by blocking the activity of polymerase enzyme.

Further, regular dietary consumption of raw or crushed garlic has shown great impact in boosting up the immunity levels.[66,67] Clinical investigations also revealed that garlic extract supplementation not only modulated inflammation and immunity of obese adults but also, alleviated the severity of cold and flu affected patients by increased production of γδ-T and NK cells, serum antioxidant concentration and decrease in the levels of inflammatory cytokines.[68,69] Thus, as a prophylactic measure, garlic intake in daily meals could definitely enhance the immune system against COVID-19.

**Clove**

Cloves (*Syzygiumaromaticum*) are dried flower buds with a deep brown color, intense flavour and a burning taste belonging to the family Myrtaceae. In India, clove is used as whole or in ground form in savory as well as sweet dishes. The medicinal property of clove is mainly attributed towards several disease-causing parasites and microbes due to its antiseptic and antimicrobial qualities.[70]

Eugenol is the principle bioactive molecule of clove along with several other natural phenolic compounds such as flavonoids (quercetin and kaempferol), hydroxybenzoic acids, hydroxycinnamic acids and hydroxyphenyl propens.[71] Besides, clove contains caffeic, ellagic, ferulic and salicylic acids belonging to the category of phenolic acids.[72] Moreover, clove oil is a transparent or pale-yellow essential oil with distinct flavor extracted from buds. Clove oil consists of eugenol, eugenol acetate and β-cariofileno.[73]

An *in-vitro* study on human dermal fibroblast system revealed that clove essential oil has anti-inflammatory properties due to its major active component eugenol.[74] Furthermore, an *in-vivo* study carried out on BALB/c mice showed that clove extract inhibited the production of IL-1 β and IL-6by macrophages and the results of this study were counter proved under *in-vitro* conditions.[75] Another *in-vitro* study brought out the immuno modulatory property of this spice to verify its therapeutic property wherein, they revealed that macrophages challenged with lipopolysaccharides when incubated with clove at a dose of 100 µg/ well suppressed the synthesis of cytokines (IL-1 β, IL-6 and IL-10).[76] They proposed a possible mechanism of action which suggested that eugenol could probably suppress the nuclear factor (NF)-κB pathway. Moreover, the anti-viral activity of clove was identified against herpes simplex virus due to another component, eugeniin, which blocked the viral DNA synthesis by inhibiting the viral DNA polymerase.[77]

Thus, in Indian homes, brewing tea with two to three clove buds along with cinnamon and crushed ginger acts as a natural remedy since ages to clear away symptoms of cold, flu and congestion.

**Cinnamon**

Cinnamon bark belonging to family Lauraceae is one of the widely used spice across the world as flavoring agent. Apart from its traditional use as a condiment, cinnamon is reported to have anti-inflammatory properties.[78-80] Cinnamon is chemically composed of a variety of resinous compounds like cinnamaldehyde, eugenol, cinnamate, cinnamic acid, and numerous essential oils.[81]

Various assays like carbon clearance test, cyclophosphamide-induced neutropenia, neutrophil adhesion test, effect on serum immunoglobulins, mice lethality test and indirect hemagglutination test were performed to screen the immuno-modulatory property of cinnamon bark which revealed that cinnamon bark at a concentration of 100 mg/kg p.o. reduced the mortality rate by 17% caused by *Pasteurella multocida* infection, increased the phagocytic index in carbon clearance test, enhanced the ability of neutrophil adhesion, raised serum immunoglobulin levels and antibody titer.[82] The transcription factor, NF- κB, is involved in the regulation of genes responsible for inflammation and therefore, chronically active in many inflammatory diseases including asthma[83] and possibly in the severe phase of COVID-19 infection. In this context, a study showed that trans-cinnamaldehyde and 2-methoxycinnamaldehyde extracted from cinnamon bark (Cinnamomum cassia Blume) blocked lipopolysaccharide activated DNA binding capacityas well as transcriptional activity of NF- κB.[84] Thus, these findings substantiate the belief that cinnamon is an immunity boosting spice and especially, in India, ground cinnamon is consumed with honey as a potent immunity booster.

**Black Pepper**

Black pepper (*Piper nigrum*) produced from the unripe drupe of the pepper plant belonging to family Piperaceae is not only used as a spice but has a vital position in Indian traditional medicine recommended against fever and chills and broncho- pulmonary disorders (asthma and chronic bronchitis).[85] The pungent flavour and biting taste of black pepper is derived from its natural component, piperine, an alkaloid, along with several essential oils. Piperine is responsible for all the therapeutic roles which can contribute to general human health including immunomodulatory, anti-inflammatory and anti-microbial activities.

Several reports demonstrate the immunomodulatory and anti-inflammatory properties of piperine of black pepper. Based on an *in-vitro* study evaluated on fibroblast stimulated with IL-1β revealed that piperine at a dose of 10- 100 µg per ml blocked the expression level of IL-6 which identified piperine as an anti-inflammatory agent.[86] Results from an *in-vivo* experiment also showed that piperine when administered on asthma induced Balb/c mice at the doserate of 4.5- 2.25 mg per kg, suppression in the synthesis rate of TH2 cytokines viz., IL-4, IL-5, IL-13, immunoglobulin E and histamine was observed while, TGF-β gene expression levels were enhanced.[87] The anti-inflammatory potential of piperine was further supported through an experimental finding on rat lung tissue damage induced by gamma rays which proved decreased levels of TNF-α, IL-6 and IL-1β in the lung tissue.[88]

Thus, based on the therapeutic potential of piperine, incorporation of black pepper as condiment in meals can enhance immune health which is a prerequisite against COVID-19.

**Cumin and Black Cumin**

Cumin and black cumin (black caraway) are seed spices obtained from *Cuminum cyminum* and *Nigella sativa* respectively belonging to the family Apiaceae and Ranunculaceae respectively. The use of these seed spices in Indian curries is due to its rich warm aroma and distinctive flavor. However, they are not without any medicinal value as they are reservoir of essential oils. The major phyto ingredients of cumin are cuminaldehyde, limonene, 1,8-cineole, α- and β-pinene, α- and γ-terpinene, o- and p-cymene, linalooland safranal while, major components found in black cumin are thymoquinone (approximately, 50%), dithymoquinone (nigellone), thymohydroquinone, carvacrol, p-cymene, sesquiterpene longifolene, thymol, 4-terpineol, α-pinene, and t-anethole.[89-90,95]

Few recent reports provide experimental evidence regarding the immuno-modulating and anti-inflammatory properties of cumin and black cumin against respiratory and pulmonary diseases (Table 3).

**Table 3: Significant immunomodulatory and anti-inflammatory properties of cumin and black cumin**

| Spice | Model | Effects(↓ Reduce, ↑ Raise) | Ref. |
|---|---|---|---|
| Cumin | Normal and immune suppressed animal model; 25- 200mg/ kg | ↑ T cells (CD4 and CD8)<br>↑ TH1 cytokines | 91 |
| Cumin essential oil | LPS induced cell line | ↓ IL-1, IL-6<br>↓ ERK and JNK signaling pathways on activation with mitogen | 92 |
| Black cumin | LPS induced cell line (microglial cells) | ↓ IL-6, CCL12 /MCP-5, CCL2 / MCP-1 | 93 |
| Black cumin | Wistar rats | Inhibition of inflammatory pulmonary responses | 94 |
| Black cumin | Patients with asthma | Improvement of respiratory and pulmonary symptoms like gasping and shortness of breath | 95 |

**Culinary Spices As Immunity Boosters Against Covid 19: An Overview**

The multi- pharmacological role of the bioactive components of various spices used in the everyday Indian diet suggests their pivotal role against SARS-CoV-2 infection. Besides, spices also carry several minerals and micronutrients like zinc, calcium, phosphorous, potassium, sodium and iron as well as vitamins, along with their major phytoactive ingredient[96] which might synergistically play a significant role during the first phase of SARS-CoV- 2 infection in immunity build up.

Hyperinflammation is one major aggravating immunological parameter in COVID-19 patients and as such, one possible measure to reduce the mortality in patients is immune suppression at the severe phase of infection .[97,98] In COVID-19 affected patients, IL-6 has been identified as the major inflammatory cytokine during the inflammatory cytokine storm and thus, in this severe phase of infection elevated levels of IL-6 has been reported.[99,100] Another clinical manifestation from SARS-CoV-2 ICU patients, revealed high plasma levels of TNFα , IL2, IL7, IL10, MCP1, GSCF, IP10 and MIP1A.[101] In this context, different scientific investigations[22,49,75,88,92,93] as discussed under this review, revealed that some of the commonly used spices in traditional Indian everyday meals do carry certain bioactive components and phytochemicals responsible for immuno-modulatory and anti-inflammatory function (Fig. 2).

Thus, in India, epigenetic factors like the food habit and the indulgence of spices with high medicinal values could be one possible reason responsible for the low COVID-19 associated fatality amongst the Indian population.

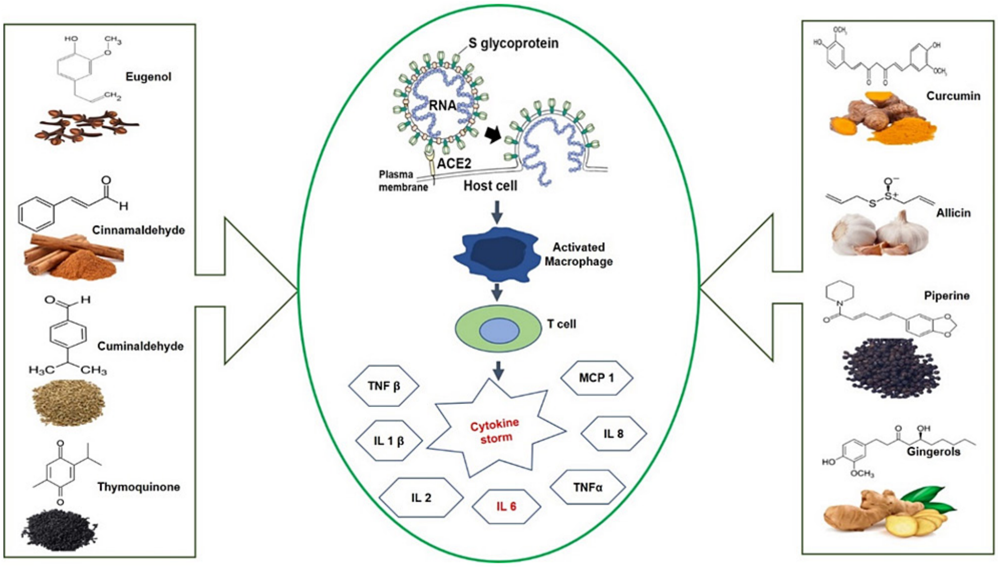


**Fig. 2: Schematic representation of the major bioactive components of the Indian culinary spices with potential immunomodulatory and anti-inflammatory properties against the SARS-CoV-2 (COVID-19)infection progression**

## Conclusion

Effective measures in the form of efficient and safe antiviral drug are still not readily available for prophylaxis and treatment against SARS- CoV-2 virus infection. Even with development of a vaccine, viruses tend to change continuously due to phenomena like antigenic drift/ shift which also results in the emergence of novel virus. As such, susceptibility against a viral disease can be significantly reduced by developing innate immunity and enhancement of immune response exploiting various factors like host, pathogen and environment interaction and adopting to food habits and diet comprising of natural bioactive components available in different Indian culinary spices. These phytoproducts are believed to be one of the major factors to enhance innate immunity and hasten the morbidity and mortality caused by COVID 19 in India. This review highlighted and suggested to open up a new dimension to the research areas for identifying the active principles and explore the mechanism of action of these natural phytoproducts present in the Indian culinary spices in immunity boosting against COVID 19 and other emerging and re-emerging viral infections world over.

## Declarations

### Authors' Contributions

SD conceived and collected the data and prepared the manuscript. PJ reviewed and approved the manuscript for communication.

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### Conflict of Interest

The authors declare no competing interests.

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