Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19, Cytokines, Inflammation, and Spices: How are They Related?

Ajaikumar B. Kunnumakkara[1#], Varsha Rana[1], Dey Parama[1], Kishore Banik[1], Sosmitha Girisa[1], Henamayee Sahu[1], Krishan Kumar Thakur[1], Uma Dutta[2], Prachi Garodia[3], Subash C Gupta[4], Bharat B. Aggarwal[5*].

[1]Cancer Biology Laboratory, & DBT-AIST International Laboratory for Advanced Biomedicine (DAILAB), Department of Biosciences and Bioengineering,
Indian Institute of Technology Guwahati, Assam-781039, India

[2]Cell and Molecular Biology Lab, Department of Zoology
Cotton University, Guwahati, Assam-781001, India

[3]Integrative Research Center, Oregon- 97520, USA

[4]Department of Biochemistry, Institute of Science,
Banaras Hindu University, Varanasi 221005, India

[5]Inflammation Research Center, San Diego, California- 92109, U.S.A.

Running title: Role of spices in the management of COVID-19

Author for correspondence:

*Prof. Bharat B. Aggarwal, Inflammation Research Center, San Diego, California- 92109; USA.

Phone: 832-754-0059; Email: bbaggarwal@gmail.com

[#]Prof. Ajaikumar B. Kunnumakkara, Cancer Biology Laboratory and DBT-AIST International Center for Translational and Environmental Research (DAICENTER), Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, Guwahati, Assam-781039, India. Phone: +91 361 258 2231 (Office); +91 789 600 5326 (Mobile); Fax: +91 361 258 2249 (Office); Email: kunnumakkara@iitg.ac.in ; ajai78@gmail.com

Abstract:

Background: Cytokine storm is the exaggerated immune response often observed in viral infections. It is also intimately linked with the progression of COVID-19 disease as well as associated complications and mortality. Therefore, targeting the cytokine storm might help in reducing COVID-19-associated health complications. The number of COVID-associated deaths (as of January 15, 2021; https://www.worldometers.info/coronavirus/) in the USA is high (1,199/million) as compared to countries like India is low (110/million). Although the reason behind this is not clear, spices may have some role in explaining this difference. Spices and herbs are used in different traditional medicines, especially in countries such as India to treat various chronic diseases due to their potent antioxidant and anti-inflammatory properties.

Aim: To evaluate the literature available on the anti-inflammatory properties of some spices which might prove beneficial in the prevention and treatment of COVID-19 associated cytokine storm.

Method: A detailed literature search has been conducted on PubMed for collecting information pertaining to the COVID-19; the history, origin, key structural features, and mechanism of infection of SARS-CoV-2; the repurposed drugs in use for the management of COVID-19 and the anti-inflammatory role of spices to combat COVID-19 associated cytokine storm.

Key findings: The literature search resulted in numerous *in vitro, in vivo* and clinical trials that have reported the potency of spices to exert anti-inflammatory effects by regulating crucial molecular targets for inflammation.

Significance: As spices are derived from Mother Nature and are inexpensive, they are relatively safer to consume. Therefore, their anti-inflammatory property can be exploited to combat the cytokine storm in COVID-19 patients. This review thus focuses on the current knowledge on the

role of spices for the treatment of COVID-19 through suppression of inflammation-linked cytokine storm.

Keywords: SARS-CoV-2, cytokine storm, COVID-19, curcumin, spices, inflammation

1. Introduction:

The ongoing novel coronavirus pandemic has taken a major toll on human lives worldwide. In December 2019, the first case of the ongoing pandemic of the novel coronavirus disease (COVID-19) was reported [1]. The epicenter of COVID-19 was identified as Wuhan, the capital of Hubei province, China. Initially, the outbreak was declared as a "Global Health Emergency" by the World Health Organization (WHO) on 30th January 2020 [2]. However, as COVID-19 spread rapidly across the globe affecting thousands of lives worldwide, the WHO finally declared it a global pandemic on 11th March 2020 [3].

As per the weekly epidemiological update released by the WHO on 10th January 2021 at 10:00 CEST, the total number of cases worldwide is reported to be 88,387,352 with 1,919,204 deaths. In India, the total cases were reported to be 10,450,284 with 150,999 deaths [4]. The geographical distribution of the COVID-19 pandemic as per 14-day COVID-19 case notification rate per 100,000 population (as of 13th January 2021) has been illustrated in Figure: 1 [5].

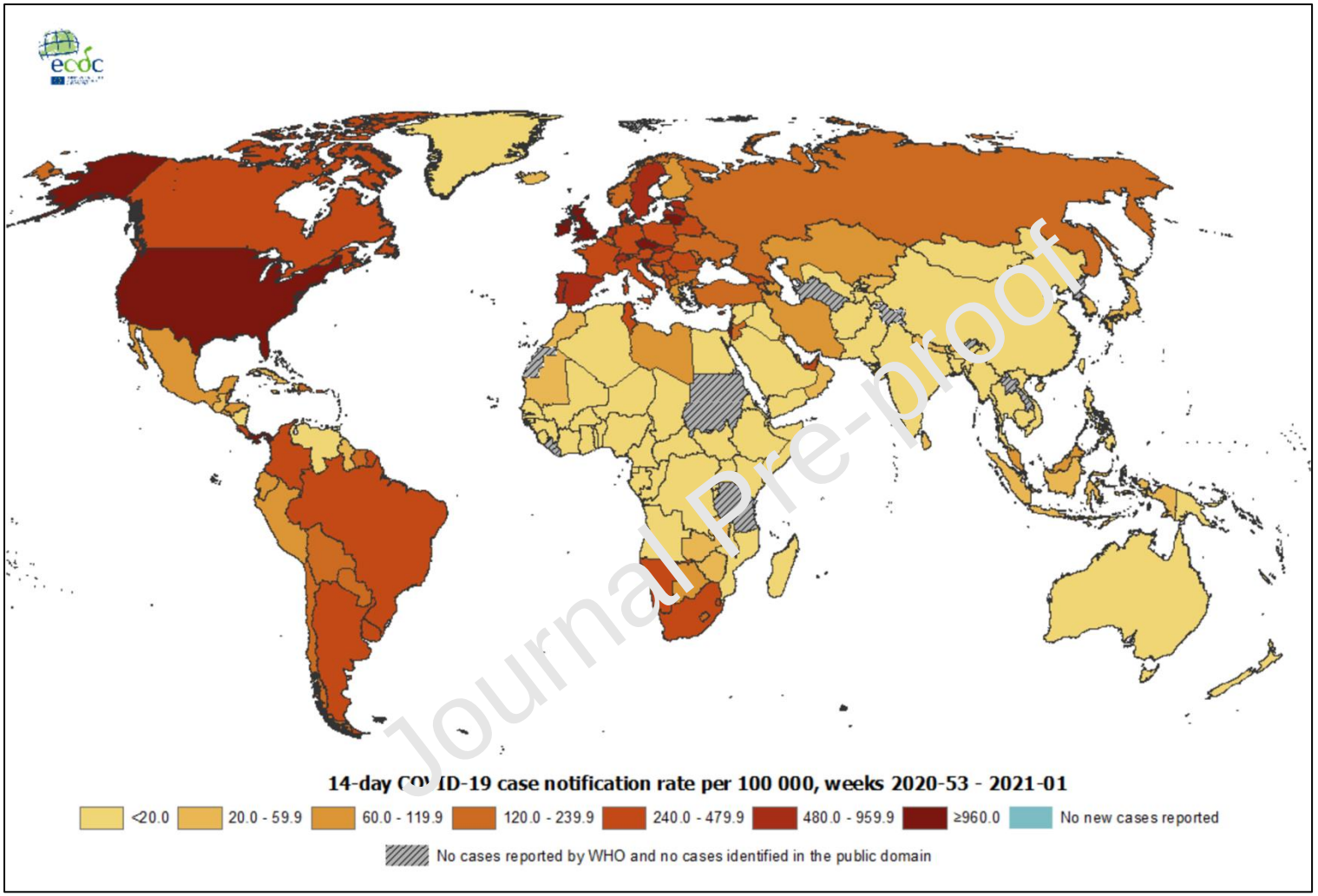

Figure 1: The geographical distribution of the COVID-19 pandemic as per 14-day COVID-19 case notification rate per 100,000 population (as of 13th January 2021) [5]

The causative pathogen of COVID-19 is identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a novel human coronavirus (HCoV) [6]. The SARS-CoV-2 is believed to have a zoonotic origin and bats are considered as their natural reservoir host. The transmission of the virus occurs from human-to-human mostly by direct and indirect contact with cough or sneeze droplets from an infected person and contaminated surfaces, respectively. The incubation period of the virus is approximately 2-14 days. Infected people may present symptoms such as fever, cough, breathlessness, etc. However, some may remain asymptomatic [7], [8]. COVID-19 is usually mild; however, infected patients with comorbidities such as hypertension, diabetes, cancer, immunodeficiency, etc. are more prone to poor prognosis. In such cases, the severity of disease progression might eventually result in pneumonia, acute respiratory distress syndrome (ARDS), a multi-organ failure which may ultimately cause death [7], [9].

Although the exact pathophysiological mechanism of COVID-19 is poorly understood; clinical evidence has revealed that COVID-19 infected patients often show an elevated rise in the cytokine levels which is termed as “cytokine storm” or “cytokine release syndrome”. This abnormal level of cytokines is considered to be correlated with severe deterioration of health conditions in the infected patients [10]. Therefore, suppressing elevated inflammatory response produced during COVID-19 may prove crucial in preventing the severity of disease as well as associated health complications [11].

Various studies have reported that naturally occurring spices as well as their isolated active components target the inflammatory pathways and induce anti-inflammatory effects in many chronic diseases [12], [13], [14].

A recent study conducted on primary data of 163 countries worldwide in respect of total cases, deaths, and recoveries of COVID-19 revealed a close association of the total number of COVID-19 cases per million population tested and the gram of spice supplied per capita per day. This study further reported that the nation with an increased number of COVID-19 cases per million population corresponds to lower consumption of spices per capita, with some exceptions such as Luxembourg and Iceland [15]. As of 10th January 2021, the cumulative cases of COVID-19 in United States of America (USA) are 21,761,186 compared to 10,450,284 cases in India. Moreover, the cumulative cases and deaths per 100 thousand population in the USA are reported to be 6574.3 and 110.5 (1.68%), respectively, as opposed to 757.3 cumulative cases and 10.9 deaths (1.439%) in India [4]. As of 20th January 12:07PM IST, in India, Lakshwadeep (0.00019%), Dadar and Nagar Havelli; Daman and Diu (0.03%), and Mizoram (0.04%) have recorded low number of cases compared to the rest of the states , while Maharashtra recorded the highest number of cases (18.82%) out of the total number of cases (10,596,449). Lakshwadeep has not reported any COVID-19 associated death so far. Further, Dadar and Nagar Havelli; Daman and Diu (0.1%), Mizoram (0.2%), Arunachal Pradesh (0.3%), and Kerala (0.4%) have recorded a low fatality ratio. Interestingly, although Kerala has reported approximately 8% of the total cases, the fatality ratio is quite low (0.4%). This low fatality ratio in Kerala can be attributed to the efficient management of the disease, healthcare system, etc. [16], [17]. Moreover, as spices and herbs are rich immunity boosters and are prevalently consumed in India and other Asian countries, it might be associated with faster recovery and lower per million population death. This was evinced by study which reported that the intake of spicy food was associated with a 14% decrease in total mortality and thus suggested their inverse association.

[15], [18]. This review thus focuses on the anti-inflammatory role of spices as potential therapeutic agents to combat the occurrence of "cytokine storm" in COVID-19.

2. Lockdown:

The outbreak of coronavirus (COVID-19) was first reported in December in Wuhan and Hubei province. Several places are majorly affected by the COVID-19 which led to the imposition of lockdown. During this lockdown period, several activities such as travel *via* international flights as well as local transports, mass gatherings at public places such as schools, universities, etc., had been restricted. Moreover, people were not allowed to go outside for any work, except for certain essential activities for a limited period with strict guidelines of social distancing. Despite, these enforcements and restrictions, the number of COVID-19 cases had increased significantly throughout the world [19], [20]. Initially, India had reported fewer COVID-19 cases because it was able to enforce strict lockdown and social distancing. Moreover, the general public was strongly advised to wear a mask and wash or sanitize hands frequently with soap or sanitizers as a preventive measure throughout the country. The WHO had praised India's early implementation of nationwide lockdown as "tough and timely". Later, when the restrictions were relaxed, the COVID-19 cases increased drastically [21], [22]. Community transfer has been observed in various countries that have not implemented early lockdown. Previous studies reported that travel restrictions and isolation have played a pivotal role in the outbreaks of Ebola, SARS-CoV, and bubonic plague [23], [24], [25]. However, the implementation of lockdown alone is not the permanent solution to prevent the further spread of COVID-19 and this raised serious concerns [19].

Some studies also reported that South Korea and Sweden have not implemented stringent lockdown and restrictions on their countries. However, the rate of infections in these countries

was observed to be lower than those which had implemented strict lockdown [26], [27]. One of the important reasons behind fewer infection and death rates in South Korea was believed to be the rapid testing of COVID-19 [21]. Sweden and Denmark have also followed different strategies rather than stringent lockdown to mitigate the virus spread. The authorities in those countries have appealed for strong awareness and a personal sense of responsibility and further encouraged people to work from home. The patients with comorbidities such as respiratory ailments, immune deficiency, hypertension, cancer, diabetes, diseases of the heart, liver, and kidneys were found to be more prone to the COVID-19 infection and death. Therefore, people with a high risk of COVID-19 due to comorbidities or age were strongly recommended to follow quarantine and self-isolation to 'flatten the curve'. Moreover, the kindergartens, nurseries, schools, and colleges remained open during this period while following the norms of social distancing and awareness [9], [27], [28], [29], [30], [31].

The USA has recorded the highest number of COVID-19 infections and deaths. Currently, India has the 2nd highest number of COVID-19 cases and the 3rd highest number of deaths. Brazil is 3rd and 2nd in terms of the number of cases and deaths, respectively. European countries (Russia, France, Spain, UK, Italy, and Germany) have also reported a significantly higher number of COVID-19 associated deaths of COVID-19; however, many people recovered and the number of active cases has declined lately [4]. A closer look has uncovered various reasons for the spread of community transfer of COVID-19 in these countries, such as frequent international travels as well as the late and casual implementation of social distancing [21], [26]. The implementation of lockdown due to the COVID-19 pandemic has given birth to certain health-related issues such as obesity, irregular sleeping behavior, anxiety, depression, etc. Moreover, it has also affected the economy very gravely throughout the world [32], [33], [34].

3. Human Coronaviruses (HCoVs):

3.1. History:

The human coronavirus (HCoV) was first characterized in the 1960s [35]. Tyrell and Bynoe from the Common Cold Unit, England, investigated samples from patients with the common cold and isolated a novel flu-like virus in the 1960s. These viruses were labeled as B814 and were reported as ether sensitive in nature. Initially, they were unable to culture B814 by utilizing the available standard culture techniques. However, in 1965, they were successful in growing B814 in organ cultures [35], [36], [37], [38]. In 1966, Hamre and Procknow from the University of Chicago isolated and reported the presence of a novel RNA virus associated with respiratory disease. This virus was labeled 229E and it exhibited ether sensitivity like the B814 virus [39].

The B814 and 229E viruses were characterized using electron microscopy by Almeida and Tyrell. These ether sensitive viruses were reportedly indistinguishable from one another as well as the avian infectious bronchitis virus (IBV) [40].

These novel viruses along with other morphologically identical animal viruses such as IBV were grouped into a new genus termed "Coronavirus" (Latin word "corona" meaning "crown") in 1968. They were named after the characteristic fringe or crown-like rounded projections on their surface (resembling the solar corona) as observed under an electron microscope [41]. In 1975, the coronaviruses were clubbed under a novel family of viruses named "Coronaviridae" [42].

Apart from the aforementioned HCoVs, several other strains of HCoVs have been identified; some of these include the HCoV-OC43 (1967), SARS-CoV (2002-2003), HCoV-NL63 (2004), HCoV-HKU1 (2005), Middle East respiratory syndrome (MERS)-CoV (2012), and SARS-CoV-2 (2019) [43], [44], [45].

The HCoVs such as 229E, OC43, NL63, and HKU1 are known as endemic CoVs. They are commonly found in the human population and are known to cause mild respiratory infections [46]. However, HCOVs such as SARS-CoV, MERS-CoV, and SARS-CoV-2 are the deadlier viruses that have caused the global outbreak and infected thousands of people worldwide [44].

Towards the latter end of 2002, the emergence of an infectious virus was reported from the Guangdong province, China. This virus was reported to transmit from human-to-human and was later identified as the SARS-CoV in 2002-2003. The infected people mostly presented with symptoms such as fever, cough, myalgia, etc. Other symptoms included headache, dyspnea, headache, hypoxemia, vomiting, etc. [45], [46], [47], [48], [49]. In some cases, the occurrence of pneumonia and ARDS had also been reported [48].

In 2012, the emergence of another novel infectious HCoV, later named MERS-CoV, was reported. The first case was reported from Saudi Arabia but soon spread across the Arabian Peninsula [50], [51]. Several cases were also reported in Asia, Europe, and Africa [52]. The transmission of MERS-CoV reportedly occurs via human-to-human as well as dromedary camel-to-human. However, the cases of camel-to-human infection are comparatively less [53]. Infected people initially exhibit symptoms such as fever, headache, cough, myalgia, etc. However, the disease might progress in severe cases and cause pneumonia, ARDS, septic shock as well as multi-organ failure which can be fatal. Besides, cases of asymptomatic MERS-CoV infection have also been reported [44].

The recently identified novel coronavirus SARS-CoV-2 belongs to the genera β-coronavirus of the Coronaviridae family [54]. It reportedly shares 96% and 79.6% sequence identity to the bat CoVRaTG13 and SARS-CoV, respectively [8].

3.2. Origin and Structural Features:

The coronaviruses (CoVs) are single, positive-strand RNA viruses. Their genome is approximately 26-32 kb in length [44]. They belong to the coronaviridae family of the order nidovirales and are categorized into the genera – alpha (α), beta (β), gamma (γ), and delta (δ) coronavirus [54]. The α- and β-CoVs include both human and animal CoVs. The HCoVs such as 229E, NL63 belong to α-CoV while the OC43, HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2 belong to the β-CoVs. The γ- and δ-CoVs primarily consists of avian coronaviruses.45

The viral genome of CoV encodes four important structural proteins. They are - the envelope (E), spike (S), membrane (M), and nucleocapsid (N) proteins [54]. The E, S, and M proteins are anchored in the lipid bilayer of the viral envelope [55] The M protein is approximately 25-30 kDa and gives shape to the virus. The E protein is approximately 8-12 kDa and promotes viral release. Together, the M and E proteins are associated with the viral assembly. Furthermore, they also facilitate the maturation of viral envelopes [56]. The N protein is involved in the formation of the nucleocapsid. It binds with the viral genome and plays an essential role in viral packaging [55]. The S protein (class I fusion protein) is approximately 150 kDa. It is responsible for the characteristic spike-like protrusions on the virus. It comprises S1 and S2 subunits and undergoes cleavage by furin-like protease in the host. The S1 subunit contains a receptor-binding domain (RBD). It binds to the host receptor angiotensin-converting enzyme 2 (ACE2). The S2 subunit of the viral S protein then fuses with the cell membrane of the host. This facilitates viral entry into the host cells [56], [57], [58].

3.3. Mechanism of SARS-CoV-2 entry in cells:

Till now, the mechanism of SARS-COV-2 infection is not completely elucidated. Several studies are being conducted globally on SARS-COV-2 to unravel the mechanism of infection and pathogenesis of the novel coronavirus. The β-CoVs - SARS-CoV and SARS-CoV-2 are

substantially identical and are considered to infect humans similarly. The S protein contributes substantially to the attachment and fusion of the virus with the host cell. The RBD of the S1 subunit of the viral S protein binds to the host cell receptor which initiates the viral infection.

Studies have reported that SARS-CoV and SARS-CoV-2 utilize the same human ACE2 (hACE2) receptor to attach themselves to the host cells [8]. The ACE2 receptor is significantly expressed in the type II alveolar, oral mucosal, and nasal epithelial cells [59], [60], [61]. The respiratory airways, cornea, heart, kidneys, etc., also express the ACE2 receptor [59]. These organs are highly vulnerable and most affected in COVID-19 [62].

A recent study reported that SARS-CoV-2 has a greater affinity to the hACE2 receptor than SARS-CoV. They further stated that structural alterations in the ACE2-binding ridge of SARS-CoV-2 RBD are responsible for the high affinity towards the hACE2 receptor [63]. The enzyme furin cleaves the SARS-CoV-2 S protein at the S1/S2 site and exposes the S2 subunit which mediates the fusion of viral and host membranes [58], [64]. This cleavage is responsible for the pre-activation of the S protein which promotes the subsequent type II transmembrane serine protease (TMPRSS2)-dependent viral entry into host cells [64]. The TMPRSS2 is considered significant for the entry of SARS-CoV in the host cell. A broader expression of TMPRSS2 is reported in the nasal cavity, lungs, colon, gall bladder, kidney, prostate, pancreas, heart, etc. Further, the nasal epithelial cells are enriched with TMPRSS2 as well as the ACE2 receptor [59]. The TMPRSS2 primes the ACE2 receptor-bound viral S protein leading to a conformational change [64], [65]. This conformational change activates S protein and facilitates the viral entry into the host cells. Moreover, it also clears the ACE2 receptor [58].

A study reported that TMPRSS2 is expressed specifically in $ACE2^{+}$ cell types. Further, they also stated that the expression of proteases such as cathepsin B (Cat B) was observed in >70–90% of

ACE2^{+} cells. Altogether, their findings implied that SARS-CoV-2 might also utilize alternative pathways for entry [59]. Similar findings were also reported in another *in vitro* study which demonstrated that SARS-CoV-2 is dependent on both Cathepsin B/L (CatB/L) and TMPRSS2 for priming and entry into the host cell. Their study showed that inhibition of any one of these proteases leads to partial inhibition of viral entry. This suggested that in the absence of TMPRSS2, the virus may utilize CatB/L for its entry and vice-versa [66].

Following the entry, SARS-CoV-2 liberates its genomic material (mRNA) in the cytoplasm. It takes over the protein synthesis machinery in the host and translates the mRNA in the nucleus. Besides, it also utilizes the machinery to synthesize viral proteins and subsequently initiates viral replication [58]. (Figure: 2)

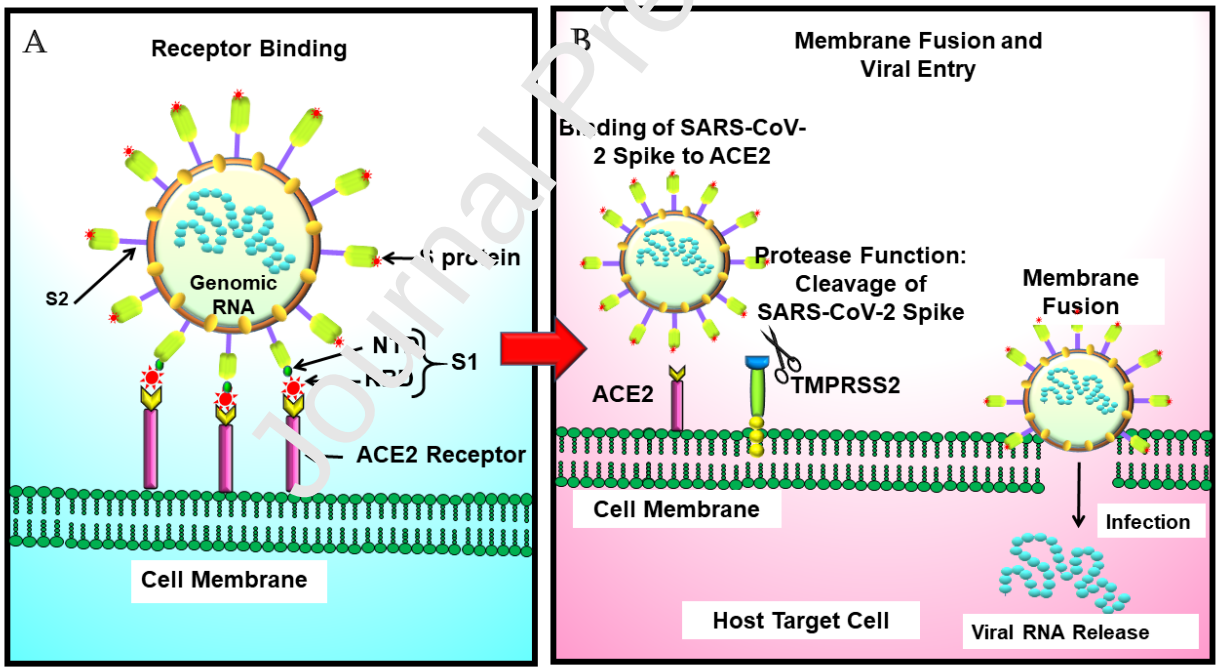

Figure 2: Mechanism of SARS-CoV-2 entry in cells. A. Binding of SARS-CoV-2 spike to the host ACE2 receptor. B. Cleavage of SARS-CoV-2 spike by TMPRSS2, membrane fusion, infection, and viral RNA release into the host cell.

Abbreviations: ACE2: Angiotensin converting enzyme-2, NTD: N-terminal domain, RBD: Receptor binding domain, S protein: Spike protein, SARS-CoV-2: Severe Acute Respiratory Coronavirus-2

4. Cytokine Storm in COVID-19:

Accumulating pieces of evidence suggest that viral infection instigates an exaggerated or hyperactive immune response in the host leading to a "cytokine storm". The novel coronavirus infection elicits a similar response in the host. This often involves the interplay of various chemokines, colony-stimulating factors, interferons, interleukins as well as tumor necrosis factor-α (TNF-α). The cytokine storm is correlated to the severity of the infection and often causes extensive damage or injury. Furthermore, it is also considered as a leading cause of ARDS, multi-organ failure, etc. which are closely associated with the severity and progression of COVID-19. Moreover, the cytokine storm and associated complications are the major cause of death in COVID-19 patients [10], [67], [68].

Several studies have investigated the clinical characteristics of the cytokine storm in COVID-19 patients [69], [70], [71].

In the extremely severe patients, elevated levels of IL-2R, IL-6 as well as IL-10 are also observed. Moreover, a gradual reduction in the absolute count of $CD4^+$ T, $CD8^+$ T, and B cells is also observed as the severity of the disease progresses. These findings suggest that there is a correlation between immune response and severity of COVID-19 progression [72], [73].

A study conducted on 43 COVID-19 patients showed that elevated IL-6 levels were observed in severe cases and thus correlated to the severity of the disease [74]. A retrospective multicenter study investigated the deceased and discharged COVID-19 cases. The study reported that

elevated IL-6 was observed in the deceased cases. Further, the cause of mortality in the deceased group was primarily due to respiratory failure (53%) [75].

A recent study was conducted to investigate the clinical features in deceased COVID-19 patients. The study showed that a majority of deceased patients were associated with comorbidities like hypertension and cardiac anomalies. Further, the majority presented with complications such as ARDS, respiratory failure, sepsis, acute cardiac injury, heart failure, etc. Moreover, the concentrations of the IL-2 receptor, IL-6, IL-8, IL-10, and TNF-α were also found to be elevated [76].

A retrospective analysis of COVID-19 patients with pneumonia demonstrated an increased expression of serum IL-6. Furthermore, a decrease in the CD3, CD4, Natural Killer (NK), and CD8 cells were also observed [71]. Cytokine profiling of the peripheral blood sample obtained from severe patients revealed an increase in the levels of the interleukins (IL) like IL-6, IL-10, IL-2, and Interferon-γ (IFN-γ). Besides, it was also observed that the lymphocyte and T cell (especially $CD8^+$ T) counts were substantially decreased while the neutrophil counts were increased [70]. Another study also showed increased levels of IL-2, IL-7, IL-10, and TNF-α. Further, it reported similar trends for Granulocyte colony-stimulating factor (GCSF), C-X-C motif chemokine 10 (CXCL10), Monocyte chemoattractant protein (MCP)-1, and Macrophage Inflammatory Protein (MIP)-1 Alpha [69].

Transcriptomic profiling of cytokines in SARS-CoV-2 infected patients have revealed elevated levels of cytokines MCP-1, CXCL10, MIP-1A, and MIP-1B [77].

Increased CXCL10, IL-6, IL-8, MCP-1, RANTES (regulated on activation, normal T cell expressed and secreted), and TNF-α was also observed in severe COVID-19 patients [78].

The diabetic COVID-19 patients showed substantially increased leukocyte and neutrophil count. Further, the elevated level of IL- 2 receptors, IL-6, IL-8, and TNF- α was also observed [79]. Altogether, the aforementioned findings indicated a pivotal role of cytokine storm in COVID-19 patients. Therefore, targeting the cytokine storm might help in attenuating the severity of disease progression.

5. Molecular Pathways Linked to Inflammation:

Inflammation is a vital cellular process or an immune response to injury, tissue damage, or infection in the body which assists in upholding the tissue homeostasis under traumatic or stressed conditions and regulate the host defense mechanism against pathogens [80]. The key molecular mediators of inflammation include inflammatory cytokines such as TNF-α; chemokines; inflammatory enzymes such as cyclooxygenase (cox)-1, and -2; matrix metalloproteinase (MMP)-9, 5-lipooxygenase (5-LOX); transcription factors such as signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa-B (NF-κB); ILs, for example, IL-1, -6, and -8. The most important mediator of inflammation is the ubiquitous expression of NF-κB transcription factor which play an essential role in the modulation of a wide array of genes encoding cell adhesion molecules, cytokines, and its receptors which helps in triggering inflammation [14], [81], [82], [83], [84]. NF-κB is a heterotrimer comprising of three subunits namely p65, p50, and an inhibitory subunit IκBα. It is mainly present in the cytoplasm, and upon activation by different inflammatory stimuli, various carcinogens, radiations such as UV-light, γ-rays, and x-rays; several free radicals, cytokines, etc. translocates into the nucleus. After translocation into the nucleus, the activated NF-κB can bind to different promoter regions of several genes and activate around 400 genes which play an important role in inflammation and various other chronic diseases [85], [86], [87], [88]. NF-κB activation can regulate the various

hallmarks of cancer such as cancer cell proliferation, survival, angiogenesis, invasion, migration, and metastasis. They also take part in instigating chemoresistance and radiation resistance. The expression of several inflammatory mediators, for instance, cox-2, inducible nitric oxide synthase (iNOS), TNF-α, and ILs are regulated through NF-KB [82], [88], [89]. TNF-α is the most potent pro-inflammatory cytokine discovered so far. Overexpression of this cytokine can ultimately lead to inflammation and various other chronic diseases, including cancer through the regulation of the NF-κB pathway [88], [90], [91]. Hence, the TNF-α blockers possess immense potential to control inflammation, and the overall global market for TNF-α blockers was valued at US$ 43.39 billion in 2017 and expected to reach US$ 121.13 billion by 2026 [81], [90], [92]. The macrophages mainly release a group of cytokines known as interleukins, for example, IL-1β, IL-6, and IL-8 which play crucial roles in inducing an inflammatory response. It is now well evinced that the augmentation of expression of iNOS, cox-2, and abnormal expression of IL-1, -6 and -8 and TNF-α have been observed in case of oxidative stress that ultimately leads to inflammation [14], [81], [93]. IL-6 is an NF-κB-dependent cytokine that controls the activation of STAT3. STAT3, a transcriptional factor, is activated through Janus-activated kinase (JAK) 1, 2, and 3 which causes tyrosine phosphorylation, homodimerization, nuclear translocation of STAT3 where it binds to the DNA and is responsible for the induction of numerous inflammatory and immune responses. Moreover, several other transcription factors such as nuclear factor erythroid 2–related factor 2 (Nrf2), activator protein-1 (AP-1), nuclear factor of activated T cells (NFAT), and hypoxia-inducible factor-1α (HIF-1α) are also regulated through various inflammatory cytokines which play a pivotal role in controlling the cellular stress responses [14], [93], [94], [95]. The mitogen-activated protein kinase (MAPK) pathway can act as a molecular target for the prevention and treatment of different inflammatory diseases. The

MAPK family consists of mainly three types of stress-activated protein kinase pathways viz. extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK) can regulate the IL-5 level and other cytokines during inflammation [14], [96].

6. Available Repurposed Drugs against COVID-19:

The molecular pathogenesis of SARS-CoV-2 is not completely known and studies are conducted globally to investigate novel drugs and targets. However, at present, there are no available drugs or vaccines to treat COVID-19 specifically. Although, many studies are currently ongoing to develop and test antiviral drugs and vaccines against the causative virus SARS-CoV-2 in preclinical and clinical settings; these vaccines or novel drugs might be unavailable until 2021 [45]. In the absence of novel antiviral drugs, "repurposed drugs" are often prescribed for the treatment of COVID-19 based on the symptoms [97]. Some of the repurposed drugs that are currently used or suggested against SARS-CoV-2 as well as COVID-19 associated cytokine storms and complications are mentioned in Table: 1.

Table 1: Repurposed drugs against the novel coronavirus (SARS-CoV-2)

Drug	Molecular target/Mechanism of action	Company	Reference
Acalabrutinib	Can potentially exert anti-viral and anti-inflammatory effects; BTK inhibitor	-	[98]
Amphotericin B	Blocks the interaction of SARS-CoV-2 S-protein with hACE-2 receptor	-	[99]
Anakinra	IL-1 inhibitor; Neutralizes SARS-CoV-2	Swedish Orphan	[97], [100]

	related hyperinflammation	Biovitrum	
Arbidol	Inhibit membrane fusion; Prevents the viral entry	-	[101]
Atorvastatin	Attenuates NF-κB activation; Decreases hazard for death	-	[102]
Azithromycin	Mechanism unknown; commonly used as adjunct with hydroxychloroquine	-	[97]
Baricitinib	JAK1 and JAK2 inhibtor, Can potentially inhibit SARS-CoV-2 entry		[103]
Bemcentinib	Can potentially reduce viral infection and blocks SARS-CoV-2 spike protein	BerGenBio ASA, Norway	[97]
Bromhexine	Transmembrane protease serine inhibitor	-	[104]
Camostat mesilate	Inhibits serine protease	-	[66], [105]
Chloroquine	Changes the pH of endosomes; prevents viral entry, transport and post-entry events	-	[106]
Cefuroxime	Inhibits the viral RNA-dependent RNA Polymerase	-	[107]
Ciclesonide	Exerts anti-viral and anti-inflammatory effects; Treated pneumonia and lung injury	-	[108]
Ciprofloxacin	Binds to SARS-CoV-2 Mpro; Inhibits viral replication	-	[109]
Clarithromycin	Exerts anti-viral activity; Inhibits protein	-	[110]

	synthesis by binding to the 50S ribosomal subunit		
Daclatasvir	Inhibits SARS-CoV-2 replication *in vitro*; Prevents the induction of pro-inflammatory cytokines	-	[111]
Darunavir/ cobicistat	HIV protease inhibitor	-	[112]
Dasatinib	Inhibits SARS-CoV-2 3CL protease		[99]
Dexamethasone	Reduces inflammation, modulates immune system	-	[113]
Disulfiram	Inhibits 3CL protease	-	[114]
Doxycycline	Decreases pro-inflammatory cytokines like IL-6, TNF-α; Inhibits SARS-CoV-2 papain-like protease, MMPs, Protects against lung injury	-	[115]
Ergotamine	Blocks the interaction of SARS-CoV-2 S-protein with human ACE-2 receptor	-	[99]
Favipiravir	Inhibits the viral RNA-dependent RNA Polymerase	Toyama Chemical, Japan	[116],[117]
Galidesivir	Binds to the viral RNA-dependent RNA polymerase	-	[118]
HCQ	Alters the pH of endosomes; prevents viral entry, transport and post-entry events	-	[106]

Imatinib	Suppresses THE NF-κB signaling pathway; Stimulates PGE2; Decreases the release of TNF-α, IL1-β and IL-6	-	[119]
Indomethacin	Blocks viral RNA synthesis	-	[120]
Interferron γ/β	Inhibits viral replication (SARS-CoV)	-	[121]
Ivermectin	Inhibits IMPα/β1-mediated nuclear import of viral proteins	-	[122]
Lactoferrin	Exerts immunomodulatory and anti-inflammatory effects; Reduces IL-6 and TNF-α; Inhibits viral entry by binding to the host cell surface HSPGs; Inhibits the SARS-CoV-2 invasion		[123]
Lopinavir/ Ritonavir	HIV protease inhibitor	-	[97]
Losarton	Blocks AT1R	-	[124]
MEDI3506	Can potentially treat respiratory failure caused by COVID, IL-33 inhibitor	-	[98]
Metformin	May induce activation of AMPK which may casuse phosphorylation of ACE2 receptor, thus interfering with viral entry; Inhibition of mTOR pathway and prevention of immune hyperactivation interference with viral endocytic cycle	-	[125],[126]

Methylpred-nisolone	Inhibits inflammatory cascade	-	[127]
Moxifloxacin	Binds to SARS-CoV-2 Mpro; Inhibits viral replication	-	[109]
Nafamostat mesylate	Inhibits TMPRSS2; Prevents viral and host membrane fusion	-	[128]
Niclosamide	Inhibits viral replication (SARS-CoV, MERS-CoV)	-	[129]
Nitazoxanide	Supresses inflammation; Antiviral effects	-	[97],[130]
Pirfenidone	Inhibits IL-1β and IL-4	-	[131]
Povidone-Iodine	Exerts virucidal activity	-	[132]
Remdesivir	Inhibits the viral RNA-dependent RNA polymerase	Gilead Sciences, USA	[133]
Ribavarin	Binds to the viral RNA-dependent RNA polymerase	-	[118]
Rivaroxaban	Inhibits SARS-CoV-2 3CL protease	-	[99]
Sacubitril/ Valsartan	Can potentially reduce pro-inflammatory cytokines and neutrophil count; Increases lymphocyte count; reduces hs-CRP levels	-	[134]
Sarilumab	Blocks IL-6 receptor	Regeneron Pharma-ceuticals and Sanofi	[97]
Saquinavir	Inhibits SARS-CoV-2 3CL protease	-	[99]
Setrobuvir	Binds to the viral RNA-dependent RNA	-	[107]

	polymerase		
Sildenafil	Inhibits SARS-CoV-2 3CL protease	-	[99]
Siltuximab	IL-6 blocker	-	[135]
Sirolimus	Modulates PI3K/AKT/mTOR pathway and inhibits MERS-CoV activity	-	[97]
Sofosbuvir	Binds to the viral RNA-dependent RNA polymerase	-	[118]
Tacrolimus (FK506)	Inhibits replication and growth of the SARS-CoV, HCoV-NL63 and HCoV-229E		[136]
Tadalafil	Inhibits SARS-CoV-2 3CL protease	-	[99]
Telmisartan	Blocks AT1R	-	[124]
Tenofovir	Binds to the viral RNA-dependent RNA Polymerase	-	[118]
Thymosin α1	Restores T cell exhaustion; Recovers the immune reconstitution via promoting thymus output	-	[137]
Tocilizumab	Inhibits the IL- 6 receptor	Roche and Chugai Pharmaceutical	[97]
Vancomycin	Blocks interaction of the SARS-CoV-2 S-protein with hACE-2 receptor	-	[99]
Zilucoplan	C5 inhibitor; can potentially block the severe inflammatory response in COVID-19	-	[98]
α-ketoamides	Binds to SARS-CoV-2 main protease (Mpro)	-	[138]

Abbreviations:

AKT: Protein kinase B; AT1R: Angiotensin receptor 1, BTK: Bruton tyrosine kinase, CoV: Coronavirus, COVID-19: coronavirus disease-19, hACE-2: Human angiotensin-Converting Enzyme-2, HCoV: Human coronavirus, HCQ: Hydroxy-chloroquine, HIV: Human immunodeficiency virus; hs-CRP: high sensitivity C-reactive protein IL: Interleukin, IMPα/β1: JAK: Janus Kinase, MERS- CoV: Middle East respiratory syndrome coronavirus, MMP: Matrix metalloproteiniases, Mpro: Main protease, mTOR: mammalian target of rapamycin, NF-κB: Nuclear factor kappa B, PGE2: Prostaglandin E_2, PI3K: Phosphoinositide 3-kinases, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, TNF-α: Tumor necrosis factor-α, 3CL: 3C-like protease

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Among the available repurposed therapeutic drugs currently used against SARS-CoV-2, the most commonly prescribed drugs are anti-viral. Several antiviral drugs previously tested against Ebola, HIV, Influenza, etc., are currently being investigated to evaluate their efficacy and safety against SARS-CoV-2 [139], [140], [141]. These antiviral drugs are used commonly to treat infected patients, in combination or alone [142].

6.1. Arbidol:

Arbidol is an indole-derivative anti-viral drug commonly used against influenza. Besides, it also exerts inhibition against viruses such as hepatitis B and C, chikungunya, reovirus, Hantaan, etc.[143] Arbidol efficiently inhibits SARS-CoV-2 infection in Vero E6 cells by effectively blocking the entry as well as post-entry stages of the virus.141 A study conducted molecular

dynamics simulation and structure-based studies to analyze the exact target of arbidol on SARS-CoV-2 and determine the associated mechanism. The study revealed that arbidol binds to the S2 domain of S protein on SARS-CoV-2 and thereby interferes with the trimerization, which is essential for the adhesion and fusion with the host cell membrane [101]. Further, SARS-CoV-2 infected hospitalized patients treated with arbidol (0.4g, three times per day for 9 days) exhibited improvement in the discharge rate as well as a reduction in the mortality rate as compared to the untreated patients. The patients were administered 0.4g of arbidol three times daily for 9 days (median duration) [144]. However, a retrospective study stated that Umifenovir does not improve the outcome of COVID-19 patients [145].

6.2. Chloroquine and Hydroxychloroquine:

Chloroquine is a well-known anti-malarial drug. It is also used against lupus erythematosus and rheumatoid arthritis (RA). The hydroxylated form of Chloroquine i.e, Hydroxychloroquine (HCQ) exhibits similar properties [97]. Chloroquine is also reported to possess antiviral activity. Various studies have reported its antiviral activity against human immunodeficiency deficiency virus (HIV)-1, hepatitis A virus, herpes simplex virus type 1, etc. HCQ exerts antiviral activity against HIV-1 [139], [140].

Chloroquine inhibits the viral infection by elevating the endosomal pH essential for viral-host cell fusion. It also interrupts the glycosylation of the SARS-CoV receptors [106]. Previously, Chloroquine was also reported to exhibit effective antiviral activity against the human coronaviruses strain OC43 (HCoV-OC43) *in vivo* [147]. It is also reported to be effective against the novel coronavirus infection in Vero E6 cells [106].

An *in vitro* study demonstrated that Hydroxychloroquine (HCQ) and Azithromycin (AZM) exert synergistic effects against SARS-CoV-2 [148]. A retrospective study reported that early

treatment of SARS-CoV-2 infected patients with HCQ and AZM resulted in low mortality rates [149]. Further, an open-label non-randomized clinical trial reported that HCQ caused a decline in the viral load in COVID-19 patients. Additionally, it was found that AZM further reinforced its effect but the mechanism by which the two drugs act is unknown [150], [151]. WHO has discontinued the HCQ arm for its Solidarity Trial as it induced little or no decrease in mortality [152]. HCQ has been associated with cardiac abnormalities like QT prolongation and AZM might enhance the risk [151].

6.3. Favipiravir:

Favipiravir (T705) is an anti-influenza drug, manufactured by Toyama Chemical, Japan. It inhibits the viral RNA-dependent RNA polymerase [117]. An open-label, non-randomized, control study reported that the treatment of infected patients with a combination of favipiravir and IFN-α checks the disease progression and results in faster viral clearance as compared to Lopinavir/Ritonavir. Favipiravir was administered orally for 14 days (1600mg twice on day 1 followed by 600mg, twice, daily for the remaining days) while IFN-α was administered via aerosol inhalation (5,000,000 U twice, daily) [116].

6.4. Lopinavir/Ritonavir:

Lopinavir a protease inhibitor prescribed for the treatment of HIV. The oral bioavailability of lopinavir is considerably poor; therefore it is often prescribed in combination with ritonavir which boosts its exposure. It also inhibits the enzymes which metabolize lopinavir and further enhances its antiviral effect [97]. A recent *in vitro* study reported that lopinavir exhibits antiviral effects against HCoVs such as 229E, SARS-CoV, and MERS-CoV [153]. It is also reported to be effective against SARS-CoV-2 *in vitro* [154]. WHO recently discontinued the Lopinavir/Ritonavir arm for its WHO-led Solidarity Trial conducted for the treatment of

COVID-19 hospitalized patients. This was done as the drug exerted little or no decrease in mortality [152].

6.5. Remdesivir:

Remdesivir (GS-5734) is a nucleoside analog of adenosine, manufactured by Gilead Sciences. It is a broad-spectrum antiviral drug that inhibits the viral RNA-dependent polymerase and thus, interferes with viral replication [133], [140]. It had been previously tested against the Ebola virus [155]. An *in vitro* study has also demonstrated its antiviral activity against viruses of the *Paramyxoviridae*, *Pneumoviridae* as well as *Filoviridae* families [156]. Remdesivir also shows promising results against SARS-CoV and MERS-CoV infection in human airway epithelial cells [157]. Therefore, various studies are conducted to investigate its efficacy against the novel coronavirus infection in both preclinical and clinical settings. An *in vitro* study demonstrated that Remdesivir is efficacious against novel coronavirus infection [106]. The synergistic inhibitory effect of Remdesivir with emetine (a protein synthesis inhibitor) against SARS-CoV-2 is also observed *in vitro* [154]. Furthermore, Remdesivir also induced substantial clinical improvement, when administered during the early stages of SARS-CoV-2 infection, in the rhesus macaque model.158 A study reported the compassionate use of Remdesivir against COVID-19 in SARS-CoV-2 infected patients. 36 out of 53 patients intravenously treated with Remdesivir (200 mg of on day 1 followed by 100 mg for 9 days) showed clinical improvement [159].

A cohort study on severe COVID-19 hospitalized patients revealed that the treatment with Oseltamivir or Ganciclovir lowered the risk of death [160]. Antiviral drugs such as Oseltamivir, Lopinavir, Ritonavir, Ganciclovir have been used commonly to treat infected patients, in combination or alone [142].

6.6. Others:

The aforementioned antiviral drugs are some of the most actively prescribed and studied repurposed drugs. However, apart from this, several other drugs are currently being tested in pre-clinical and clinical settings. Some of these drugs are anti-helminthic, corticoids, immunomodulators, protease inhibitors, anti-fibrotic, anti-inflammatory, etc. These drugs have shown effectiveness either in the hospitalized COVID-19 patients or against SARS-CoV-2 *in vitro/in vivo/in silico*. Moreover, some of these drugs are hypothesized to target COVID-19 associated complications such as hyper inflammation (cytokine storm), pneumonia, ARDS, etc. [97].

Ivermectin and niclosamide are potent anti-helminthic drugs [97]. A study demonstrated that ivermectin also shows antiviral activity against SARS-CoV-2 *in vitro* [122]. Previously, Niclosamide had been shown effective against SARS-CoV, MERS-CoV, Ebola virus, rhinovirus, etc. Therefore, this broad-spectrum anti-helminthic drug might be quite promising in inhibiting SARS-CoV-2 [129].

Glucocorticosteroids show anti-inflammatory effects and effectively inhibits the cytokine levels. Therefore, they might be used to combat the cytokine storm in COVID-19 patients. Dexamethasone is a synthetic glucocorticoid that has shown promising results against COVID-19. A recent study investigated the short-term treatment with dexamethasone in SARS-CoV-2 patients with hypoxic respiratory failure. The study reported that dexamethasone was well-tolerated and may help in attenuation of the hyper-inflammatory phase [113]. Methylprednisolone is an anti-inflammatory and anti-fibrotic drug [97]. It efficiently inhibits the inflammatory response. Further, methylprednisolone might also be associated with an improved outcome as well as lung function in COVID-19 patients [127]. Although these corticosteroids show effective results, their usage for the treatment of COVID-19-associated pneumonia remains

controversial. As their continuous administration can suppress the immune system, it is necessary to determine the appropriate dose as well as the rationale for its usage [97], [127].

The interleukin-6 inhibitors Tocilizumab, Sarilumab, and Siltuximab are hypothesized to be effective against COVID-19 patients. These IL-6 receptors antagonists are also tested against SARS-CoV-2 in both clinical and preclinical studies [97], [135]. Early treatment with Tocilizumab reportedly improves the clinical outcome as well as causes a decline in mortality in COVID-19 pneumonia patients [161]. A recent study investigated the effectiveness of Tocilizumab for the treatment of mechanically ventilated COVID-19 patients. It was observed that Tocilizumab was associated with a low death rate [162]. A study in severe COVID-19 pneumonia patients showed that treatment with Sarilumab exhibited promising results [163].

IL-1 promotes pro-inflammatory cytokines such as IL-6 and contributes significantly to cytokine storm. Anakinra, an IL-1 receptor antagonist, blocks both IL-1 α and IL-β. It is therefore believed to be highly effective in combating COVID-19 associated cytokine storm [164]. The Ana-COVID study has shown that it reduces SARS-CoV-2 associated hyper inflammation [100].

Baricitinib is a JAK 1 and JAK 2 inhibitor [103]. A study showed that it improved the respiratory function in COVID-19 patients who failed to respond completely to sarilumab [165]. Further, Baricitinib reportedly decreases the SARS-CoV-2 viral load pneumonia as well as the COVID-19-associated mortality rate [103]

Bromhexine hydrochloride is a mucolytic cough suppressant that also acts as a TMPRSS2 inhibitor. As TMPRSS2 is responsible for the SARS-CoV-2 entry in the host cell, bromhexine might be effective in inhibiting the virus [104], [166], [167]. Nafamostat mesylate inhibited MERS-CoV infection by acting as a TMPRSS2 inhibitor. A study reported that it also efficiently inhibits the SARS-CoV-2 infection *in vitro.* Further, it blocked the viral S protein-mediated

fusion [128]. Camostat mesylate (also known as camostat mesilate) is a serine protease inhibitor. *In vitro* studies have shown that camostat mesylate can prevent SARS-CoV-2 infection by inhibiting the TMPRSS2 activity. Therefore, camostat mesylate might prove promising in the treatment pf COVID-19 patients [66], [105].

Several studies have shown that the administration of the anti-diabetic drug metformin in diabetic COVID-19 patients is associated with a decrease in mortality [168], [169], [170], [171]. A limited study has been conducted on Metformin in association with COVID-19 *in vitro* and therefore, the exact mechanism of action is unknown. However, a few possible mechanisms of action have been reported [125], [126].

Darunavir is a potent HIV protease inhibitor [112]. Cobicistat is an effective booster that enhances the pharmacokinetics of the anti-retroviral drugs and is hence often co-administered with darunavir [172]. A pilot study (NCT04252274) showed that Darunavir/cobicistat in COVID-19 patients is well-tolerated. However, it did not show any significant improvement as compared to the control group [172]. The aforementioned findings aligned with another *in vitro* study which showed that Darunavir/cobicistat is ineffective against SARS-CoV-2 *in vitro* [112].

Indomethacin, a cox inhibitor, has been reported to exhibit anti-viral effect activity against canine CoV (CCoV) as well as SARS-CoV. It inhibits viral RNA synthesis *in vitro* [120]. A recent study has shown that Indomethacin is also effective against the SARS-CoV-2 *in vitro* as well as CCoV *in vivo* [174].

Doxycycline, an antibacterial drug, reduces the pro-inflammatory cytokines such as IL-6 and TNF-α. This anti-inflammatory property of Doxycycline might repress cytokine storm and prove essential in preventing lung damage associated with COVID-19. Further, a computational study

revealed that Doxycycline might inhibit SARS-CoV-2 papain-like protease and thereby prevent the infection [115], [175].

A retrospective study conducted on severe COVID-19 patients showed that the administration of thymosin-α1supplement substantially decreased the mortality of severe COVID-19 patients. Further, it also induced the reversion of exhausted T cells [137].

Ciclesonide, an inhaled steroid, effectively inhibits SARS-CoV-2 infection *in vitro*. It inhibits the infection by interacting with the viral non-structural protein 13 (NSP13) [176]. A study reported three cases where ciclesonide, an inhaled steroid, attenuated COVID-19 associated pneumonia [108].

Imatinib is an Abelson (Abl) kinase inhibitor and a potent anti-cancer drug. It also modulates immune response and exerts anti-inflammatory effects. Further, it also exhibits anti-viral effects against SARS-CoV and MERS-CoV. Therefore, it is believed that Imatinib might also be effective against SARS-CoV-2 and have an immunomodulatory effect against COVID-19 pneumonia [119], [177]. Lactoferrin exerts immunomodulatory and anti-inflammatory properties. Therefore, it has been proposed lactoferrin might be used with other drugs as an adjunct to treat COVID-19 [123]. Povidone-Iodine also exhibits potent virucidal activity against SARS-CoV-2 [132]. The drug Tacrolimus (FK506) has been previously tested effective in inhibiting the replication of HCoVs such as SARS-CoV, NL63, and 229E. Therefore, it is proposed that it might be inhibitory against SARS-CoV-2 [136]. Pirfenidone is an anti-fibrotic drug which is used to treat idiopathic pulmonary fibrosis. Further, this drug inhibits IL-1β as well as IL-4 and thus exerts an anti-inflammatory effect, which might be effective in combating cytokine storm [131]. It also modulates the angiotensin II type 1 receptor/p38 MAPK/renin-angiotensin system (AT1R/p38 MAPK/RAS axis) [178]. Therefore, it has been hypothesized that

Pirfenidone might be useful in combating COVID-19 associated cytokine storm as well as lung fibrosis [131].

Sirolimus (rapamycin) is a commonly used immunosuppressant. It exerts inhibition on the mammalian target of rapamycin (mTOR) kinase.[97], [125] A study showed that sirolimus inhibits MERS-CoV infection effectively [179]. A Phase II clinical study is initiated to investigate if sirolimus is associated with the improvement of outcomes in COVID-19 patients placebo (NCT04341675) [180]

Atorvastatin treatment was also reported to be related to a reduction in the progress to death in COVID-19 patients [102].

Another study showed that the administration of Chloroquine and Clarithromycin in a COVID-19 patient with pneumonia improved the outcome [110].

The ACCORD study (EudraCT 2020-001136-95) is initiated to investigate the efficacy of drugs such as Bemcentinib, MEDI3506, Acalabrutinib, Zilucoplan, and Nebulised heparin in COVID-19 patients [98]. A study hypothesised that blocking the AT1R might be beneficial to COVID-19 patients. Losartan and Telmisartan effectively blocks the AT1R and might be useful against SARS-CoV-2 [124].

Sacubitril/valsartan is an angiotensin receptor-neprilysin inhibitor [181]. Further, it has anti-inflammatory activity and hence decreases the pro-inflammatory cytokines. It has been suggested that Sacubitril/valsartan can be used for the treatment of COVID-19 patients [134].

An *in silico* study shows that Disulfiram inhibits the 3CLpro enzyme. This property of disulfiram may be further tested in clinical and preclinical studies for further validation [114]. Molecular docking and simulation study also revealed that α-ketoamides, Ciprofloxacin, and Moxifloxacin bind to SARS-CoV-2 main protease (Mpro) *in silico* which might be effective in inhibiting the

SARS-CoV-2 infection [109], [138]. The drugs Setrobuvir and Cefuroxime effectively bind to the SARS-CoV-2 RdRp *in silico* and hence can be used for treatment against the virus [107]. Similar findings were observed for Ribavirin, Sofosbuvir, Galidesivir, and Tenofovir [119]. Another *in silico* study reported that Rivaroxaban, Saquinavir, Tadalafil, Sildenafil, Dasatinib inhibits the SARS-CoV-2 3CL protease. Further, it showed that Ergotamine, Amphotericin B, Vancomycin blocks interaction of SARS-CoV-2 S-protein with the ACE2 receptor *in silico* [99]. IFN-β and IFN-γ exert synergistic inhibitory effects on SARS-CoV replication [121]. Nitazoxanide is reported to inhibit inflammation. Apart from this, it also exerts antiviral activity against SARS-CoV, MERS-CoV, and influenza virus *in vitro* [130].

Daclatasvir inhibits SARS-CoV-2 *in vitro* by inhibiting the viral replication. Further, it also prevented the production of pro-inflammatory cytokines [111].

Various studies have also suggested that compounds derived from natural products can also be effective in treatment against COVID-19. A recent molecular docking study evaluated the binding potential of various phytochemicals to the non-structural protein 15 (Nsp15) which is associated with viral replication. The study reported that ajmalicine, alpha terpinyl acetate, curcumin, gingerol, novobiocin, piperine, rosmarinic acid, silymarin, and aranotin, sarsasapogenin, and ursolic acid exhibited binding with the Nsp15 protein. Therefore, these phytochemicals might effectively inhibit viral replication and their efficacy should be evaluated in pre-clinical as well as clinical studies [182]. Another study conducted molecular docking simulations between functional foods and SARS-CoV-2 Mpro. It reported that quercetrin exhibited inhibition against SARS-CoV-2 Mpro *in silico* [183]. Curcumin also demonstrated a high binding free energy for the enzymes Cat K, COVID-19 Mpro, and SARS-CoV 3 C-like protease [184].

The natural compounds such as andrographolide, berberine, curcumin, mangiferin, nimbin, piperine, thebaine, and withaferin A exhibited a binding affinity for the ACE2 receptor and SARS-CoV-2 S protein. Further, the compounds gallic acid, luteolin, naringenin, quercetin, resveratrol, and zingiberene showed an affinity to only the ACE2 receptor. These compounds might inhibit the attachment of the SARS-CoV-2 virus to the host cell [185]. (Figure: 3)

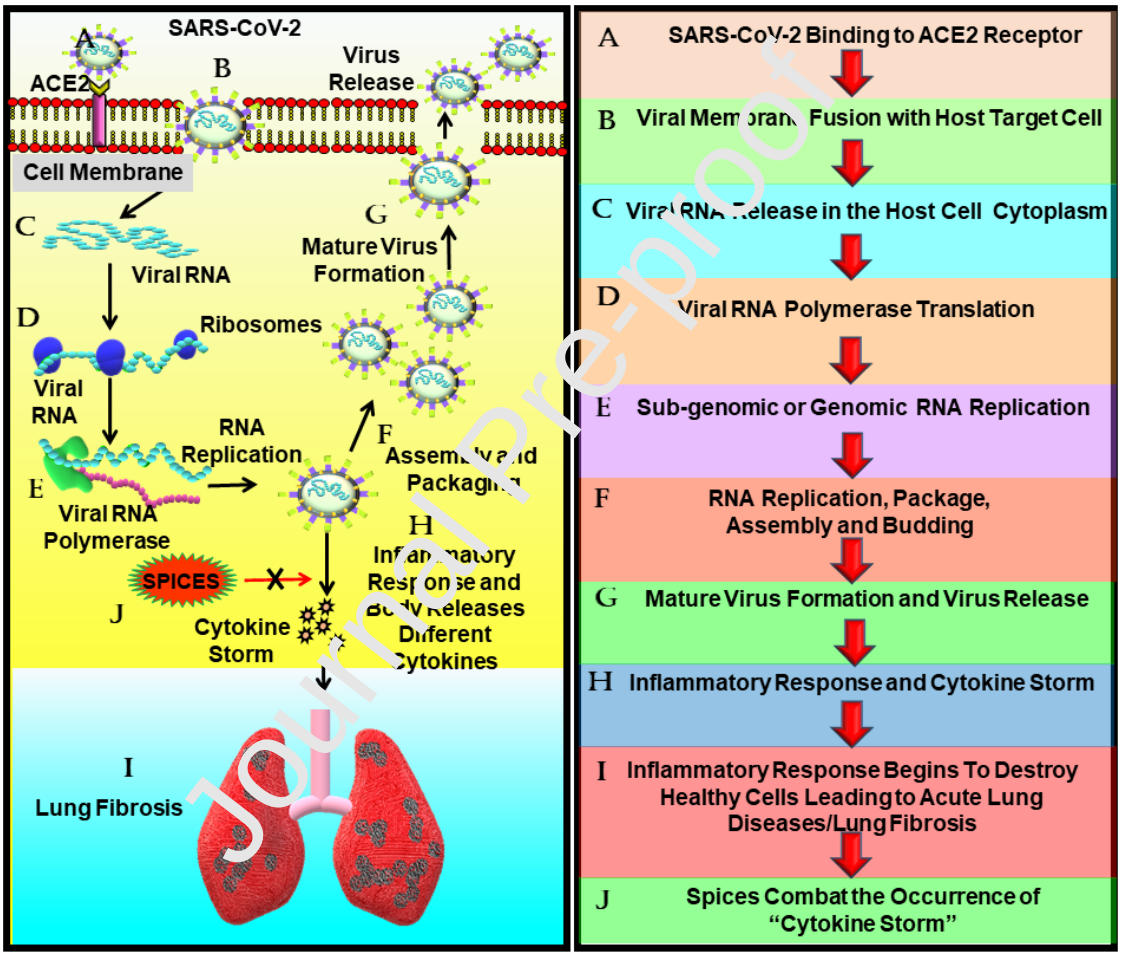

Figure 3: The potential of spices in suppressing SARS-CoV-2 cytokine storm-induced lung fibrosis. The binding of SARS-CoV-2 to the ACE2 receptor causes the fusion of the viral membrane and the target cell which eventually leads to the release of the viral RNA in the cytoplasm of the host cell. Following its release, the virus utilizes the host machinery to synthesize viral proteins and subsequently initiates viral replication, which is followed by

packaging and assembly of the viral particles. The mature virus thus formed and released illicits aggravated inflammatory response or cytokine storm in the host which causes ARDS or lung fibrosis in severe cases. As spices are potent anti-inflammatory agents, they might prove effective in combating the SARS-CoV-2 induced cytokine storm and thus might be beneficial in preventing cytokine storm-induced complications such as ARDS or lung fibrosis.

Abbreviations: ACE2: Angiotensin converting enzyme-2, SARS-CoV-2: Severe Acute Respiratory Coronavirus-2

7. Anti-Inflammatory Role of Spices :

Mother Nature has bestowed us with various promising medicinal plants as well as plant-based products such as fruits, vegetables, herbs, and spices that are abundantly consumed [186], [187], [188], [189], [190], [191], [192], [193], [194]. Apart from their high nutritional value, these are also rich in therapeutic properties [189], [193], [195], [196], [197], [198], [199], [200].

Various phytochemical and natural compounds obtained from different parts of plants have been a part of traditional medicine for ages and consumed for their health benefits as well as efficacy against a plethora of diseases [201], [202], [203], [204], [205], [206], [2017, [208], [209], [210], [211], [212], [213], [214], [215].

The leaves of the plants which are utilized for culinary purposes and consumed fresh are known as herbs. Spices, on the other hand, are consumed as dried parts of a plant. It can be a bud, root, seed, bark, berries, or even stigma of a flower [14], [186], [216]. In addition to their usage in culinary purposes for imparting flavor and taste to food, they are also beneficial to health. Spices and herbs, as well as their active components, have been used in various traditional medicines since time immemorial. They effectively act against many diseases such as arthritis, asthma, cancer, diabetes, etc. [217], [218], [219], [220]. In severe cases of COVID-19,

cytokine storm is commonly observed and is majorly responsible for the degradation of health conditions [10]. As spices and herbs exhibit potent anti-inflammatory activities, they could be used to combat the elevated levels in COVID-19 associated cases and boost immunity with minimal or no side-effects [14]. Some of the spices, as well as their anti-inflammatory roles, are mentioned below and in Table: 2. (Figure: 4)

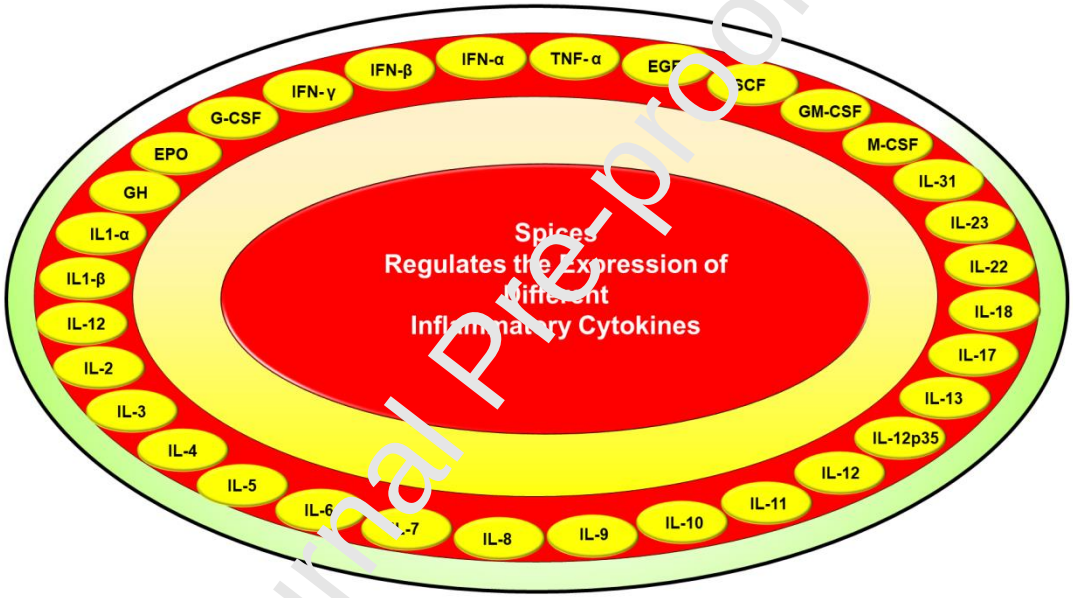

Figure 4: Spices regulates the expression of different inflammatory cytokines.

Abbreviations: EPO: Erythropoetin, EGF: Epidermal growth factor, IL- Interleukin, IFN: Interferon, G-CSF: Granulocyte colony-stimulating factor, SCF: Stem cell factor, M-CSF: Macrophage colony-stimulating factor GM-CSF: Granulocyte-macrophage colony-stimulating factor

Table 2: Anti-inflammatory role of spices

Spices	Active compound /Form of use	Disease	*in vitro/ in vivo*	Model	Mechanism	References
Asafetida *(Ferula asafetida* L.*)*	-[A]	Liver cancer	*in vitro*	HepG2, SK-Hep1	↓ NF-κB, ↓ TGF-β1, ↑ caspase-3, ↑ TNF-α	[221]
	-[B]	Breast cancer	*in vivo*	BALB/c mice	↓ LOX	[222]
	-	Breast cancer	*in vivo*	SD rats	↓ cyt-P450, ↓ cyt b5, ↑ catalase, ↑ GSH, ↑ GST, ↑ SOD, ↓ TBARS, ↑ DT-diaphorase	[223]
	-[B]	-	*in vivo*	Albino mice	↓ LOX	[224]
Basil *(Ocimum sanctum)*	-[C]	Asthma	*in vivo*	Wistar rats	↓ IL-4, ↓ IgE, ↓ PLA_2, ↓ TP, ↑ IFN-γ/IL-4 ratio	[225]
	-[C]	Gastric ulcer	*in vivo*	Swiss albino CD1 mice	↓ TBARS, ↓ NO, ↓ H_2O_2, ↑ GSH, ↑ GPx, ↑ GST, ↑ catalase, ↑ GR, ↓ TNF-α, ↓ IL-6, ↑ PGE2, ↑ IL-4	[226]
Bay leaves *(Laurus nobilis)*	-[C]	-	*in vitro*	BMDMs	↓ p-IκB, ↓ p-STAT3, ↓ pro- IL- 1β, ↓ procaspase- 1, ↓ IL- 1β, ↓ caspase- 1, ↓ NLRP3 inflammasome, ↓ NF- κB signaling, ↓ mRNA expression of IL- 6, TNF- α, and iNOS	[227]
	-[C]	ALI	*in vivo*	C57BL/6 mice	↓ MPO activity, ↓ IL- 1β, ↓ IL- 6, ↓ TNF- α	[227]

	1,8- Cineole	-	*in vitro*	BMDMs	↓ IL- 1β, ↓ caspase- 1, ↓ Activation of NF- κB and STAT, ↓ mRNA expression of IL- 6, TNF- α, and iNOS	[227]
Black cumin (*Nigella Sativa*)	-[C]	Lung inflammation	*in vivo*	Wistar rats	↓ TGF-β1, ↓ IFN-γ, ↓ PGE2, ↑ IL-4, ↑ catalase, ↑ SOD, ↓ MDA, ↑ thiol	[228]
	-[A]	Low-grade inflammation	*in vitro*	THP-1 cells	↓ IL-1β, ↓ MCP-1, ↓ gene expression of DNMT3A and HDAC1	[229]
	-[C]	Diabetes	*in vivo*	Wistar rats	↓ mRNA expression of VCAM-1 and LOX-1, ↑ mRNA expression of eNOS,	[230]
	-[C]	-	*in vivo*	Wistar rats	↓ MDA, ↓ NO, ↓ IL-6, ↑ thiol, ↑ SOD, ↑ catalase, ↓ AST, ↓ ALT, ↓ ALP, ↑ serum protein, ↑ albumin	[231]
	-[A]	Allergic asthma	*in vivo*	Wistar rats	↓ IL-4, ↓ NO	[232]
	TQ	AD	*in vivo*	SD rats	↓ TLR-2, ↓ TLR-4, ↓ TNF-α, ↓ MyD88, ↓ IL-1β, ↓ IRF-3, ↓ NF-κB	[233]
Black Pepper *(Piper nigrum)*	-[C]	Asthma	*in vivo*	BALB/c mice	↓ IL-1β, ↓ TNF-α, ↓ IL-4, ↓ RORγt, ↓IgE, ↓ IL-17A	[234]
	-[C]	AR	*in vivo*	BALB/c mice	↓ E-cadherin, ↑ HO-1, ↑ Nrf2	[235]
	-[C]	AR	*in vivo*	BALB/c mice	↓ p-STAT3, ↓ IL-6, ↓ TNF-α, ↓ NF-κB p65, ↓ IL-1β	[236]
	Pipernigramides	Edema	*in vitro*	RAW 264.7	↓ TNF-α, ↓ IL-1β, ↓ IL-6, ↓ PGE2, ↓ p-IKKβ	[237]

	Pipernigramides	Edema	*in vivo*	ICR mice	↓ NO, ↓ neutrophils infiltration	[237]
	Piperine	Lung metastasis	*in vivo*	C57BL/6 mice	↓ tumor nodule formation, ↑ survival rate, ↓ SA, ↓ GGT	[238]
	Piperine	Bacterial sepsis	*in vitro*	J774A.1, BMDM	↓ IL-1β, ↓ HMGB1, ↓ p-AMPK	[239]
	Piperine	Bacterial sepsis	*in vivo*	C57BL/6 mice	↓ IL-1β release	[239]
	Piperine	AP	*in vitro*	PAC	↓ MPO, ↓ TNF-α, ↓ IL-1β, ↓ IL-6,	[240]
	Piperine	AP	*in vivo*	C57BL/6 mice	↓ p-ERK1/2, ↓ p-p38, ↓ p-JNK	[240]
	Piperine	Lupus nephritis	*in vitro*	HK-2 cell	↓p-AMPK, ↓ IL-1β, ↓ HMGB1, ↓ pro-caspase-1,	[241]
			in vivo	BALB/c mice	↓ NLRP3 inflammasome activitation	[241]
	Chabamide	Inflammation	*in vitro*	RAW264.7	↑ HO-1, ↑ Nrf2, ↓ iNOS	[242]
Capsicum *(Capsicum annum L.)*	-[C]	-	*in vivo*	Wistar rats	↓ ALT, ↓ AST, ↓ ALP, ↓ TNF-α, ↓ IL-6, ↓ LPO , ↓ Cu-Zn-SOD, ↓ GPx, ↑ CAT, ↑ Mn-SOD, ↑ GR, ↑ GSH, ↓ GST, ↑ G6PD, ↓ TG, ↓ CHLS, ↓ LDL, ↓ VLDL, ↑ HDL	[243]
	-[C]	Asthma	*in vivo*	BALB/c mice	↓ IL-4, ↓ IL-5, ↓ IL-13, ↓ NF-κB p65	[244]
	Capsaicin	-	*in vitro*	THP-1	↓ IL-1β, ↓ IL-6, ↓ TNF-α, ↑ LXRα expression	[245]
	Capsaicin	SGI	*in vitro*	HSG	↓ IL-6, ↓ TNF-α	[246]

Cardamom	-[C]	Cardiotoxicity	*in vivo*	Albino rats	↓ NO, ↓ MDA, ↓ NF-κB, ↓ capase-3, ↑ VEGF, ↑ catalase, ↑ SOD, ↑ GPx	[247]
(Elettaria cardamomum)						
Celery seeds	-[A], -[C]	Hyperuricemia	*in vivo*	BALB/c mice	↓ ROS ↑ SOD, ↑ GPx	[248]
(Apium Graveolens)						
	-[C]	Gouty arthritis	*in vivo*	Wistar rats	↓ IL-1β, ↓ IL-6, ↓ TNF-α, ↑ IL-10	[248]
	-[A]	Gouty arthritis	*in vivo*	Wistar rats	↓ IL-1β, ↓ TNF-α, ↑ IL-10	[248]
	Sedanolide	Liver cancer	*in vitro*	J5 cells	↓ PI3K-I, ↓ mTOR, ↓ Akt, ↑ PI3K-III, ↑ LC3-II, , ↑ nuclear p53, ↑ DRAM, ↓ cytosolic p53, ↓ TIGAR, ↑ Beclin-1	[249]
	-[C]	AD	*in vivo*	Hairless mice	↓ IL-4, ↓ TNF-α, ↓ IFN-γ, ↓ IL-6, ↓ TSLP, ↓ IL-31	[250]
	-[C]	AD	*in vitro*	RAW264.7	↓ NO, ↓ IgE	[250]
	Luteolin	AD	*in vitro*	RAW264.7	↓ NO	[250]
	-[C]	-	*in vitro*	RAW264.7	↓ IL-6, ↓ TNF-α, ↓ NF-κB	[251]
Cinnamon	TCA	OA	*in vitro*	SW1353, HPC	↓ mRNA expression of MMP-1, -3 and -13, ↓ mRNA expression of ADAMTS-4 and -5, ↑ p-IκBα, ↓ NF-κB, ↓ IκBα, ↓ p-JNK 1/2, ↓ p-p38	[252]
(Cinnamom sp.)						

	TCA	-	*in vitro*	RAW 264.7	↓ NO, ↓ iNOS	[253]
	TCA	Neuroinflam-mation	*in vitro*	BV2	↓ NO, ↓ iNOS, ↓ cox-2, ↓ IL-1β, ↓ IκBα, ↓ NF-κB	[254]
	-[A]	Skin disease	*in vitro*	HDF3CGF system	↓ MCP-1, ↓ MIG, ↓ IP- 10, ↓ IL-8, ↓ VCAM-1, ↓ M-CSF, ↓ PAI-1, ↓ ICAM-1, ↓ EFGR, ↓ MMP-1, ↓ TIMP-1, ↓ TIMP-2	[255]
	-[C]	Inflammation	*in vitro*	Murine macrophage	↓ mRNA expression of TNF-α, ↓ p-p38, ↓ IκBα degradation, ↓ p-ERK 1/2, ↓ p-JNK	[256]
	-[C]	Inflammation	*in vivo*	BALB/c mice	↓ TNF-α, ↓ IL-6	[256]
	-[C]	Inflammation	*in vitro*	Splenocytes	↑ IL-2, ↓ IL-4, ↓ IFN-γ, ↓ p-ERK1/2, ↓ p-p38, ↓ p-STAT4, ↓ p-JNK	[257]
	-[C]	Inflammation	*in vivo*	BALB/c mice	↓ IL-4	[257]
	BCA, HCA	-	*in vitro*	Murine splenocytes	↓ IFN-γ, ↓ IL-2Rα, ↓ IgM	[258]
	BCA, HCA	-	*in vivo*	BALB/c mice	↓ AFC response	[258]
Coriander *(Coriandrum sativum)*	-[C]	Inflammation	*in vitro*	RAW264.7	↓ pro-IL-1β, ↓ PGE_2, ↓ p-MAPK, ↓ NF-κB p65, ↓ cox-2, ↓ NO, ↓ iNOS	[259]
	-[C]	CD	*in vivo*	ICR mice	↓ IL-1, ↓ IL-4, ↓ IL-13, ↓ TNF-α, ↓ IFN-γ, ↓ IgE, ↑ GSH, ↑ HO-1	[260]

	-[C]	Arthritis	*in vivo*	Wistar rat	↓ IL-1β, ↓ IL-6, ↓ TNF-R1	[261]
Cumin *(Cuminum cyminum)*	-[E]	Hypertension	*in vivo*	SD rats	↓ mRNA expression of IL-6, Bax, and TNF-α, ↑ mRNA of expression TRX1, TRXR1, eNOS, and Bcl-2	[262]
	-[E]	Gastric ulcer	*in vivo*	SD rats	↓ TNF-α, ↓ MDA, ↑ GSH, ↑ catalase, ↑ ATPase activity	[263]
Curry leaves *(Murraya koenigii)*	-[C]	Pancreatic Inflammation	*in vitro*	RAW 264.7	↑ GSH, ↓ MDA, ↓ IL- 1β, ↓ IL- 6, ↓ TNF-α	[264]
		Pancreatic Inflammation	*in vivo*	Swiss albino mice	↓ MDA, ↑ GSH, ↓ IL- 1β, ↓ IL- 6, ↓ TNF-α, ↑ Nrf2, ↓ p65- NFκB activity, ↓ cox-2, ↓ ICAM-1	[264]
	-[C]	Breast cancer	*in vivo*	4T1-inoculated BALB/c mice	↓ NF-kB, ↓ IL-6, ↓ IL-1β, ↓ IL-10, ↓ iNOS ↓ ICAM, ↓ c-myc	[265]
	Mahanimbine	-	*in vivo*	Swiss albino	↓ TNF-α, ↓ IL- 1β, ↓ IL- 6	[266]
	Girinimbine	Peritonitis	*in vivo*	ICR mice	↓ TNF-α, ↓ IL-1β	[267]
Fenugreek *(Trigonella foenum-graecum L.)*	-[E]	IPF	*in vivo*	SD rats	↑ mRNA expression of Nrf2 and Bcl-2, ↓ mRNA expression of HO-1, TNF- α, IL-1β, IL-6, TGF-β, IL-8, NF-κB, Smad-3, collagen-1, ET-1, Bax and caspase-3	[268]
	-[E]	Testicular	*in vivo*	Wistar rats	↓ NF-κB p65, ↓ iNOS,	[269]

		damage				
	-[E]	Diabetes	*in vivo*	Wistar rats	↓ TNF-α, ↓ IL-1β, ↓ VEGF, ↓ PKC-β	[270]
	-[D]	RA	*in vivo*	SD rats	↓ TNF-α, ↓ IL-6, ↓ cox, ↓ LOX	[271]
	Trigonelline	AD	*in vivo*	Wistar rats	↓ TNF-α, ↓ IL-6, ↓ cox-2, ↓ GFAP, ↓ MDA, ↓ LDH, ↓ protein carbonyl, ↑ SOD, ↑ GSH	[272]
Garcinia *(Garcinia indica)*	Garcinol	Colitis	*in vivo*	ICR mice	↓ iNOS, ↓ cox-2, ↓ PCNA	[273]
	Garcinol	Colon cancer	*in vivo*	ICR mice	↓ β-catenin, ↓ VEGF, ↓ cyclin D1, ↓ p-ERK1/2, ↓ p-Akt, ↓ p-p70S6K (Ser371 and Thr389), ↓ p-PI3K	[273]
	Garcinol	HNSCC	*in vitro*	CAL27	↓ STAT3, ↓ c-Src, ↓ JAK1, ↓ JAK2, ↓ NF-κB, ↓ TAK1↓ IKK, ↓ cyclin D1, ↓ Bcl-2, ↓ Bcl-xL, ↓ Mcl-1, ↓ survivin	[274]
	Agegarcinol	HNSCC	*in vivo*	Nude mice	↓ Tumor growth	[274]
Garlic *(Allium sativum)*	-[C]	Asthma	*in vivo*	BALB/c mice	↓ IgE, ↓ IgG1, ↑ IgG2a, ↓ IL-13, ↓ IL-5, ↓ IL-4, ↑ IL-12, ↑ IFN-γ, ↓ TNF-α, ↓ IL-1β, ↓ IL-6	[275]
	-[C]	-	*in vitro*	A549	↓ IL-6/PI3K/Akt/NF-κB pathway	[275]
	DADS	AP	*in vivo*	Swiss albino mice	↓ H2S, ↓ CSE, ↓ MPO, ↓ IκB degradation, ↓ TNF-α, ↓ mRNA expression of PPTA and NK1R	[276]

	DATS	RA	*in vitro*	RA-FLS	↓ IL-8, ↓ IL-1β, ↓ p-p65, ↓ p-NF-κB, ↓ p-IκBα, ↑ IκBα, ↓ c-myc, ↓ β-catenin	[277]
	DATS	RA	*in vivo*	DBA/1J mice	↓ IL-6, ↓ IL-1β, ↓ TNF-α	[277]
	SAC	PF	*in vivo*	C57BL/6 mice	↓ α-SMA, ↓ p-Akt, ↓ p-p65, ↓ mRNA expression of α-SMA, TNF-α, iNOS, IL-6, IL-12p35, and TGF-β	[278]
	SAMC	ALI	*in vivo*	BALB/c mice	↓ MPO, ↓ TNF-α, ↓ IL-1β, ↓ IL-6, ↓ NF-κB, ↓ cox-2, ↓ p-NF-κB p65, ↑ Nrf-2, ↑ HO-1, ↑ GSH, ↑ NQO1, ↑ SOD, ↓ MDA	[279]
Ginger (*Zingiber officinale)*	6-Shogaol	OSCC	*in vivo*	Syrian hamsters	↓ c-jun, ↓ c-fos, ↓ AP-1, ↓ iNOS, ↓ TNF-α, ↓ IL-6, ↓ IL-1, ↓ cox-2, ↓ PCNA, ↓ cyclin D1, ↓ Ki-67	[280]
	6-gingerol	Steatohepatitis	*in vitro*	HepG2	↓ MCP-1, ↓ TNF-α, ↓ IL-6	[281]
	6-gingerol	Steatohepatitis	*in vivo*	C57BL/6 mice	↓ MCP-1, ↓ TNF-α, ↓ IL-6, ↓ IκBα degradation, ↓ NF-κB	[281]
Ginseng (*Panax sp.*)	Isofraxidin	ALI	*in vivo*	ICR mice	↓TNF-α, ↓ IL-1β, ↓ IL-6, ↓ MIP-2, ↓ p-PI3K, ↓ p-AKT	[282]
	-[C]	Lung injury	*in vivo*	Balb/c mice	↓ p38 MAPKs, ↑ Akt	[283]
	PNS	HAND	*in vivo*	SD rats	↓ Bax/Bcl-2 ratio, ↓ caspase-3, 8, and -9	[284]
	PNS	Colitis	*in vivo*	SD rats	↓ M1 macrophages, ↓ PI3K/AKT, ↑ M2 macrophages	[285]

	NR	Renal injury	*in vivo*	Wistar rats	↓ TNFα, ↓ TGF-ß1, ↓ INF-γ, ↓ IL-6,↑ IL-10	[286]
	GRg3	RA	*in vivo*	mice	↑ $CD4^+CD25^+Foxp3^+$Treg cells	[287]
	GRg1	Lung injury	*in vivo*	SD rats	↓ TNF-α, ↓ α-SMA, ↓ Collagen I, ↓ TGF-β1, ↓ IL-6, ↓ TGF-βR1, ↓ p-Smad3	[288]
	GRg1	Lung injury	*in vitro*	MRC5	↓ IL-6, ↓ TNF-α, ↓ α-SMA, ↓ TGF-β1/Smad3	[288]
	Ginsenoside Rd	Ischemic stroke	*in vivo*	SD rats	↓ NF-κB activity, ↓ IκB, ↓ MMP-9	[289]
Long Pepper	PL	Leukemia	*in vitro*	KBM-5	↓ p- p65, ↓ cox-2	[290]
(Piper longum)						
	PL	Myeloma	*in vitro*	U266	↓ IL-6	[290]
	PL	LN	*in vitro*	Splenocytes	↓ IL-6, ↓ IL-17, ↓ IL-23, ↓ TNF-α, ↓ p-STAT3, ↓ p-JAK1	[291]
	PL	LN	*in vivo*	MRL-Fas(lpr) mice	↓ IL-6, ↓ IL-17, ↓ IL-23, ↓ TNF-α, ↓ IgG	[291]
	PL	RA	*in vivo*	DBA/1 mice	↓ TNF-α, ↓ IL-1β, ↓ IL-23, ↓ IL-17	[292]
	PL	Asthma	*in vivo*	C57BL/6 mice	↓ TNF-α, ↓ IL-6, ↓ IL-1β, ↓ IκBα, ↓ ICAM-1, ↓ IgE, ↓ MMP-9, ↓ IL-4, ↓ IL-5, ↓ IL-13	[293]
	PL	Asthma	*in vitro*	Beas-2B	↓ TNF-α, ↓ IL-6, ↓ IL-1β, ↓ ICAM-1, ↓ MCP-1, ↓ IκBα	[293]
	PL	-	*in vitro*	HUVEC	↓ TNF-α, ↓ IL-6, ↓ NF-κB, ↓ p-p38, ↓ ICAM-1, ↓ VCAM-1, ↓ E-Selectin	[294]

	PL	-	*in vivo*	C57BL/6 mice	↓ p-p38, ↓ICAM-1, ↓VCAM-1, ↓E-Selectin	[294]
	PL	Neuro-inflammation	*in vitro*	BV2	↓ PGE2, ↓ NO, ↓ iNOS, ↓ cox-2, ↓TNF-α, ↓IL-6, ↑ IL-10	[295]
	PA	-	*in vitro*	PBMC	↓ IL-1β, ↓ TNF-α, ↓IFN-γ, ↓IL-2	[296]
	PA	-	*in vivo*	BALB/c mice	↓ IFN-γ, ↓IL-2	[296]
	PL	AD	*in vitro*	BV2	↓ cox-2, ↓ iNOS, ↓ NF-κB	[289]
	PL	AD	*in vitro*	Astrocytes	↓ cox-2, ↓ iNOS, ↓ NF-κB	[297]
	PL	AD	*in vivo*	ICR mice	↓ NF-κB, ↓ β-, γ-secretases	[297]
	-[C]	-	*in vitro*	HUVEC	↓ ICAM-1, ↓ VCAM-1, ↓ NF-κB, ↓ ROS	[298]
	PL	Atherosclerosis	*in vitro*	VSMC	↓ NF-κB p65, ↓ p-Akt, ↓ p-ERK1/2, ↓ p-PLC-γ1	[299]
	PL	Atherosclerosis	*in vivo*	ApoE KO mice	↓ NF-κB p65	[299]
	PL	-	*in vitro*	HUVEC	↓ TNF-α, ↓ IL-1β, ↓ TACE, ↓ p-p38, ↓p-JNK, ↓ p-ERK1/2	[300]
	PL	-	*in vivo*	BALB/c mice	↓ EPCR shedding	[300]
	PL	COPD	*in vivo*	BALB/c mice	↑ AnxA1, ↓ cox-2, ↓ NF-κB,	[301]
Mint	-[C]	-	*in vitro*	RAW 246.7	↓ MDA, ↓ NO	[302]
(Mentha sp.)						
	-[C]	-	*in vivo*	SD rats	↓ MDA, ↓ NO, ↓ cox-2, ↓ MAPK signaling	[302]
	-[C]	-	*in vitro*	MH-S	↓ NO, ↓ TNF- α, ↓ IL-1α, ↓ ROS, ↓ p38, ↓ JNK,	[303]

					↓ p-p38, ↓ p-JNK	
Mustard seeds *(Sinapis alba)*	-[C]	Ear edema	*in vivo*	BALB/c mice	↓ MPO activity, ↓ TNF-α, ↓ ILβ, ↓ IL-6, ↓ mRNA expression of TNF-α and IL-6	[304]
	-[E]	Psoriasis-like inflammation	*in vivo*	BALB/c mice	↓ NLRP3, ↓ ASC, ↓ IL-1β, ↓ caspase-1 and 11, ↓ IL-18	[305]
	-[E]	Psoriasis	*in vivo*	BALB/c mice	↑ $CD4^+$/$CD8^+$ T cell ratio, ↑ $CD4^+$ T cells, ↑ GPx, ↓ NF-κB p65, ↓ IFN-α, ↓ IL-17, ↓ IL-22, ↑ SOD, ↑ catalase, ↓ MDA, ↓ iNOS	[306]
Nutmeg *(Myristica fragrans)*	-[C]	Cortical injury	*in vivo*	Wistar rats	↓ TNF-α, ↓ IL-1β, ↓ iNOS, ↑ HO-1, ↑ Bcl-2, ↓ Bax	[307]
	Macelignan	Asthma	*in vivo*	C57BL/6J mice, OT-II mice	↓ IL-4	[308]
	Macelignan	Leukemia	*in vitro*	RBL-2 H3	↓ PGE2, ↓ mRNA expression of cox-2, 5-LOX, TNF-α, IL-4, and IL-13, ↑ GSH	[309]
	Macelignan	Renal I/R injury	*in vivo*	SD rats	↓ IL-6, ↓ TNF-α, ↓ IFN-γ, ↑ catalase, ↑ SOD, ↓ MDA, ↓ Bax, ↓ caspase-3, ↑ Bcl-2	[310]
	Myrislignan	Inflammation	*in vitro*	RAW 264.7	↓ iNOS, ↓ IL-6, ↓ TNF-α, ↓ NF-κB activation, ↓ cox-2	[311]
	Myristicin	Inflammation	*in vitro*	RAW 264.7	↓ NO, ↓ IL-6, ↓ IL-10, ↓ IP-10, ↓ GM-CSF, ↓ LIF, ↓ MCP-1, ↓ MCP-3, ↓ MIP-1α	[312]

Onion *(Allium cepa)*	-[C]	IBD	*in vivo*	BALB/c mice	↓ p-ERK1/2, ↓ p-p38MAPK, ↓ p-Akt, ↓ mTOR, ↓ caspase-3, and -8, ↓ cox-2, ↓ cyt-c, ↓ Bcl-xL, ↓ IFN-γ, ↓ TIMP-1, ↓ MCP-1, ↓ MCP-5, ↓ MIG, ↓ MIP-1α, ↓ MIP-2, ↓ ACE-2, ↓ Bcl-2,	[313]
	-[C]	APH	*in vivo*	Wistar rats	↓ IL-6, ↓ IL-10, ↓ TNF-α	[314]
	Quercetin	Atherosclerosis	*in vitro*	VSMC	↓ IL-1β, ↓ IL-1α, ↓IL-6, ↓TNF-α, ↑ HO-1, ↑ Nrf-2, ↑ SOD1, ↑ SOD2	[315]
	Quercetin	Atherosclerosis	*in vivo*	C57BL/6 mice	↑ SOD, ↑ HO-1, ↑ Nrf-2, ↓ MDA, ↓ p-NF-kB, ↓ TNF-α, ↓ IL-1β, ↓ ROS,	[315]
	QG, QE	Inflammation, Hyperlipidemia	*in vitro*	THP-1	↓ TNF-α, ↓ IL-6, ↓ cox-2, ↓ PGE2	[316]
	QG	Inflammation, Hyperlipidemia	*in vivo*	Wistar rats	↓ IL-6	[316]
Rosmary *(Rosmarinus officinalis L.)*	Rosmarinic acid	Asthma	*in vivo*	Wistar rats	↓ IL-4, ↓ IgE, ↓ IFN-γ, ↓ PLA2, ↓ TP	[317]
	Rosmarinic acid	Asthma	*in vivo*	BALB/c mice	↓ IL-4, ↓ IL-13, ↓ p-JNK/JNK ratio, ↓ p-p38/p38 ratio,↓ p-IκBα, ↓ mRNA expression of Ym2, CCR3 CCL11, AMCase, E-selectin	[318]

Saffron	Crocin	Inflammation	*in vitro*	H9c2	↓ TNF-α, ↓ PGE2, ↓ IL-1β, ↓ IL-6, ↓ mRNA	[319]
(Crocus sativus)					expression of TNF-α, cox-2, IL-1β, IL-6, NO, iNOS	
	Crocin	Osteoporosis	*in vivo*	Wistar rats	↓ IL-6, ↓ TNF-α, ↓ TRAP, ↓ CTXI, ↑ osteocalcin, ↑ ALP	[320]
	Safranal	Colitis	*in vitro*	RAW264.7, BMDM	↓ NO, ↓ iNOS, ↓ cox-2, ↓ IL-6, ↓ TNF-α, ↓ p-ERK, ↓ p-p38, ↓ p-JNK	[321]
	Safranal	Colitis	*in vivo*	BALB/c mice	↓ IL-6, ↓ TNF-α, ↓ p-ERK, ↓ p-JNK, ↓ p-IκBα ↓ p-p38	[321]
	Safranal	AD	*in vivo*	Wistar rats	↓ MDA, ↑ SOD, ↓ AChE, ↓ NF-κB, ↓ TNF-α, ↓ IL-6, ↓ IL-1β, ↓ GFAP, ↓ MPO, ↓ ROS	[322]
	Safranal	Gastric ulcer	*in vivo*	Wistar rats	↑ SOD, ↑ TAC, ↓ MDA, ↓ TNF-α, ↓ caspase-3	[323]
Sesame	Sesamol	Asthma	*in vivo*	BALB/c mice	↑ GSH, ↓ MDA, ↓ ICAM-1	[324]
(Sesamum indicum)						
	Sesamol	Asthma	*in vitro*	BEAS-2B cells	↓ CCL11, ↓ CCL24, ↓ CCL5, ↓ MCP-1, ↓ IL-6, ↓ IL-8, ↓ Eotaxin, ↓ROS	[324]
	Sesamin	ALI	*in vivo*	BALB/c mice	↓ MPO, ↓ TNF-α, ↓ IL-6, ↓ IL-1β ↓ TLR4, ↓ NF-κB	[325]
	Sesamin	Kidney injury	*in vivo*	C57BL/6 mice	↑ GSH, ↓ MDA, ↑ SOD, ↑ Nrf2, ↑ catalase, ↓ IL6, ↓ NF-κB, ↓ TLR4, ↓ cox-2, ↓ TNFα	[326]
`	Sesamin	Depression	*in vivo*	CD-1 mice	↓ iNOS, ↓ cox-2, ↓ TNF-α, ↓ IL-1β	[327]

	-[A]	Asthma	*in vivo*	BALB/c mice	↓ IL-1 β, ↓ IL-6, ↓ NO, ↓ iNOS, ↓ IgE	[328]
Star anise	-[C]	Atherosclerosis	*in vitro*	HASMC	↓ TNF-α, ↓ IL-1β, ↓ NF-κB, ↓ cox, ↓ E-selectin, ↓ ICAM-1, ↓ VCAM-1	[329]
(Illicium verum)	-[C]	Atherosclerosis	*in vivo*	C57BL/6 mice	↓ TNF-α, ↓ IL-1β, ↓ NF-κB, ↓ cox, ↓ E-selectin, ↓ ICAM-1, ↓ VCAM-1, ↓ iNOS	[329]
	-[C]	-	*in vitro*	HaCaT	↓ IFN-γ Rα, ↓ ICAM-1, ↑ SOCS1, ↓ p-JAK2, ↓ p-STAT1	[330]
	Anethole	ALI	*in vivo*	BALB/c mice	↓ MMP-9, ↓TNF-α, ↓ NO, ↑ IκBα, ↓ NF-κB p65	[331]
	-[C], AET	Asthama	*in vitro*	Splenocyte	↓ IL-4, ↑ IFNγ	[332]
	-[C], AET	Asthama	*in vivo*	BALB/c mice	↓ IgE, ↓ IL-4, ↓ IL-5, ↓ IL-13, ↑ mRNA expression of Foxp3,↓ mRNA expression of IL-5, and IL-13	[332]
Tamarind	-[C]	Pulmonary inflammation and fibrosis	*in vivo*	Wistar rats	↓ ROS, ↓ LPO, ↓ PCC, ↓ NF-κB, ↓ p38α MAPK, ↓ NOX4, ↓ cox-2, ↑ HO-1, ↑ SOD2, ↑ catalase, ↑ GST, ↑ GSH, ↑ GPx	[333]
(Tamarindus Indica)	-[C]	Arthritis	*in vivo*	Wistar rats	↓ IL-1β, ↓ IL-6, ↓ IL-23, ↓ TNF-α, ↓ cox-2, ↓ MMP	[334]
	Xyloglucan	Ulcerative colitis	*in vivo*	C57Bl6 mice	↓ IL-1β , ↓ IL-6, ↓ TLR4, ↓ NF-κB	[335]
Turmeric	Curcumin	PIVP	*in vitro*	A549, BMMF	↓ IL6, ↓ TNF-α, ↓ MCP-1, ↓ NF-κB, ↑ IκBα,	[336]
(Curcuma longa)		PIVP	*in vivo*	BALB/c mice	↑ HO-1	[336]

Curcumin	Cystic fibrosis	*in vitro*	16HBE14o	↑ CFTR, ↓ cox-2, ↓ PGE2, ↓ IL-8	[337]
Curcumin	Cystic fibrosis	*in vivo*	SD rats	↑ CFTR , ↓ cox-2, ↓ PGE2, ↓ IL-8	[337]
Curcumin	Diabetes	*in vivo*	SD rats	↓ NF-κB, ↓ TNF-α, ↓ IL-1β, ↓ IL-6 ↓ NO, ↓ PGE2, ↓ cox-2	[338]
Curcumin	ALI	*in vivo*	SD rats	↓ TNF-α, ↓ IL-8, ↓ MIF	[339]
Curcumin	Asthma	*in vivo*	BALB/c mice	↓ NICD1, ↓ Notch 1/2 receptors	[340]
Curcumin	Cerebral I/R injury	*in vivo*	SD rats	↓ IL-1β, ↓ IL-8, ↑ p-JAK2, ↑ p-STAT3	[341]
ATM	Psoriasis	*in vivo*	BALB/c mice	↓ NF-κB, ↓ cox-2, ↓ p-p38 MAPK, ↓ TNF-α, ↓ IL-6, ↓ mRNA synthesis of IL-17, -22, and -23	[342]
MTrPP	Ulcer	*in vivo*	Wistar rats	↓ TNF-α, ↓ IL-8, ↓ NF-κB, ↓ p-p38, ↓ MMP-9, ↓ cox-1 and -2	[343]

[A] = Oil; [B] = Resin; [C] = Extract; [D] = Mucilage; [E] = Seed

Abbreviations:

AA: Arachidonic acid, Ach: Acetylcholine, AChE: Acetylcholinesterase, AD: Alzheimer's disease, ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs, AET: Trans-Anethole, AKT: Protein kinase B, ALI: Acute lung injury, ALP: Alkaline phosphatase, ALT: Alanine aminotrans-ferase, AMCase: Acidic mammalian chitinase, AMPK: Adenosine monophosphate-activated protein kinase, AP: Acute pancreatitis, AP-1: Activator

protein-1, APH: Atypical prostatic hyperplasia, AR: Allergic rhinitis, AST: Aspartate aminotransferase, ATM: Aromatic-turmerone, ATPase: Adenosine triphosphatase, Bax: B-cell lymphoma 2 (Bcl-2)-associated X protein, BCA: 2'-benzoxy-cinnamaldehyde, Bcl-2: B-cell lymphoma 2, CCL: *C-C Motif Chemokine Ligand*, *CCR3: C-C chemokine receptor type 3*, CHLS: total cholesterol, CFTR: *Cystic fibrosis transmembrane conductance regulator*, *COPD: Chronic obstructive pulmonary disease*, *cox*-2: cyclooxygenase-2, CSE: Cystathionine-γ-lyase, CTXI: Collagen cross-linking carboxyterminal telopeptide, type I, DADS: Diallyl disulfide, DATS: Diallyl trisulfide, DNMT3A: DNA methyltransferase 3A, DRAM: Damage-regulated autophagy modulator, EFGR: Epidermal growth factor receptor, eNOS: endothelial nitric oxide, EPCR: Endothelial protein C receptor, ERK: Extracellular signal-regulated kinase, ET-1: endothelin-1, Foxp3: Forkhead Box Protein 3, GFAP: Glial fibrillary acidic protein, GGT: Gamma-glutamyl transpeptidase, GM-CSF: Granulocyte macrophage colony-stimulating factor, GPx: glutathione peroxidase, GR: Glutathione reductase, GRg3: Ginsenoside Rg3, GSH: Glutathione, GSK3β: glycogen synthase kinase 3β, GST: Glutathione S-transferase, G-6P-D: Glucose-6-phosphate dehydrogenase, HAND: Human immunodeficiency virus, HAND: (HIV)- associated neurocognitive disorders, HCA: 2'-hydroxycinnamaldehyde, HDAC1: Histone Deacetylase 1, HDL: High-density lipoprotein, HO-1: Heme oxygenase-1, HMGB1: High mobility group box-1 protein, HNSCC: Squamous cell carcinoma of the head and neck, H_2O_2: Hydrogen peroxide, H_2S: Hydrogen sulfide, ICAM-1- intercellular cell adhesion molecule-1, IFN: Interferon, IFN-γRα: IFN-γ receptor α, IKK: Inhibitor of M kinase, IL: Interleukin, iNOS: Inducible nitric oxide synthase, IBD: Inflammatory bowel disease, IPF : Idiopathic pulmonary fibrosis, IP-10: Interferon-inducible protein 10, IRF-3: Interferon regulatory factor 3, I/R: ischemia-reperfusion, JAK: Janus kinase 2: JNK: c-Jun N-terminal kinase, LC3: Light chain 3, LDH: Lactate dehydrogenase, LDL: Low density lipoprotein, LIF: leukemia inhibitory factor, LN: Lupus nephritis, LOX: Lipoxygenase, LPO: Lipid peroxidation, LXRα: Liver X receptor α, MAPK: Mitogen-activated protein kinase, MDA: Malondialdehyde, MCP: Monocyte chemoattractant protein, M-CSF: Macrophage colony-stimulating factor, MIF: Migration inhibitory factor, MIG: Monokine induced by gamma, MIP: Macrophage inflammatory protein, MMP: matrix metalloproteinases, MPO: Myeloperoxidase, mTOR: mammalian target of rapamycin, MTrPP: Modified pectin polysaccharide from turmeric, MyD88: Myeloid differential factor 88, NAFLD: Non-alcoholic fatty liver disease, NF-κB p65: Nuclear factor-κB p65, NICD: Notch intracellular domain, NK1R: Neurokinin-1-receptor,

NLRP3: Nucleotide oligomerization domain (NOD)-like receptor protein 3, NO: Nitric oxide, NOX4: Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4, NR: Notoginsenoside R1, Nrf2: Nuclear factor erythroid 2-related factor 2, OA: Osteoarthritis, OSCC: Oral squamous cell carcinoma, p: phosphorylated, PA: Piperinic acid, PAI-1: Plasminogen activator inhibitor-1, PCC: Protein carbonyl content, PIVP: Primary influenza viral pneumonia, PI3K: Phosphoinositide 3-kinases, PKC-β: Protein kinase C-β, PCNA: Proliferating cell nuclear antigen, PF: Pulmonary fibrosis, PGE2: prostaglandin E2, PL: Piperlongumine, PLA2: Phospholipase 2, PNS: *Panax notoginseng* saponins, PPTA: Preprotachykinin A, QE: Quercetin-3-O-glucoside, QG: Quercetin-3-O-glucoside, RA: Rheumatoid arthritis, RA-FLS: Rheumatoid arthritis synovial fibroblast, ROS: Reactive oxygen species, RORγt: Retinoic acid-related orphan receptor-γt, SA: serum sialic acid, SAC: S-allyl-L-cysteine, SD: Sprague- Dawley, SGI: Salivary gland inflammation, Smad-3: small mothers against decapentaplegic homolog 3, SMC: S-allyl-mercapto cysteine, SOCS1: Suppressor of cytokine signaling 1, SOD: Superoxide dismutase, STAT: Signal transducer and activator of transcription, STZ: Streptozotocin, TACE: Tumour necrosis factor alpha converting enzyme, TBARS: Thiobarbituric acid reactive substances, TAC: Total anti-oxidant capacity, TAK1: TGF-β-activated kinase 1, TCA: Trans-cinnamaldehyde, TG: Triglyceride, TGF-β : Transforming growth factor-β, TIGAR: Tp53 induced glycolysis and apoptosis regulator, TIMP-1: Tissue inhibitor of metalloproteinase, TLRs: Toll-like receptors, TP: Total protein, TRAP: Tartrate-resistant acid phosphatase, TRX1: Thioredoxin 1, TRXR1: Thioredoxin reductase 1, TSLP: Thymic stromal lymphopoietin, VCAM-1: Vascular cell adhesion protein 1, VEGF: Vascular endothelial growth factor, VLDL: Very low density lipoprotein, α-SMA: α-smooth muscle actin

7.1. **Asafetida** (*Ferula asafetida* Linn.):

It is derived from the roots of the *F. asafetida* (Umbelliferae family). Several studies have reported that asafetida exhibits protective effects against cancer, obesity, hepatotoxicity, etc. [344] It has also been extensively used in traditional medicine for ages for the treatment of whooping cough, asthma, bronchitis, etc. [345] The essential oil extracted from *F. asafetida* induces apoptosis and cytotoxicity against hepatocarcinoma. It modulates the NF-κB and transforming growth factor (TGF)-β pathway by downregulating the expression of NF-κB1 and TGF-β1. Furthermore, it enhances the production of caspase-3 and TNF-α [221] Asafetida exhibits potent antitumor effects against breast cancer in BALB/c nude mice [222] It also enhances the activities of antioxidant enzymes such as catalase, glutathione (GSH), glutathione-s-transferase (GST), superoxide dismutase (SOD), in an N-methyl-N-nitrosourea (MNU)-induced breast cancer in Sprague-Dawley rat [223]. The activity of LOX is reportedly decreased by asafoetida [222], [224].

7.2. **Basil** (*Ocimum sanctum*)

Basil is a popular spice consumed all over the world [346]. It belongs to the Lamiaceae family [347]. Studies have shown that basil possesses medicinal properties such as gastroprotective, anti-oxidant, anti-microbial, etc. [226], [348]. An *in vivo* study has also demonstrated the cardioprotective effects of basil leaves against isoproterenol-induced myocardial infarction in rats [349]. Hydro-ethanolic extract of basil leaf attenuates airway inflammation and exerts immunoprotective effects against asthma in the ovalbumin-sensitized rat model. It decreases the levels of IL-4, IgE, Phospholipase A_2 (PLA_2), and increases the IFN-γ/IL-4 ratio in the bronchoalveolar lavage fluid (BALF) of the rats [225]. Furthermore, the hexane extract of basil (whole plant) modulates the expression of inflammatory markers such as TNF-α, IL-6,

Prostaglandin E-2 (PGE-2), and IL-4. It exerts anti-inflammatory as well as gastroprotective effects against an aspirin-induced-gastric ulcer *in vivo* [226].

7.3. Bay leaf (*Laurus nobilis*):

Bay leaves belong to the family Lauraceae and are commonly used in cuisine for flavoring [227], [350]. The administration of *L. nobilis* leaf extract attenuated the lipopolysaccharide (LPS)-induced mRNA expression of IL- 6, TNF- α, and iNOS. It also inhibited the phosphorylation of IκB and STAT3 *in vitro*. Further, it exerts the inhibition of the Nucleotide oligomerization domain (NOD)-like receptor protein 3 (NLRP3) inflammasome activation via the suppression of apoptosis-associated speck-like protein containing a CARD (ASC) oligomerization. In the BALF of the acute lung injury (ALI) model, the extract reduces the activity of the myeloperoxidase (MPO) enzyme as well as the levels of cytokines such as IL- 1β, IL- 6, and TNF- α. This suggests that bay leaf extract exerts ameliorative effects against ALI [227]. 1,8- Cineole is a bioactive component of *L. nobilis*. Similar to the leaf extract, 1,8- Cineole also downregulates the elevated LPS-induced mRNA expression of IL- 6, TNF- α, and iNOS. It also inhibited the activation of NF- κB and STAT [227]

7.4. Black cumin (*Nigella sativa*):

Black cumin belongs to the family Ranunculaceae. They are consumed as a spice or seasoning predominantly in the Middle Eastern as well as Mediterranean countries [351]. *N. sativa* plant is widely known for its medicinal properties such as anti-diabetic, anti-inflammatory, hepatoprotective, hypotensive, etc. [352]. Cumin effectively ameliorates LPS-induced lung damage as well as inflammation. It downregulates the expression of the inflammatory mediators such as IFN-γ, TGF-β1, and prostaglandin 2 (PGE_2) but upregulates the anti-inflammatory cytokine IL-4. It also exhibits potent antioxidant properties by enhancing the activity of SOD and

catalase [228]. Besides, it attenuates low-grade inflammation *in vitro* by reducing the levels of IL-1 β and MCP-1 [229]. It also reduces the mRNA expression of endothelial nitric oxide synthase (eNOS) in a streptozotocin (STZ)-induced diabetic rat model. However, it increases the mRNA expression of vascular cell adhesion molecule-1 (VCAM-1) and LOX-1 [230]. *N. sativa* demonstrates renal and hepatoprotective effects in LPS-treated rats. Moreover, it also exhibits anti-inflammatory effects by decreasing the levels of cytokine IL-6 as well as NO [231]. Further, it also declines the levels of IL-4 and nitric oxide (NO) in an allergic asthma model in Wistar rats [232]. Thymoquinone (TQ) is one of the major active components of cumin seeds. Studies have shown that TQ exerts an anti-inflammatory effect on Alzheimer's disease (AD) by downregulating the expression of toll-like receptor (TLR)-2 and -4. This leads to a decrease in the production of their downstream effectors NF-κB and Interferon regulatory factor 3 (IRF-3). TQ also significantly reduces the expression of the pro-inflammatory cytokines TNF-α and IL-1β [233].

7.5. **Black pepper** (*Piper nigrum*):

Black pepper from the Piperaceae family is a popular spice due to its dietary importance and beneficial agent for various chronic health ailments [353].

The administration of ethanol extracts of *Piper nigrum* in ovalbumin-induced asthma mice model was observed to decrease IL-4, IL-6, IL-1β, retinoic acid-related orphan receptor gamma t (RORγt), IL-17A, TNF-α, IgE, and increase IL-10, INF-γ. It decreased the state of fibrosis and inflammatory cells infiltration and also regulated the production of cytokines like Th1, Th2, Th17. Further, the extract treatment blocked the allergy through the prevention of degranulation of peritoneal mast cells [234] Further, the effect of fruit extract from *P. nigrum* in allergic rhinitis ovalbumin-induced BALB/c mice model prevented allergic reactions by reducing antibodies,

histamine release by mast cells. It has also decreased E-cadherin and was protective against nasal epithelial barrier impairment through increased Nrf2 leading to elevated heme oxygenase-1 (HO-1) level [235]. Similarly, the extract has also decreased the expression of STAT3, IL-6, IL-1β, TNF-α, and NF-κB p65 [236].

The ethanolic extract containing pipernigramides A-G decreased iNOS-induced NO and levels of IL-1β, IL-6, TNF-α, and PGE_2 in RAW 264.7 cells. It also reduced the degradation of IκB and targets IKK-β that inhibits p65, which leads to decrease inflammation [237]. Further, the treatment of piperine in B16F-10-induced lung metastasis in C57BL/6 mice decreased collagen hydroxyproline in lungs, hexosamine level, uronic acid, serum sialic acid, and gamma-glutamyl transpeptidase, and it increased the lifespan of treated animals [238].

Piperine was showed to be effective against bacterial sepsis by preventing pyroptosis through the reduction of IL-1β and Adenosine monophosphate-activated protein kinase (AMPK) levels, both *in vitro* and *in vivo* [239]. Piperine could reduce the condition of acute pancreatitis through reduction of TNF-α, IL-1β, IL-6, p-ERK1/2, p-p38, p-JNK, and MAPKs expressions [240]. Piperine improved lupus nephritis in HK-2 cells by inhibiting pyroptosis, NLRP3 inflammasome, HMGB1, caspase-1, and activation of AMPK. Similarly, piperine inhibited NLRP3 inflammasome and serum IL-1β in the BALB/c mice model of lupus nephritis [241]. The effect of Chabamide from fruits of Piper nigrum in lipopolysaccharide (LPS)-stimulated RAW264.7 cells produced an anti-inflammatory effect via the Nrf2/HO-1 pathway through the reduction in iNOS and increased Nrf2 and its targets- NAD(P)H: quinone oxidoreductase 1 and γ-glutamyl cysteine synthetase [242].

7.6. **Capsicum** (*Capsicum annum* L.):

Capsicum belongs to the family Solanaceae. It exerts anti-inflammatory effects against ethanol-induced inflammation in rats by reducing the expression of pro-inflammatory cytokines TNF-α and IL-6. Additionally, it also exerts potent hepatoprotective effects by attenuating the elevated levels of malondialdehyde (MDA) in the liver, a marker for lipid peroxidation, as well as enzymes like alanine aminotransferase (ALT), aspartate transaminase (AST) which are the markers for liver damage. Capsicum also restores the abnormal levels of cytosolic Cu-Zn-SOD, mitochondrial Mn-SOD, as well as critical antioxidant enzymes [243]. The extract of capsicum also significantly elevates the expression of Th type 2 cytokines such as IL-4, IL-5, IL-13 in an ovalbumin-induced asthma mouse model [244].

Capsaicin is one of the major active components of capsicum. It is known to possess protective activities against asthma, cancer, diabetes, etc. [14]. It also ameliorates inflammation by reducing the levels of TNF-α, IL-6, and IL-1β. Enhanced expression of liver X receptor α (LXRα) is also regulated by capsaicin via the peroxisome proliferator-activated receptor γ (PPARγ) pathway [245]. Inflammation of the salivary glands is also attenuated by capsaicin. It markedly reduces the mRNA as well as protein expression of TNF-α and IL-6 in HSG cells [246].

7.7. **Cardamom** (*Elettaria cardamomum*):

Cardamom belongs to the Zingiberaceae family. It is commonly referred to as the "queen of spices" [354]. Several studies indicated that cardamom possesses different therapeutic activities such as chemopreventive, anti-diabetic, anti-cancer, gastroprotective, etc. [354], [355]. Treatment with cardamom extract ameliorates oxidative stress by enhancing the levels of antioxidant enzymes. It also attenuates inflammation by downregulating the expression of NF-κB and NO. Further, it also exerts protective effects against doxorubicin-induced cardiotoxicity in rats [247].

7.8. **Celery seeds** (*Apium graveolens*):

Celery seeds belong to the Apiaceae (Umbelliferae) family. It is consumed as a spice and herbal medicine [251]. Preclinical studies conducted on hyperuricemia mice model and monosodium urate-induced gouty arthritis rats reported that the aqueous and oil extracts of celery seeds exhibit anti-inflammatory and anti-oxidant properties. The administration of the extracts reduced the pro-inflammatory cytokines like IL-1β, TNF-α, and enhanced anti-inflammatory IL-10 levels [248]. Sedanolide, celery (*A. graveolens*) seed essential oil, induces autophagy to kill the human hepatocarcinoma cells, due to the reduced phosphatidylinositol-3-kinase (PI3K), mTOR, Protein kinase B (Akt) expression levels in those cells [249]. Another recent study shows that the hydrolyzed celery (*A. graveolens*) extract suppresses the inflammation in the chronic atopic dermatitis mice model. It effectively reduces the pro-inflammatory cytokines like IL-4, TNF-α, IFN-γ, IL-6, IL-31, and IgE as demonstrated from the preclinical experimental models.250 The extract of celery seeds also exerts anti-inflammatory effects by downregulating IL-6, TNF-α, and NF-κB levels [251].

7.9. **Cinnamon** (*Cinnamomum sp.)*

The spice cinnamon is derived from the bark of plants belonging to the family Lauraceae and genus *Cinnamomum* [356]. It is a multipotential medicinal plant that possesses diverse properties such as antiseptic, antifungal, antiviral, anti-inflammatory, immunomodulatory, etc. [357].

Trans-cinnamaldehyde (TCA) is one of the components of Cinnamon. TCA inhibits NF-κB as well as the p38-JNK signaling pathway in the IL-1β-induced osteoarthritis model. Furthermore, it inhibits the activation of NF-κB as well as the degradation of IκB. It also slowed down the progression of osteoarthritis *in vivo* [252]. Suppression of NO due to a decrease in iNOS expression is also observed after TCA treatment in RAW 264.7 cells [253]. The administration

of TCA also suppresses the production of NO in LPS-induced BV2 microglial cells. Furthermore, it also downregulates the expression of iNOS, cox-2, as well as IL-1β and induces NF-κB inactivation [254]. The essential oil extracted from cinnamon also possesses anti-inflammatory properties. A study showed that it downregulates inflammatory biomarkers such as MCP- 1, interferon gamma- induced protein 10 (IP-10), interferon- inducible T- cell alpha chemoattractant (I-TAC) monokine induced by gamma interferon (MIG) as well as IL-8 in a human skin disease model [255]. The water extract of cinnamon (CWE) substantially reduces the secretion of TNF-α and IL-6 in LPS-induced *in vivo* model. In LPS-induced macrophages, the extract did not reduce the secretion of TNF-α; however, a substantial decrease in its mRNA expression was observed. Additionally, it also inhibits IκBα degradation as well as MAP kinase phosphorylation [256]. CWE also significantly decreases the levels of anti-CD3-induced IFN-γ in the serum of mice model. It also decreased the mRNA expression as well as the release of IFN-γ and IL-4 in murine splenocytes. Additionally, CWE increased the secretion of IL-2 in splenocytes [257]. 2´-hydroxycinnamaldehyde (HCA) and 2´-benzoxycinnamaldehyde (BCA) are the derivatives of cinnamaldehyde. HCA and BCA both exhibit an inhibitory effect on the secretion of IgM as well as IFN-γ in murine splenocytes [258].

7.10. Coriander (*Coriandrum sativum*):

Coriander is an annual herb of the Apiaceae family [358]. It is commonly known as coriander, and its different parts are consumed worldwide. In addition to its culinary values, coriander is also often consumed as a traditional medicine against different ailments such as diabetes, cancer, hypertension, etc. [359]. It also possesses different pharmacological activities such as hepatoprotective, antihelminthic, neuroprotective, anti-microbial, etc.[359], [360], [361].

Numerous studies have suggested that extracts prepared from different parts of coriander also induce potent anti-inflammatory effects in both *in vitro* as well as *in vivo* models [259], [260], [261]. A study demonstrated that the ethanolic extract of coriander leaves and stem downregulates the expression of inflammatory mediators, including IL-1β, NO, and cox-2, as well as decreases the production of PGE2 and iNOS. It further inhibits NF-κB activation as well as MAPK signaling in LPS-induced RAW 264.7 cells [259]. It also substantially attenuates the 2,4-dinitrochlorobenzene-induced elevated expression of IL-1, IL-4, IL-13, TNF-α, IFN-γ as well as immunoglobulin E (IgE) in the contact dermatitis *in vivo* model [260]. The hydroalcoholic extract of coriander induces a reduced production of TNF-R1 protein as well as downregulates the levels of the cytokines IL-1β and IL-6 [261].

7.11. **Cumin** (*Cuminum cyminum*):

Cumin belongs to the Apiaceae family. It is commonly used for the treatment of diseases like diabetes, cancer, hypolipidemia, etc. [262]. In the renal hypertension *in vivo* model, the aqueous extract of cumin seeds attenuates inflammation and oxidative stress as well as induces anti-hypertensive effects by modulating the gene expression of IL-6, TNF-α, thioredoxin 1 (TRX1), and eNOS [262]. The methanol extract of cumin also ameliorates inflammation and imparts protection against a diabetes-associated gastric ulcer *in vivo* [263].

7.12. **Curry leaves** (*Murraya koenigii*):

Curry leaves belong to the Rutaceae family. Curry leaves are popularly used in Indian cuisine and have been a part of Indian traditional medicine for centuries due to its versatile medicinal properties [363]. A recent study showed the anti-inflammatory effect of the hydroalcoholic extract of curry leaves *in vitro* and *in vivo*. It reduced the expression of pro-inflammatory cytokines such as TNF-α, IL- 1β, and IL- 6 in LPS-induced macrophages. Similar effects were

observed in the cerulein- induced acute pancreatitis *in vivo* model. Additionally, it also downregulates the activity of p65- NFκB as well as the expression of cox-2 and intercellular adhesion molecule-11 (ICAM- 1) *in vivo* [264]. The aqueous extract reduced the levels of cytokines such as IL-6, IL-1β, and IL-10 in 4T1-inoculated mice. It also downregulated the expression of inflammation regulator NF-kB [265]. Mahanimbine is a carbazole alkaloid found in curry leaves. It attenuated the elevated levels of pro-inflammatory cytokines such as TNF-α, IL- 1β, and IL- 6 in high-fat diet (HFD)-induced mice, thereby exerting a potent anti-inflammatory effect [266]. Girinimbine, another carbazole alkaloid, is also a potent anti-inflammatory agent. It reduced the production of TNF-α and IL- 1β in carrageenan-induced peritonitis [267].

7.13. **Fenugreek** *(Trigonella foenum-graecum* L.):

Fenugreek belongs to the Fabaceae family [364]. It is rich in pharmaceutical and nutritional properties. It possesses different activities such as anti-carcinogenic, anti-inflammatory, anti-diabetic, etc. [365].

Standardized fenugreek seed extract-glycoside base (SFSE-G) exhibits potent anti-inflammatory effects by downregulating the expression of inflammatory mediators, including TNF-α, IL-1β, IL-6, IL-8 in a bleomycin-induced pulmonary fibrosis model. It also inhibits the mRNA expression of the fibrotic markers such as small mothers against decapentaplegic homolog 3 (Smad-3), collagen-I, endothelin-1 (ET-1), etc. eventually leading to amelioration of pulmonary fibrosis *in vivo* [268]. A study has demonstrated that the extract of fenugreek seeds exerts inhibitory effects on cisplatin-induced enhanced expression of iNOS and NF-κB-p65 in testicular tissues of Wistar rats [269]. It also reduces the expression of retinal inflammatory markers such as TNF-α and IL-1β in STZ-induced diabetic rat retina [270]. In RA, expression of the pro-

inflammatory cytokines TNF-α and IL-6 is significantly down-regulated by fenugreek mucilage prepared from fenugreek seeds thereby asserting its anti-inflammatory role [271] The pretreatment of, trigonelline derived from fenugreek exerts neuroprotective effects against amyloid β-induced AD *in vivo*. The mechanism is attributed to a decrease in hippocampal glial fibrillary acidic protein (GFAP) as well as pro-inflammatory cytokines [272]

7.14. **Garcinia** (*Garcinia indica*):

Garcinia is a spice which belongs to the family of Clusiaceae. Its fruit is commonly called kokum and it exhibits various pharmacological effects such as cardioprotective, hepatoprotective, antibacterial, anti-ulcer, anti-arthritis, etc. [366]. Garcinol is a major component of *Garcinia* which possesses medicinal properties such as anti-proliferative, antibacterial, anti-inflammatory, etc. [367]. A study showed that it significantly reduced the expression of inflammatory mediators like iNOS and cox-2 in a dextran sulfate sodium (DSS)-induced colitis mice model. Furthermore, it also prevents DSS/azoxymethane (AOM)-induced colon tumorigenesis by inhibiting the PI3K/Akt/p70S6K, as well as ERK signaling pathways [273]. Garcinol inhibits NF-κB activation in head and neck cancer cells - CAL27. It mediates the inhibition by suppressing TGF-β–activated kinase 1 (TAK1) as well as an inhibitor of IkB kinase (IKK). Further, it also inhibits STAT3 as well as its upstream kinases c-Src, JAK1, and JAK2. Moreover, it exerts anti-tumor effects in nude mice with CAL27 xenografts [274].

7.15. **Garlic** (*Allium sativum*)

Garlic is a bulbous plant belonging to the family Liliaceae. It is commonly used as a spice and flavor additive in many cuisines across the globe. Apart from this, garlic has been used since ancient times in different cultures for its medicinal values [275].

An in vivo study has demonstrated that the aqueous extract of garlic exerts inhibitory effects against *Dermatophagoides pteronyssinus* (Der p)-induced allergic asthma. The study showed that aqueous extract of garlic substantially downregulates the levels of cytokines such as IL-13, IL-5, IL-4 but upregulates the levels of IFN-γ and IL-12 in the BALF of the experimental mice. Moreover, it also decreases the levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 and thereby induces anti-inflammatory effects [275]. The treatment of Der p-stimulated A549 cells with aqueous garlic extract also inhibits inflammation by suppressing the IL-6/PI3K/Akt/NF-κB pathway [275].

Different bioactive components present in garlic are associated with its anti-inflammatory property as well as other pharmacological activities. Diallyl disulfide (DADS) is an organosulfur compound and is one of the key components of garlic. A study has shown that DADS ameliorates cerulein-induced acute pancreatitis *in vivo* by suppressing the substance P/neurokinin 1 receptor (SP/NK1R) signaling as well as the NF-κB pathway [276]. Another organosulfur compound Diallyl trisulfide (DATS) inhibits the NF-κB and Wnt pathway in human fibroblast-like synoviocytes (FLS) obtained from RA patients. Moreover, key inflammatory mediators such as IL-1β, IL-6, and TNF-α are also downregulated by DATS in collagen-induced arthritis (CIA) mouse model [277]. Garlic also contains S-allyl-L-cysteine (SAC), an organosulfur compound [368]. An *in vivo* study revealed that in a bleomycin-induced pulmonary fibrosis model, SAC reduces the mRNA expression of fibrosis markers such as α-smooth muscle actin (α-SMA), fibronectin, collagen-I, and –III. Additionally, it also downregulates the mRNA expression of markers associated with inflammatory responses such as TNF-α, iNOS, IL-6, and IL-12p35. Furthermore, SAC also suppresses the Akt/NF-κB pathway in the *in vivo* model [278]. The bioactive component S-allyl-mercapto cysteine (SAMC) found in garlic also exerts potent anti-

inflammatory, anti-fibrotic, anti-oxidative, as well as anti-metastatic effects [369], [370]. A study demonstrated that SAMC attenuates inflammation by inducing inhibitory effects on pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and suppressing the NF- κB pathway in LPS-induced ALI in mice model [279].

7.16. **Ginger** (*Zingiber officinale*):

Ginger is a widely consumed spice which belongs to the Zingiberaceae family. It is also known for its medicinal properties such as anti-tumor, anti-inflammatory, antioxidant, etc. [14], [280], [371]. Some of the active components of ginger are 6-shogaol, 6-gingerol, 6-paradol, 6-gingerdiol, etc. [14].

An *in vivo* study revealed that 6-shogaol exerts anti-inflammatory effects in 7,12-dimethylbenz[a]anthracene induced oral cancer mice model by modulating the NF-κB pathway. It downregulates the lvels of cytokines such as IL-1, IL-6, and TNF-α [280]. A study demonstrated that 6-gingerol shows protective effects against steatohepatitis in both *in vivo* and *in vitro.* In the HepG2 cells, gingerol reduces the enhanced levels of a pro-inflammatory cytokine such as MCP-1, TNF-α, and IL-6. A similar effect of 6-gingerol was observed in the methionine and choline-deficient (MCD) diet-fed animal model. Besides, the upregulated NF- κB level was also attenuated by 6-gingerol [281].

7.17. **Ginseng** (*Panax sp.*):

Ginseng belongs to the Araliaceae family and is commonly used in herbal therapies. Both its extract and isolated active compounds are reported to show extensive biological properties [372], [373]. For instance, an active compound, Isofraxidin (IFD), isolated from Siberian ginseng, exerted significant anti-inflammatory effects on a mouse model of ALI. The property of the compound was attributed to its ability to reduce the serum levels of various inflammatory

cytokines such as TNF-α, IL-1β, IL-6, and MIP-2. Besides, IFD modulated various inflammatory factors linked to the PI3k/Akt and MAPK signaling pathways [282]. Black ginseng (BG) also displayed efficient activity against lung injury through modulation of AKT and reactive oxygen species (ROS)-induced p38-MAPK signalling [283]. Additionally, saponins isolated from *Panax Ginseng* (PNS) displayed a wide range of efficacy against various diseases. PNS imparted protective roles against human immunodeficiency virus (HIV)-associated neurocognitive disorders (HAND) and DSS-induced colitis via regulating the levels of caspase-3, 8, 9, and PI3K/AKT signaling pathway respectively [284], [285]. Further, Notoginsenoside R1 (NR), isolated from *Panax notoginseng*, imparted protective effects against the rat model of renal ischemia-reperfusion (I/R) injury via downregulation of certain oxidative and inflammatory factors such as TNF-α, TGF-ß1, IFN-γ, and IL-6 [286]. Ginsenoside Rg3 (GRg3) induces anti-inflammatory effects and ameliorates RA *in vivo* via the $CD4^{+}CD25^{+}Foxp3^{+}$Treg cells [287]. *In vitro* and *in vivo* studies evaluating the efficacy of ginsenosides Rg1 and Rg3 reported the anti-inflammatory efficacy of the compounds against chronic obstructive pulmonary disease (COPD). Rg1 significantly suppresses the TGF-β1/Smad3 signaling pathway and Rg3 mitigated neutrophilic inflammation, migration, and the levels of PI3K thus exerting protective effects [288]. Ginsenoside Rd was found to prevent neuroinflammation in the case of ischemic stroke via significantly inhibiting the NF-κB/MMP-9 signaling pathway [289].

7.18. **Long Pepper** (*Piper longum* L.):

The powdered dry fruits of *P.longum* (family Piperaceae), are used as a hot spice and seasoning. The whole plant of this spice is known to yield many biologically important chemicals, for example, alkaloids like piperine and piperlongumine (PL), piperinic acid, etc. It is used to treat numerous inflammation-mediated diseases like cancer, allergy, lupus nephritis, arthritis, asthma,

inflammatory bowel disease, etc. [290], [291], [292], [293]. This is mediated by suppressing the activity of proinflammatory cytokines such as TNF- α and IL-6 and inducing the anti-inflammatory cytokines like IL-10, as depicted in several pre-clinical studies [294], [295], [296]. The compound PL is known to relieve the inflammation- associated neurotoxicity upon the activation of stress-inducing molecules like NO, PGE2, etc. in the cultured LPS-stimulated BV2 cells [295], [297]. The pathogenesis in the vasculature is a crucial step that leads to cardiovascular diseases, atherosclerosis, etc. which is mostly due to the modulation of NF-κB signaling molecules, cox-2, etc. PL is shown to reduce the expression of these inflammation mediators in VSMC (vascular smooth muscle cells) and HUVEC (human umbilical vein endothelial cells) as demonstrated *in vitro* [298], [299]. In the disease-induced mice models of sepsis and asthma, PL and other long pepper extracts prevent the cell-adhesion and migration of leukocytes to sites of inflammation by reducing the expression of cell adhesion molecules like ICAM-1, VCAM-1, etc. [293], [294], [298]. The systemic downregulation of elevated expression levels of MAPK proteins like p38, ERK1/2, JNK by PL is also involved in showing anti-inflammation activity.[294], [299], [300]. In the ovalbumin-induced asthmatic lung tissue of mice and bronchial epithelial cell line Beas-2B, PL alleviates the overactivation of Th2 cytokines IL-4, IL -5, and IL -13 as well as the IgE levels. Besides, PL prevented the airway remodeling in the mice models caused due to extracellular matrix degradation, by reducing expression levels of MMP-9, collagen deposition, elastase, etc. [298], [301] In the collagen-induced arthritis mice model, PL is shown to suppress the expression of TNF- α, IL-1β, IL-23, and IL-17 [292].

7.19. **Mint** (*Mentha sp.*):

Mint. belongs to the genus *Mentha* of the Lamiaceae family. *M. spicata*, *M. pulegium*, and *M. rotundifolia* are some of the species belonging to the mint family. They are commonly consumed

as herbal tea and spice. It is rich in antimicrobial, anti-inflammatory, neuroprotective, cardiovascular, and antitumor properties [374], [375].

A study reported that *Mentha spicata* exerts ameliorative effects against acute and chronic inflammation *in vivo* [376]. *M. arvensis* reduced the levels of MDA and NO in LPS-induced RAW 246.7 cells. It also attenuated the elevated levels of NO which was induced due to immobilization stress in the rat model. Further, it also inhibited the MAPK signaling and inflammatory mediator cox-2. These results suggest that *M. arvensis* might attenuate stress and associated inflammation [302]. The ethyl acetate extract of *M. arvensis* reduced the levels of the cytokines TNFα, and IL-1α. It also modulated the LPS-activation of MAPK. Rosmarinic acid and L-menthone are some of the constituents of *M. arvensis*. It also decreased the LPS- or H2O2-induced ROS levels *in vitro* [303].

7.20. **Mustard** (*Sinapis alba*):

White mustard belongs to the family of Brassicaceae [377]. They are widely consumed as a condiment. The dried mature seed of white mustard is also known as *sinapsis* semen [304]. The extract of *S. alba* efficiently inhibits the mRNA as well as protein expression of inflammatory cytokines such as TNF-α, IL-6, and IL-1β *in vivo*. Further, it also suppresses the activity of MPO, which is a marker for inflammation [304]. Mustard seeds also ameliorate inflammation in psoriasis models. They repress the expression of NLRP3 inflammasome. This further leads to the inhibition of IL-1β and IL-18 induced inflammation [305]. Furthermore, it induces an increased $CD4^+$ T cell count as well as a decrease in the plasmacytoid dendritic cells (pDC) and macrophages. Low levels of pDC results in a decrease in the secretion of IFN-α. The expression of the NF-κB p65 subunit, as well as the IL-17 and IL-22, were significantly inhibited which indicated that mustard seeds further abrogates inflammation. Moreover, the expression of the

antioxidant enzymes such as GSH, glutathione peroxidase (GPx), and SOD are also enhanced by mustard seeds. This results in inhibition of oxidative stress which is further evidenced by a decrease in the lipid peroxidation marker MDA as well as the reactive nitrogen species (RNS) generating iNOS [306].

7.21. **Nutmeg** (*Myristica fragrans*) :

Nutmeg belonging to the Myristicaceae family is a widely consumed spice [378], [379]. Many studies have been conducted to evaluate the potential of its extract and isolated phytochemicals in the treatment and prevention of different diseases. Nutmeg extracts displayed potential anti-inflammatory and antioxidant activity and thus imparted protection against cortical and liver injury *in vivo* [307], [380]. Macelignan, an active compound of *M. fragrans*, was reported to exhibit anti-inflammatory effects *in vivo* in an asthmatic model via significantly reducing the expressions of IL-4 and Th2 cell-specific master transcription factor, GATA3 [308]. The compound was further reported to exert significant anti-allergic and anti-inflammatory effects via modulation of p-AKT, p38-MAPK, and JNK. It also inhibited the expressions of other inflammatory mediators such as cox-2, 5-LOX, IL-4, IL-13, and TNF-α [309]. Moreover, macelignan induces protective effects against renal I/R injury by imparting anti-oxidant activity as well as regulating the inflammatory and apoptotic mediators such as IL-6, TNF-α, IFN-γ and B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax), caspase-3, respectively [310]. Myrislignan, a lignan found in *M. fragrans*, also ameliorates inflammation by inhibiting the activation of the NF-κB pathway as well as the expression of inflammatory mediators such as IL-6, TNF-α, and cox-2 [311]. Myristicin is an aromatic compound isolated from nutmeg. It exerts inhibitory effects on the production of cytokines (such as IL-6, IL-10), chemokines (such as

MCP-1, MCP-3, MIP-1α, MIP-1β) granulocyte-macrophage colony-stimulating factor (GMCSF), and leukemia inhibitory factor (LIF) [312].

7.22. **Onion** *(Allium cepa)*:

Onion belongs to the Liliaceae family. It is consumed widely for its flavor and nutritional value. Moreover, it is also used in traditional medicine for its variety of therapeutic properties such as anti-cancer, cardioprotective, anti-microbial, anti-fungal, anti-viral, etc. [381]. The extract of onion bulb exerted protective effects in the DSS-induced colitis rat model by downregulating MAPK/Akt/mTOR signaling as well as the cox-2 levels. Moreover, pro-inflammatory cytokines and chemokines were also downregulated [313]. The extract of red onion scales decreases the levels of IL-6, IL-10, and TNF-α in atypical prostatic hyperplasia *in vivo* model [314]. Quercetin is a flavonoid found in onion [315]. A recent study demonstrated that it exerted protective effects against high fructose-induced atherosclerosis in mice. The protective effect was attributed to the suppression of ROS, by modulating the expression of SOD, HO-1, Nrf-2, H2O2, O2, and MDA. Quercetin also suppressed inflammation and apoptosis by regulating the NF-κB and PI3K/AKT pathway, respectively. In LPS-induced VMSCs, it down-regulated the cytokines such as IL-1 β, IL-18, TNF- α, and IL-6. Additionally, it also improved LPS-induced atherosclerosis by inhibiting PI3K/AKT-regulated NF-κB [315].

Quercetin-3-O-glucoside and eicosapentaenoic acid ester of quercetin-3-O-glucoside (QE) reduced the levels of TNF-α, IL-6, cox-2, PGE2 *in vitro*. The treatment of QE in hyperlipidemic control rats also decreased the expression of LPS-induced IL-6 [316].

7.23. **Rosemary** (*Rosmarinus officinalis* L.):

Rosemary belongs to the Lamiaceae family. It possesses several therapeutic properties such as hepatoprotective, antifungal, antioxidant, antibacterial, etc. [382].

Rosmarinic acid is one of the major components of rosemary. It is a phenolic compound that possesses anti-inflammatory, hepatoprotective, anti-hyperlipidemic property, etc. [383], [384] A study has shown that rosmarinic acid downregulates the enhanced levels of key inflammatory as well as immunological mediators such as IL-4, IgE, IFN-γ, and PLA2 induced by ovalbumin in asthmatic rats [317]. Another study revealed that it also modulates the MAPK and NF-κB signaling pathways in ovalbumin-induced asthma in mice model [318]

7.24. **Saffron** (*Crocus sativus*):

Saffron belongs to the Iridaceae family. It is known to exert therapeutic effects such as anti-convulsant, anti-depressant, anti-inflammatory, antitumor, etc. [385]. Crocin ameliorates LPS-induced sepsis as well as cardiotoxicity in H9c2 cells. It significantly downregulating the inflammatory mediators TNF-α, PGE2, IL-1β, and IL-6. It also decreases the mRNA expression of cox-2, iNOS, as well as NO [319]. Crocin exerts an osteoprotective effect by inhibiting inflammation in a metabolic syndrome (MeS)-induced osteoporosis model. It exhibits anti-inflammatory activity by reducing the levels of the pro-inflammatory cytokines IL-6 and TNF-α. Furthermore, it suppresses and elevates the levels of markers for bone resorption and bone formation respectively in (MeS)-induced osteoporosis model [320]. Safranal is another major component of saffron. A study shows that safranal inhibits MAPK and NF-κB pathways which lead to a reduction in the expression of pro-inflammatory cytokines such as IL-6 and TNF-α. It also inhibits the expression of iNOS and cox-2 *in vitro*. Furthermore, safranal exhibited similar anti-inflammatory responses in DSS-induced colitis mice [321]. Safranal also partially restored the levels of inflammatory mediators such as IL-1β, IL-6, TNF-α, and NF-κB to normal levels, in

the hippocampus of the amyloid β-induced AD model. It also attenuated cognitive deficits and exhibited anti-oxidant effects in the AD model [322]. In addition to the anti-inflammatory effect, safranal also exhibits potent anti-oxidant and gastro-protective effects [323].

7.25. **Sesame** (*Sesamum indicum)*:

Sesame belongs to the Pedaliaceae family and is rich in medicinal properties such as anti-cancer, hepatoprotective, anti-hypertensive, etc. [386]

Sesamol is an active compound of sesame. A study reported that it decreased the eosinophil infiltration in lungs, Th2 cytokines, and MDA levels in asthmatic BALB/c mice, and BEAS-2B cells. Further, it reduced the levels of eotaxin, ROS, and ICAM-1 (suppressing adherence of monocytic cell), which might attenuate inflammations in the lungs [324]

Sesamin is a lignan isolated from *S. indicum* [387] The administration of sesamin attenuated LPS-induced acute lung injury by reducing the expression of NF-κB, TNF-α, IL-6, and IL-1β. It also inhibited the TLR4 pathway [325]. It also ameliorated renal oxidative stress and inflammation by upregulating antioxidant enzymes such as SOD, GSH, catalase, and downregulating inflammatory mediators such as TNF-α, IL-6, cox-2, respectively.326 Similarly, sesame oil exerted a protective effect against the asthmatic mice model by resulted in reducing the levels of IL-1 β, IL-6, IgE, and iNOS [327].

7.26. **Star anise** (*Illicium verum*):

The spice star anise belongs to the Illiciaceae family.388 It possesses a variety of pharmacological properties such as anti-bacterial, anti-nociceptive, anthelmintic, antiviral, gastroprotective, etc. [389], [390].

The extract of star anise exerted inhibitory effects on key inflammatory biomarkers such as TNF-α, IL-1β, NF-κB, and cox in an apolipoprotein E-knockout ($ApoE^{-/-}$) mice. Similar findings were

observed when TNF-α-stimulated-HASMC cells on the administration of star anise extract [329]. Another study revealed that star anise extract exhibited potent anti-inflammatory effects by substantially reducing the expression of IFN-γ receptor α (IFN-γRα) as well as a suppressor of cytokine signaling 1 (SOCS1) protein in IFN-γ-induced human keratinocytes. Moreover, it also inhibits JAK/STAT signaling and leads to a decreased production of ICAM-1 [330].

Anethole is one of the compounds responsible for the aroma and flavor of star anise. It exerts a potent anti-inflammatory effect by inhibiting the activation of NF-κB. It also substantially reduces the levels of pro-inflammatory mediators such as TNF-α, and IL-6 [331]. Trans-anethole is another major constituent found in star anise. It attenuates the elevated level of cytokines such as IL-4, IL-5, and IL-13, in the asthmatic *in vivo* model. The mRNA expression of forkhead box P3 (Foxp3), a transcription factor involved in the development and function of regulatory T cells, is also downregulated by trans-anethole. Besides, it also modulated the production of IL-4 and IFN-γ *in vitro* [332].

7.27. **Tamarind** (*Tamarindus indica* L.):

Tamarind (family Fabaceae) is one of the highly diverse and ethnopharmacologically valuable plant species known to man. A recent study showed that tamarind seed coat extract (TSCE) possesses an anti-oxidant property that prevents oxidative stress-induced- erythrocyte loss. It is also known to prevent anemia, reduces lipid peroxidation, and regulates glutathione levels [391]. Besides, TSCE attenuates the pulmonary inflammation which is attributed to the reduced levels of inflammation-inducing NF-κB and cox-2 levels as well as oxidative stress-inducers such as nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase 4 (NOX4) and p38α MAPK. It also attenuated pulmonary fibrosis *in vivo* [333]. The seed extract also exerted anti-arthritic effects *in vivo* by modulating the levels of anti-inflammatory mediators such as IL-10, TNF-α,

IL-1β, IL-6, cox-2, and IL-23 [334]. Its fruit extract also possesses anti-inflammatory properties [392]. The mucoadhesive tamarind xyloglucan (TXG) was shown to exert anti-inflammatory effects against ulcerative colitis *in vivo*. TXG inhibits the levels of pro-inflammatory cytokines IL-1β and IL-6 and further attenuates inflammation by inhibiting the TLR4/NF-κB signaling pathway [335].

7.28. **Turmeric** (*Curcuma longa*):

Turmeric from the Zingiberaceae family has been used since ancient times in various traditional medicines. It is profoundly rich in activities such as anti- inflammatory, anti-cancer, anti-atherosclerotic, anti-depressant, anti-diabetic, anti-arthritic, etc. Its potent biological properties can be mostly attributed to one of its active components namely "Curcumin" [393], [394], [395], [396], [397]. Curcumin is enriched in several pharmacological activities such as anti-viral, anti-fungal, anti-cancer, etc, and is therefore rightfully proclaimed to be the "Golden nutraceutical" [14], [394], [398]. Moreover, it is highly efficacious against cancer (breast, cervical, colorectal, ovarian, pancreatic, prostate, etc.), RA, inflammatory bowel disease, psoriasis, neurological diseases, etc. [393], [399], [400], [401], [402], [403].

Congregated evidence from various preclinical and clinical studies has shown the efficacy of curcumin in the prevention and treatment of diverse health ailments [404], [405], [406], [407], [408], [409], [410], [411]. Studies have shown that curcumin helps in regulating the cytokine storm both *in vitro* and *in vivo* in case of influenza virus A (IAV) infection thereby relieving chronic influenza pneumonia and lung injuries associated with these conditions. It attenuated the elevated levels of IL-6, MCP-1, TNF-α as well as inhibited NF-κB, besides inhibiting the replication of IAV. Curcumin also elevated HO-1 which amelioration lung injuries [336]. An *in vivo* study on experimentally induced pulmonary inflammation in a rat model has evidenced that

curcumin significantly upturned the expressions of various inflammatory and fibrotic mediators involved such as Cystic fibrosis transmembrane conductance regulator (CFTR) and cox-2/PGE2/IL-8 [337]. Moreover, the anti-inflammatory and anti-oxidative potential of curcumin helped in relieving lung injury in diabetic rats through the inhibition of NF-κB, NO, PGE2, iNOS and cox-2 [338]. An *in vivo* study also evidenced the efficacy of curcumin against cecal ligature puncture (CLP)-induced lung injury through the suppression of the inflammatory mediators such as TNF-α, IL-8, and MIF [339]. The protective effects of curcumin against asthma were also reported where the compound significantly modulated the Notch1-GATA3 signaling pathway thus inhibiting the inflammation of the airways [340]. Curcumin imparted neuroprotective effects against cerebral I/R injury as well via downregulation of IL-1β and IL-8 besides triggering the JAK2/STAT3 signaling [341]. Apart from curcumin, modified polysaccharides and components of essential oils obtained from *C. longa* were also reported to have diverse biological activities. An important component of the essential oil is aromatic-turmerone (ATM) which is reported to have strong anti-inflammatory and antioxidant properties and thus proved to be useful in the treatment of psoriasis. It significantly inhibited the expressions of NF-κB, cox-2, p-p38 MAPK, TNF-α, and IL-6. ATM further suppressed the mRNA synthesis of IL-17, IL-22, and IL-23 [342]. Furthermore, the anti-inflammatory activity of a modified pectin polysaccharide from turmeric (MTrPP) contributed to its anti-ulcer activity and thus it aided in the treatment of LPS-induced ulcer in a rat model. MTrPP worked through inhibiting the release of inflammatory markers such as TNF-α, IL-8, NF-κB, MMP-9, and cox-1, -2. It also prevented the phosphorylation of p38 thus imparting protective effects [343].

8. Anti-Inflammatory Spices in Clinical Trials

Apart from the aforementioned preclinical studies, the anti-inflammatory activity of many of these spices has been evaluated in clinical trials and these were found to be very efficacious against many diseases. The administration of spices to the patients under study, regulate cytokine storm and several other inflammatory mediators. This leads to an improvement of symptoms as well as treatment of various diseases. Some clinical studies are summarized below and are mentioned in Table: 3.

Table 3: Anti-inflammatory activity of Spices against different diseases in Clinical Trials

Spice	Active compound	Health Issues	Phase	Pts No.	Dosage ranges (mg)/day	Clinical Outcome (Mechanism)	References
Cardamom	-	pre-diabetic subjects	-	80	3000	Significant anti-inflammatory and anti-oxidant effects (↓ hs-CRP, ↓ hs-CRP:IL-6 ratio)	[412]
	-	T2D	-	63	3000	Improvement in clinical symptoms (↓ TG, ↑ Sirt1)	[413
	-	NAFLD	-	87	3000	Improvement in clinical symptoms, safe to use (↑ Sirt1, ↑ irisin)	[414]
Cinnamon	β-caryo-phyllene	*H. pylori* infection	-	66	126	Improvement in clinical symptoms (↓ IL-1β)	[415]

Coriander	-	Erythema	-	40	0.5%[a]	Moderate anti-inflammatory effect	[416]
Garlic	-	Obesity	-	51	3600[b]	Significant anti-inflammatory effect (↓ TNF-α, ↓ IL-6, ↓ LDL)	[417]
	-	OA	-	80	1000	Relieved pain (↓ Resistin)	[418]
Ginger	-	RA	-	70	1500	Improvement in clinical symptoms (↓ gene expression of NFκB, RORγt and T-bet)	[419]
	-	OA	-	120	1000	Significant anti-inflammatory effect (↓ IL-1β, ↓TNF-α)	[420]
	-	TB	-	69	3000	Significant anti-inflammatory and anti-oxidant effect (↓ TNF-α)	[421]
	-	CRC	-	20	2000	Well tolerated and safe (↑ LTB4)	[422]
Ginseng	-	CHD	-	24	1.35/kg[c]	Inhibition of gastrointestinal injury and inflammatory response	[423]

						(↓ IL-6, ↓ LPS, ↓ MDA)	
	-	RA	-	84	-[d]	Improved anti-inflammatory immunity, and analgesic effect (↓ CRP)	[424]
Saffron	-	Asthma	-	80	100	Improvement in clinical symptoms, safe to use (↓ TG, ↓ LDL cholesterol, ↓ basophil, ↓ eosinophil)	[425]
	Crocin	MS	-	40	30	Significant anti-inflammatory and anti-oxidant effects (↓ TNF-α, ↓ IL-17)	[426]
Sesame seed	-	OA	-	50	40000	Significant anti-inflammatory effects, safe to use (↓ IL-6)	[427]
Turmeric	CU	MetS	-	117	1000[e]	Significant anti-inflammatory and anti-oxidant effect, Safe to use (↓ hs-CRP)	[428]

CU	Obesity/ Hypertension	-	90	900[h]	Significant anti-inflammatory effect, improvement in general health, safe to use (↓ CRP, ↓ TNF-α, ↓ IL-6, ↓ sVCAM-1)	[429]
Curcumin	T2D	-	118	1000[e]	Significant anti-inflammatory effects (↓ TNF-α)	[430]
Curcumin	T2D	-	44	1500	Significant anti-inflammatory effect, reduced complications (↓ hs-CRP, ↓ TG)	[431]
-	KOA	-	160	500	Significant anti-inflammatory and anti-oxidant effects, improvement in clinical symptoms (↓ IL-1β)	[432]
-	OA	-	42	1300-1950[f]	Significant anti-inflammatory effects, relieved pain, well tolerated	[433]
Curcumin	RA	-	36	500-1000	Significant anti-inflammatory and analgesic effects,relieved pain, safe	[434]

					to use, well tolerated (↓ CRP)	
-	CKD	-	16	-[g]	Significant anti-inflammatory effects, safe to use, well tolerated (↓ IL-6)	[435]
Curcumin	Hemodyliasis	-	71	1500	Significant anti-inflammatory effects, (↓ hs-CRP, ↓ IL-6, ↓ TNF-α)	[436]
CU	SM-induced CPC	-	89	1500[j]	Significant anti-inflammatory and pulmonoprotective effects, safe to use, well-tolerated (↓ IL-6, ↓ IL-8, ↓ TNF-α, ↓ TGF-β, ↓ hs-CRP,↓ CGRP, ↓ MCP-1)	[437]
Curcumin	COPD	-	39	180[k]	Significant anti-inflammatory effects, safe to use (↓ AT-LDL)	[438]
Curcumin	Migraine	-	74	80[i]	Significant neuromodulatory effects, relieved headache, safe to use	[439]

(↓COX-2/iNOS)

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[a]: Coriander oil; [b]: Aged Garlic Extract; [c]: Shen-fu injection (the major component=extract of *Panax ginseng*); [d]: *Panax notoginseng* Saponins; [e]: Combination with piperine (10 mg/day); [f]: Combination of *H procumbens*, *C longa*, and bromelain (AINAT); [g]: Herbal supplement composed of purified turmeric extract (824 mg), curcuminoids (95%), and *Boswellia serrata* extract (516 mg), 3-acetyl-11-keto-β-boswellic acid (10%); [h]: Combination of bisacurone (400 μg), turmeronol A (80 μg) and turmeronol B (20 μg); [i]: Combination with ω-3 fatty acids (5000mg/day); [j]: Curcumin C3 Complex® capsules containing 500mg curcuminoids plus 5mg bioperine®; [k]: Theracurmin® capsules

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Abbreviations: AGE: Aged Garlic Extract, AT-LDL: α1-antitrypsin-low-density lipoprotein, CGRP: Calcitonin gene related peptide; CHD: Congenital Heart Disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, cox-2: Cyclooxygenase-2, CP/CPPS: chronic prostatitis/ chronic pelvic pain syndrome type III, CPM: Chronic Pulmonary Complications, CRC: Colorectal cancer, CU: Curcuminoids, CVD: Cardiovascular disease, H. pylori: Helicobacter pylori, hs-CRP: High-sensitivity C-reactive protein**,** IL: Interleukin, iNOS= Inducible nitric oxide synthase, KOA: Osteoarthritis of knee, LPS: Lipopolysaccharide, MCP-1: Monocyte chemotactic protein-1, Pts: Patients, SM= Sulfur Mustard; TB: Tuberculosis, TG: Triglycerides, TGFβ: Transforming growth factor-β, TNF: Tumour necrosis factor, LDL: Low density lipoprotein, LTB4: Leukotriene B4, MS: Multiple

sclerosis, NAFLD: Non-alcoholic fatty liver disease, OA: Osteoarthritis, RA: Rheumatoid Arthritis, Sirt1: Sirtuin-1, sVCAM-1= soluble vascular cell adhesion molecule-1 T2D: Type 2 diabetes, WEC: Water extract of *C. longa* L.

8.1. Cardamom:

Clinical studies on cardamom have shown that this spice is effective against metabolic disorders such as diabetes and non-alcoholic fatty liver disease (NAFLD). Randomized double-blind clinical trials evaluating the effects of cardamom on both pre-diabetic and diabetic subjects have reported significant clinical improvements. A dosage of 3 g cardamom supplement daily for 8 weeks regulated the levels of high-sensitivity C-reactive protein (hs-CRP): IL-6 ratio in pre-diabetic, obese subjects thus showing significant anti-inflammatory and anti-oxidant effects. Likewise, in the case of type 2 diabetes (T2D) patients, administration of the same dose of cardamom for 10 weeks regulated the serum levels of triglycerides, insulin, SIRT1 besides improving the glycemic indices [412], [413]. Moreover, the efficacy of this spice was also evaluated against NAFLD where it was found that treatment with 3 g of supplement for 3 months significantly improved the grade of fatty liver in overweight or obese individuals. It further improved the clinical symptoms of the disease by modulating the levels of glucose indices, lipids, and other biomarkers of the disease. Moreover, the administration of cardamom supplement did not show any side effects and thus it was found safe to use [414].

8.2. Cinnamon:

β-caryophyllene, one of the active compounds of cinnamon, was found to be effective against gastrointestinal disease caused due to *Helicobacter pylori* (*H. pylori*) infections. A randomized double-blind placebo-controlled study has reported that administration of 126 mg β-caryophyllene daily for 8 weeks showed significant anti-inflammatory properties via downregulating the level of IL-1β. It further improved conditions of nausea, epigastric pain, and dyspepsia associated with the disease thereby proving that it can stand as a potential therapy against gastrointestinal ailments [415].

8.3. Coriander:

A study evaluating the potency of essential oil from coriander has evidenced that topical administration of a lipolotion (containing 0.5% coriander oil) during UV exposure reduced the risk of UV induced erythema to some extent. The treatment was found to show minimal anti-inflammatory activity and well-tolerated when applied on the skin of healthy volunteers [416].

8.4. Garlic:

Clinical trials investigating the potency of garlic extracts and its supplements against different diseases have reported that the spice showed significant anti-inflammatory and other beneficial properties. Supplementation of 3.6 g aged garlic extracts (AGE) daily was found to diminish the serum levels of TNF-α and IL-6 in obese adults, thus lessening the risk of occurrence of multiple inflammatory chronic diseases associated with obesity [417]. Garlic extract supplementation also relieved pain and other clinical symptoms associated with knee osteoarthritis. Administration of 1 g of the supplement for 12 weeks significantly reduced the level of resistin, an inflammatory cytokine, thus displaying anti-inflammatory effects [418].

8.5. Ginger:

Ginger powder supplementation was found to be effective against both RA and osteoarthritis as evidenced by several clinical studies. In the case of RA patients, on receiving 1.5 g ginger supplements daily for 12 weeks, an improvement in the clinical symptoms was observed. Ginger powder effectively regulated the levels of NF-κB, RORγt, T-box transcription factor TBX21 (T-bet) genes thus leading to a decline in the severity of the disease. Similarly, the administration of ginger powder to osteoarthritis patients displayed potent anti-inflammatory effects via downregulating the inflammatory cytokines IL-1β and TNF-α [419], [420]. A clinical trial of

ginger extract on tuberculosis patients has conveyed that administration of 3 g of the supplement daily for 3 months reduced the blood levels of inflammatory cytokine TNF-α and other markers of the disease such as ferritin and MDA, thus displaying anti-inflammatory and anti-oxidant properties [421].

Furthermore, a pilot clinical study on the subjects at an increased risk of colorectal cancer (CRC) has shown that ginger extract was found to be well tolerated by the subjects and did not show any adverse side effects. It regulated the levels of arachidonic acid (AA) and leukotriene B4 (LTB4) but did not show any change in the levels of eicosanoid. Thus further studies are essential to investigate the exact mechanism behind the chemopreventive effects of this spice [422].

8.6. Ginseng:

Ginsenosides, the saponins extracted from ginseng, are found effective against many diseases. A clinical study investigating the potency of *Panax notoginseng* saponins (PNS) against RA, which displayed that the saponins, when administered for 28 days, led to significant improvement in clinical symptoms of the disease in terms of joint pain, swelling, tenderness, and stiffness. It also managed the dysregulated immune response and displayed significant anti-inflammatory and analgesic effects [423]. Further, the efficiency of ginsenosides therapy (in the form of shen-fu injection) was also evaluated against gastrointestinal mucosal injury which is associated with cardiopulmonary bypass in children suffering from congenital heart disease (CHD). It was found that administration of the intravenous injection before and during the bypass surgery resulted in a reduction of characteristic injury and inflammation post-surgery in patients [424].

8.7. Saffron:

The anti-inflammatory property of saffron is evaluated by many studies and thus it was thought to have protective effects against allergies such as asthma. Asthmatic patients, on receiving 100 mg/day saffron capsules for 8 weeks, showed improvement in clinical symptoms of the disease such as frequency of asthmatic attacks, usage of salbutamol inhaler, waking up at night due to asthmatic symptoms, and limitation in the activity. The severity of the disease declined, and the supplement was well tolerated by the patients without any adverse side-effects [425].

Crocin, an active component of saffron, was found to be an effective therapy against multiple sclerosis due to its efficient anti-inflammatory and anti-oxidant properties. It was found that the administration of two capsules of crocin (15mg) for 28 days showed an improvement in the antioxidant status of the body. Additionally, a reduction in inflammatory mediators such as TNF-α and IL-17 in the blood of the patients was also found [426].

8.8. Sesame seed:

Sesame seed therapy was found to improve the factors of inflammation and oxidation in patients suffering from osteoarthritis of the knee. Consumption of 40 g of sesame seed daily for 2 months resulted in a decrease in the level of IL-6 in the serum of patients, thus proving that it can serve as a potential supplementary therapy in patients with osteoarthritis [427].

8.9. Turmeric:

A handful of clinical studies have been performed to examine the potency of turmeric against various diseases. Curcumin and curcuminoids, the active components of turmeric, are found as effective therapies over the years. These are found to be very helpful in managing metabolic syndrome and disorders. For instance, a classic combination of curcuminoid-piperine in the ratio of 100:1 was administered daily for 8 weeks to patients with metabolic syndrome. It was found to regulate the levels of CRP, MDA, SOD in patients thus imparting significant anti-

inflammatory and anti-oxidant effects [428]. In the case of patients with obesity/hypertension, the hot water extract of C. longa L. (WEC) was found to reduce the levels of CRP, TNF-α, IL-6, and soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1), thereby amending chronic low-grade inflammation and overall health of patients [429]. Furthermore, in T2D patients, the uptake of curcuminoid-piperine has shown a decline in the level of TNF-α and an inclined level of adiponectin. Furthermore, another study evaluating the effects of curcumin against T2D showed that the compound modulated the levels of hs-CRP and TG thereby imparting significant anti-inflammatory activity [430], [431]. The compounds are further found effective against osteoarthritis and RA. In the case of osteoarthritis, *Curcuma longa* L. (CL) extract showed significant anti-inflammatory effects via the down-regulation of IL-1β and anti-oxidant effects via the down-regulation of MDA and ROS. Thus, the administration of the extract was found to improve clinical symptoms of the disease such as pain and inflammation [432]. Another clinical study showed that the administration of a combination of *H. procumbens*, *C. longa*, and bromelain in the form of AINAT capsules showed similar improvements in terms of pain in osteoarthritis patients. Further, the capsules were well tolerated and thus can be used as a safe and effective replacement for non-steroidal anti-inflammatory drugs (NSAIDs) [433]. Besides, the intake of 0.5-1 g of curcumin formulation daily 90 days in two different treatment groups has shown significant anti-inflammatory and analgesic effects in patients suffering from RA. The treatment caused improvements in the levels of CRP and rheumatoid factor (RF) values without causing any adverse side effects [434].

A clinical study evaluating the effects of a combination of turmeric extract and *Boswellia serrata* as a treatment of patients with chronic kidney disease (CKD) has reported that the supplement is well tolerated by the patients and is safe to use. The treatment efficiently enhanced the

inflammatory status of the patients via the downregulation of the inflammatory cytokine, IL-6 [435]. Moreover, regular intake of curcumin was found to impart anti-inflammatory effects in patients undergoing hemodialysis. The supplement helped in reducing the levels of hs-CRP, IL-6, and TNF-α in plasma without causing any side-effects [436].

Curcuminoids were also found to relieve chronic inflammation in patients suffering from chronic pulmonary complications (CPC) resulting from sulfur mustard (SM) intoxication. Treatment with curcuminoids supplement helped in modulating inflammatory responses via reducing the levels of IL-6, IL-8, TNF-α, TGF-β, hs-CRP, calcitonin gene related peptide (CGRP), substance P, and MCP-1. The supplements were also well tolerated and did not cause any adverse side effects in the patients [437]. Also, in the case of chronic obstructive pulmonary disease (COPD), a curcumin supplement namely Theracurmin(®) was found to significantly amend the inflammatory status and levels of α1-antitrypsin-low-density lipoprotein (AT-LDL) in the blood of patients when taken for 24 weeks. This change might be useful in reducing the risk of any further cardiovascular events in COPD patients [438].

Furthermore, a nano-curcumin formulation in combination with omega-3 fatty acids was found to show neuroprotective effects against migraines. The therapy significantly reduced the levels of cox-2/iNOS which is associated with neuroinflammation and pain of the CNS. Hence, a decline in the rate and duration of repeated painful attacks and the severity of the disease was observed, making this a safe and useful therapy for the treatment and prevention of migraine [439].

9. Curcumin and COVID-19:

Curcumin is a multipotential compound from C. longa that possesses diverse medicinal properties. It is a potent anti-inflammatory agent that is effective against numerous chronic diseases [14], [440], [441], [442], [443].

Elevated cytokine levels or cytokine storm is considered as one of the critical process responsible for multi-organ failure and death in COVID-19 infected patients [444], [445], [446]. TNF-α also plays a pivotal role in pulmonary edema caused during COVID-19-associated lung diseases. Natural compounds like curcumin downregulate the levels of TNF-α [447].

Moreover, the coronavirus is also associated with the symptoms of pneumonia that causes severe respiratory distress. The treatment of the pneumonia model with curcumin was shown to decrease lung injury and inflammation through the modulation of HIF and NF-κB [448]. The treatment of curcumin in viral infected models has exhibited inhibition of cytokines, MMPs, and inflammatory cells. It also inhibited the fibrosis and expression of myofibroblasts in the lung tissues [449]. A study demonstrated the potency of a novel combination of vitamin C, curcumin and glycyrrhizic acid (VCG) against SARS-CoV-2 infection. System biology tools also found that VCG modulated various genes associated with immune and inflammatory responses via the regulation of crucial pathways such as NOD-like, Toll-like, PI3K/Akt, NF-κB and MAPK signaling pathways [450]. TMPRSS2 is a crucial protease involved in the priming of ACE2 receptor-bound viral S protein and thus acts a therapeutic target for COVID-19 therapy [451]. Bromolein, a cysteine protease traditionally used for the treatment of arthritis, possesses potent immunomodulatory properties. Besides, studies have demonstrated that bromolein inhibits the expression of ACE-2 and TMPRSS2 *in vitro*. It has been hypothesized that the combination of curcumin and bromolein might exert a beneficial synergistic effect against SARS-CoV-2 infection [452], [453]. Another study reported the potential immunomodulatory and antiviral efficacy of the combination of black pepper and curcumin extract along with multiactive ingredients such as pentatricontane, sitosterol, termerone, lupeol, amyrines, and vitamin D3 (EGYVIR). The administration of EGYVIR in SARS-CoV-2 infected cells decreased the levels

of inflammatory mediators such as TNF-α and IL-6 which might be effective in attenuating the virus-induced cytokine storm [454]. The combination of curcumin and zinc has also been hypothesized as an effective therapeutic strategy against COVID-19 [455], [456].

A randomized clinical trial has been initiated to investigate the potency of the co-administration of curcumin and piperine on COVID-19 patients [457]. Another randomized clinical trial has been initiated to determine the efficacy of that nano micelles containing curcumin on the levels of various serum cytokines such as IFN-γ, IL-17, IL-4, and TGF-β in COVID-19 patients [458]. Nanonutraceuticals of vitamins, antioxidants, probiotics, etc. can modulate immune responses and therefore effectively strengthen the immune system of COVID-19 patients [459]. Nano-curcumin also significantly reduced the expression of serum IL-6 and IL-1β in COVID-19 patients [460]. Furthermore, nano-formulation of curcumin is also associated with faster recovery of COVID-19 patients [461]. It also exerted immunomodulatory effects and also decreased the levels of Th17 cell-related cytokines in the patients [462]. Therefore, it might be useful as a traditional medicine to treat COVID-19-associated complications such as cytokine storm, acute lung injury or acute respiratory distress syndrome, pneumonia [463], [464].

Apart from the anti-inflammatory effects, several studies have also reported that curcumin exhibits antiviral effects [465], [466], [467]. Curcumin was reported to inhibit the replication of the SARS-CoV *in vitro*. Therefore, the potency of curcumin as an antiviral agent might also be effective against the SARS-CoV-2 [465]. Numerous molecular docking studies have shown the efficacy of curcumin to target various key components of the novel SARS-CoV-2 *in silico*. A study reported that curcumin showed high-affinity binding towards the viral spike glycoprotein and ACE2 receptor [185]. Another study demonstrated its binding affinity towards the viral Nsp15 protein which is associated with replication. Therefore, curcumin might cause the

inhibition of the viral replication by binding with Nsp15 [182]. Curcumin has also been reported as a potential inhibitor of Mpro protein of SARS-CoV-2 [468], [469], [470], [471], [472]. It inhibits the human cellular transmembrane serine proteinase [473]. Furthermore, curcumin and catechin also bind to the RBD of the viral S protein and inhibit the entry of SARS-CoV-2 in the host cell [474]. Multi-omics analyses have also demonstrated the potential of compounds such as curcumin, resveratrol, etc., as effective agents to inhibit SARS-CoV-2 viral infection [475].

Thus, several studies have hypothesized that the immunomodulatory and anti-viral activities of curcumin might be beneficial in the treatment of SARS-CoV-2 and COVID-19 associated diseases [182], [440], [470], [476], [477], [478], [479], [480], [481]. Curcumin possesses a huge potential as a drug against SARS-CoV-2 as well as COVID-19-associated diseases. Therefore, it should be further evaluated in the pre-clinical and clinical studies to determine its efficacy [479].

10. Discussion and Conclusion:

The COVID-19 pandemic has posed a great threat to healthcare across the globe. The causative pathogen is a novel coronavirus and there are currently no specific treatment strategies against it. Although several studies are going on to develop a specific drug targeted towards SARS-CoV-2, it might take some more time. Several vaccine development trials are also underway, but the end products will require some time to clear the safety studies. Moreover, a new variant of the SARS-CoV-2 had been reported for the first time on 14th December 2020 in the United Kingdom (UK). This variant of concern (VOC) had been labelled as the VOC 202012/01 and had been detected in over 50 countries in the UK. Other variants such as 501Y.V2 and B.1.1.28 were also reported from South Africa (18th December 2020) and Japan (9th January 2021), respectively. Therefore, considering the rapid evolution of this virus and urgency of the situation, one of the best options for management and treatment is repurposed drugs. These drugs are already

approved for the treatment of some diseases in humans and are thus readily available in the market. In the paucity of SARS-CoV-2 specific drugs, these repurposed drugs with anti-viral or inhibitory effects are prescribed to hospitalized patients [4], [97]. Cytokine storm or hyper inflammation is commonly observed in severe COVID-19 patients. It is associated with the progression of the disease and poor clinical outcome [482]. Respiratory failure, ARDS, and pneumonia are some of the most common and fatal COVID-19 associated complications. Therefore, some repurposed drugs are known to exhibit potent anti-inflammatory effects and are thus used to combat COVID-19-associated inflammatory complications [76], [97].

Some of these repurposed drugs show very promising results. However, most of them raise serious concerns as they are reported to have adverse side effects [97]. Therefore, it is necessary to look for alternative medicines that may be effective against the novel virus and associated health complications which cause little or no side effects.

Mother Nature has provided us with several natural compounds that have been used throughout the ages for the treatment of various diseases like cancer, asthma, diabetes, respiratory and cardiovascular disorder, etc. Spices are nature's most potent anti-inflammatory and antioxidant agents. Besides enhancing the taste, flavor, aroma, and color of food and beverages but also imparts protection against various health ailments. These therapeutic properties of spices and culinary herbs are due to the presence of various bioactive components with significant biological activities. Besides, the consumption of spices has been proven to reduce inflammation and boost our immune response [14]. Therefore, in the absence of a drug or vaccine against SARS-CoV-2, spices might serve as an alternative treatment for infected patients. It can serve a dual purpose of both as a means of primary prevention, as well as help mitigate the exaggerated

immune response and cytokine storm. However, pre-clinical and clinical studies should be conducted to validate its efficacy in COVID-19 patients.

Authors' Contributions:

BBA and ABK contributed to the conceptualization of the study design. VR, DP, SG, HS, KB and KKT performed the bibliographic search and contributed to the writing of the manuscript. VR, DP, SG, and HS contributed to the tables. VR and DP contributed to the reference editing. KB contributed to the figures. BBA, ABK, UD, PG, and SCG contributed in the reviewing and proofreading of the manuscript.

Declaration of Conflicting Interests:

The authors declare no conflict of interests related to this study.

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Graphical abstract