Review

Phytotherapy for treatment of cytokine storm in COVID-19

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1. Abstract

In 2020, a novel strain of coronavirus (COVID-19) has led to a significant morbidity and mortality worldwide. As of the date of this writing, a total of 116 M cases has been diagnosed worldwide leading to 2.5 M deaths. The number of mortalities is directly correlated with the rise of innate immune cells (especially macrophages) in the lungs that secrete inflammatory cytokines (IL-1β and IL-6) leading to the development of "Cytokine Storm Syndrome" (CSS), multi-organ-failure and death. Given that currently the treatment of this condition is rare and release of effective vaccine might be months away, here, we review the plants and their pharmacologically active-compounds as potential phytopharmaceuticals for the virus induced inflammatory response. Experimental validation of the effectiveness of these natural compounds to prevent or reduce the cytokine storm might be beneficial as an adjunct treatment of SARS-CoV-2.

2. Introduction

In December 2019, uncommon pneumonia like symptoms began to appear in citizens of Wuhan city, China. A research group at virology institute of China started identifying the agent responsible for the development of these

atypical symptoms. Next generation sequencing (NGS) data of nucleic acids isolated from the bronchoalveolar lavage fluid (BALF) of diseased patients revealed the presence of a novel coronavirus strain which was provisionally named as 2019-nCoV [1]. The NGS data analysis revealed that the RNA genome of 2019-nCoV resembles the Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) genome responsible for the SARS-epidemic during 2003–2004 [2]. Thus, 2019-nCoV was ultimately renamed as SARS-CoV-2. Later, the disease caused by the novel SARS-CoV-2 was designated as COVID-19 by World Health Organization (WHO) which also declared it as an international public health emergency in March 2020 (Fig. 1). The early clinical symptoms associated with SARS-CoV-2 infection are fever, muscle pain, chills, sore throat, loss of taste, dry cough, dyspnea (difficulties in breathing), headache and pneumonia. As of March 2021, 116 million confirmed cases of COVID-19 have been reported worldwide (https://coronavirus.jhu.edu/map.html). The onset of COVID-19 leads to respiratory failure that further causes alveolar damage [3]. This novel strain of coronavirus has become a source of augmenting morbidity and mortality worldwide for the last few months. An extreme inflammatory immune response is believed to be the major cause of disease severity and death in COVID-19 patients which involves elevated level of inflammatory cytokines and chemokines (Interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, chemokine (CC) ligand-2, CCL-3 and CXCL10), and lymphopenia. Surprisingly, it has been found that the cytokine profile of COVID-19 patients resembles with the patients having cytokine release syndrome. In severe cases, infiltration of mononuclear cells into lungs, spleen, heart and kidney has also been observed [4–6]. The global desolation due to COVID-19 can be partially elucidated by the nature of viral transmission. The incubation period between viral infection and onset of symptoms is around four to seven days that opens a large window for the transmission of SARS-CoV-2 from asymptomatic carriers to healthy individuals [7–9]. Transmission occurs from one person to another mainly through the respiratory droplets released during sneezing or coughing, touching contaminated surfaces or by personal contacts. Most of the patients with severe disease conditions develop acute respiratory distress syndrome (ARDS); a clinical condition that is marked by hypoxemia (reduced ratio of arterial PO_2 to inhaled FiO_2) and bilateral infiltrates [10, 11].

In the case of viral infections, the most commonly adopted therapeutic strategies include the blockage of the viral entry and replication or modulation of humoral and cellular immunity in the uninfected population. Unfortunately, till date, no FDA approved drug is available that can target or limit the entry and replication of SARS-CoV-2. Till date, the pertinent factor involved in disease severity relates to either activation or suppression of immune responses in the host. Several drugs have been repurposed for the treatment of COVID-19 patients like chloroquine, hydroxychloroquine, remdesivir, favipiravir, ritonavir, lopinavir, ribavirin, dexamethasone, arbidol, anti-inflammatory medicines viz. glucocorticoids, tocilizumab and siltuximab (IL-6 cytokine inhibitors) and anakinra (IL-1 cytokine inhibitor) [12]. Currently, convalescent plasma therapy showed effective results against COVID-19 [13]. But these synthetic drugs and therapies exhibit various adverse effects like heart failure, permanent damage to retina as observed in case of hydroxychloroquine and liver damage in case of remdesivir etc. [14]. Thus, there is an exigent need to identify safe and effective therapies with negligible side effects against COVID-19. Several *in silico* analysis showed that plant derived natural compounds could be effective therapeutic agents against SARS-CoV-2. Plants produce an unbelievable variety of natural compounds with immense therapeutic potential. However, the limited awareness regarding the mechanism of action of natural compounds is a shortcoming that basically prevents the acceptance of plants as phytotherapy by medical professionals. The Ministry of AYUSH, Government of India has recently recommended various immunity promoting measures based on the Ayurveda (the oldest healing science, 5000 years ago) for the prevention and management of COVID-19. Recently, WHO too had endorsed the use of traditional herbs in tackling COVID-19 induced health complications (https://www.afro.who.int/news/expert-panel-endorses-protocol-COVID-19-herbal-medicine-clinical-trials). In the present review we have discussed some of the most potent phytotherapeutics available from natural traditional medicines that can be employed by clinicians as therapeutic agents to control viral titer as well as toxicity associated with SARS-CoV-2 infection. Also, we offer suggestions to understand the significance of natural herbs and their utilization to enhance anti-viral immunity in the host.

3. Pathogenesis of COVID-19

Coronavirus belongs to a large family of enveloped, non-segmented, positive (+) sense single stranded RNA viruses that circulate in animals including bats, cats, dogs, camels etc. These viruses are named as coronaviruses due to the resemblance of their structure to a crown or corona. Coronavirus are known to cause disease in both animals and humans. Among all coronaviruses, four human coronavirus strains (OC43, NL63, HKU1 and 229E) are known to infect upper respiratory tract with minor symptoms [15]. On the other hand, three human coronavirus strains (SARS-CoV, SARS-CoV-2 and MERS) are known to infect lower respiratory tract that can develop pneumonia and lead to deadly condition. SARS-CoV-2 is a beta coronavirus that shares 79% genetic sequence similarity with SARS-CoV and 98% homology with RaTG13 coronaviruses residing in chrysanthemum bats [1]. Moreover,
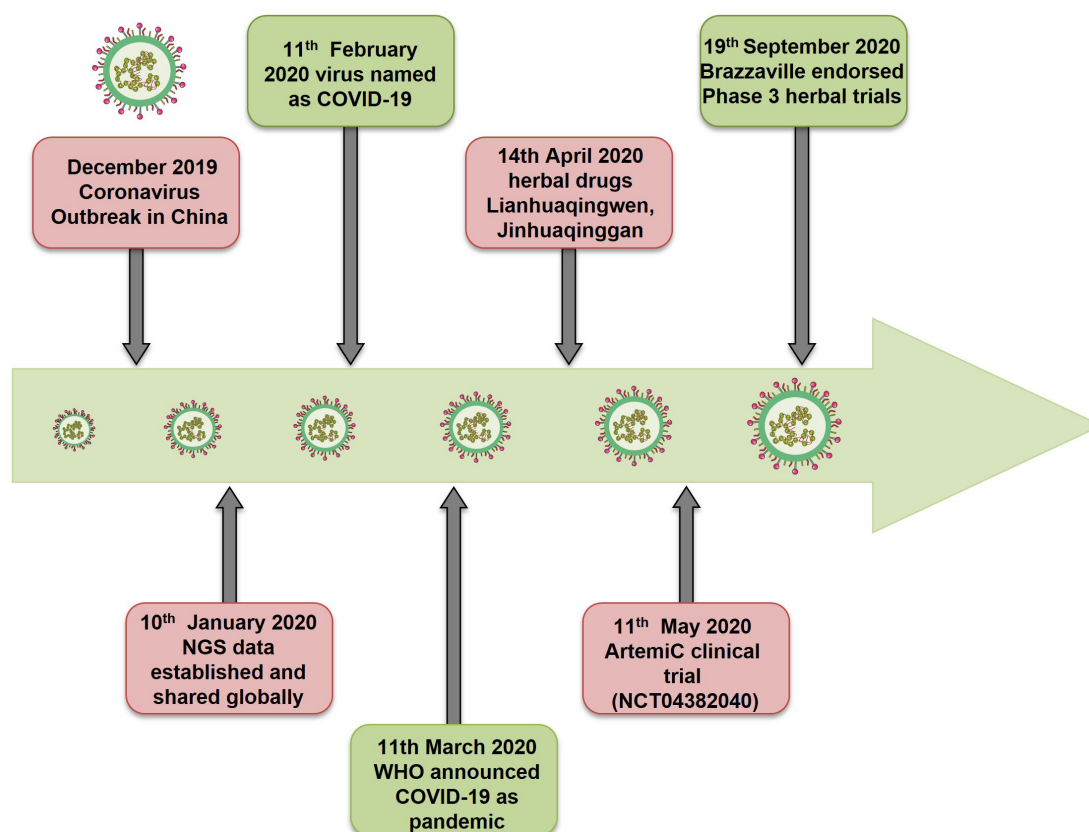
Fig. 1. Timeline of COVID-19. Revisiting the events of Coronavirus pandemic and therapeutics.

immunopathogenesis of SARS-CoV-2 that leads to airways destruction closely resembles with SARS-CoV [16]. In severe cases of infection with SARS-CoV-2, ARDS condition develops that causes respiratory failure which is found to be the major cause of mortality [17]. In addition to this, mounting of immune responses against viral infection causes release of enhanced levels of inflammatory cytokines from the innate immune cells thereby leading to the development of "Cytokine Storm Syndrome" (CSS) [17]. This condition results in uncontrollable inflammation that further impose multiple-organ failure eventually leading to death. Thus, we can infer from these findings that viral infections are not solely responsible for airways destruction, but the host immune response also plays a vital role in the advancement of disease. Furthermore, severity of the disease is found to be correlated with advanced ageing and with the presence of comorbidities [18].

The first step involved in the pathogenesis of COVID-19 is the binding of virus to the host cells (such as airway epithelial cells, endothelial cells, alveolar macrophages, and alveolar epithelial cells) in the lungs. All these cells express Angiotensin Converting Enzyme 2 (ACE2); the target receptor that makes these cells susceptible to coronavirus infection [5]. After infection, a reduction in the pulmonary ACE2 expression is observed and loss of ACE2 might be responsible for enhanced severity

of the disease. Generally, ACE2 is known to regulate the Renin-Angiotensin-System (RAS) which in turn regulates the blood pressure and electrolytes/fluid levels and dysfunction of RAS system has been observed in patients infected with SARS-CoV-2. The corona virion comprises of four proteins (viz. spike-S, envelop-E, membrane-M and nucleocapsid-N) and a single stranded RNA genome having a length of 29,900 nucleotides (Fig. 2). Spike (S) protein of SARS-CoV-2 aids the interaction of the virus with target cells expressing ACE2 on their surface. In addition to ACE2, serine protease TMPRSS2 known to be the priming factor for S protein that facilitates the entry of SARS-CoV-2 into the host cell [19]. However, the reason behind the broad dissemination of SARS-CoV-2 is not reported till date. Recently, it is observed that host protease furin which results in cleavage of full-length S glycoprotein into polybasic S1 and S2 polypeptides resulting in exposure of Arg-Arg-Ala-Arg C-terminal sequence (CendR motif) in S1 polypeptide that aids in binding of virus to host cells via Neuropilin-1 (NRP1) receptor. NRP-1 is expressed on various human tissues such as respiratory tract, neurons and blood vessels. Thus, we can conclude that NRP serves as a second key host receptor that involves in SARS-CoV-2 infection and may provide a therapeutic target for COVID-19 [20].
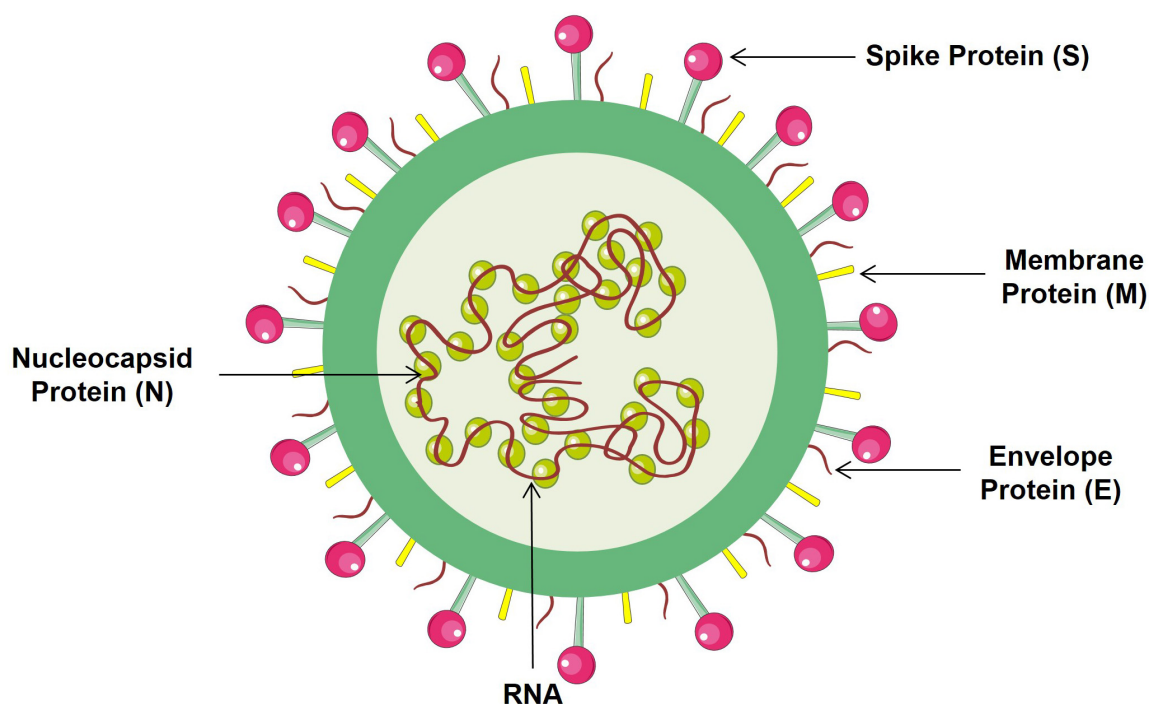
Structural Proteins	Functions of Proteins
Spike Protein (S)	Facilitates the interaction between COVID-19 and host cells expressing ACE2
Membrane Protein (M)	Abundant protein that defines the shape of viral envelope and plays a vital role in formation of virus particles
Envelope Protein (E)	Interacts with M proteins to form the envelope of virus
Nucleoprotein (N)	Interacts with viral RNA genome and assist in RNA synthesis and folding

Fig. 2. Structure of COVID-19. COVID-19 structure is comprised of four proteins and single stranded RNA genome. (Figure illustrated with the help of https://smart.servier.com/).

Surprisingly, it has also been observed that males are highly susceptible to SARS-CoV-2 infection as compared to females [21]. Further, the sex-hormones like estrogen and testosterone exhibit different immunomodulatory properties [22–24]. Thus, highlighting the significance of sex steroid hormones for their possible role in disease severity among males in comparison to females. In case of SARS-CoV, a study reported that treatment with estrogen receptor antagonist or estrogen deficiency in ovariectomized female mice dramatically enhanced the morbidity and mortality in female mice due to virus infection [21, 25]. Recently, a study highlighted the association between Kawasaki disease (KD) and COVID-19 in infants [26]. Furthermore, a study revealed that the developing human embryo also expresses ACE2 receptor and TMPRSS2 protease necessary for virus internalization [27]. Thus,

these findings abolish the misconception that only the aged population is highly susceptible to SARS-CoV-2 infection.

4. Immunopathogenesis of COVID-19

Viral infections induce the host innate and adaptive immune responses. These responses are initiated with the activation of the innate immune system that recognizes various molecular patterns such as pathogen associated molecular patterns (PAMPs) and death associated molecular patterns (DAMPs) like ATP, nucleic acids and ASC oligomers. Adaptive immune system is activated with the induction of T cells and the release of various antigen specific antibodies by the B cells. Activation of innate and adaptive immune response stimulates the release

of various proinflammatory cytokines and chemokines that further promote the recruitment of macrophages and neutrophils at the site of infection. These cells secrete various cytotoxic substances which are required to clear the infection. These well-coordinated adaptive and innate immune responses generally eliminate the viral infection but sometimes viral infection results in activation of intense inflammatory response resulting in excessive destruction of host tissue. This disproportionate immune response has been hypothesized to be the reason of immunopathogenesis observed in COVID-19. SARS-CoV-2 infection induced extreme inflammation causing the production of large amount of pro-inflammatory cytokines and chemokines. Remarkably, it has been observed that COVID-19 patients who were admitted to intensive care unit (ICU) had higher levels of inflammatory cytokines such as IL-2, IL-7, IL-10, IFN-γ induced protein (IP)-10, TNF, Granulocyte-colony stimulating factor (G-CSF), macrophage inhibitory protein 1-alpha (MIP1-α), macrophage chemoattractant protein-1(MCP-1) as compared to the plasma of patients not admitted in the ICU [28]. Other studies also showed that COVID-19 patients have higher levels of IL-6 as compared to healthy individuals [29]. In consistent to this in a clinical study, it has been observed that COVID-19 patients harbor extended population of IL-1β and IL-6 secreting CD14$^+$ CD16$^+$ monocytes in circulation as compared to healthy controls [14, 18]. The elevation in levels of these cytokines leads to the generation of "cytokine storm" which is primarily responsible for ARDS and multi-organ failure observed in COVID-19 patients. These inflammatory cytokines also further upregulate the inflammatory cascade in resident macrophages that in turn leads to the release of pronounced levels of IL-1β and IL-6 inflammatory cytokines causing the recruitment of neutrophils and CD8$^+$ T cells to the site of infection [29]. These cells produce cytotoxic substances like reactive oxygen species (ROS), matrix-metalloproteinase (MMPs), leukotriene that causes tissue injury in lung parenchyma of host resulting in diseases like acute lung injury (ALI) and ARDS. Surprisingly, a study demonstrated that level of IL-6 is also interrelated with SARS-CoV-2 RNA (RNAemia) [30] and higher level of IL-6 is further interrelated with the need for mechanical ventilation. Thus, IL-6 can be utilized as a biomarker for the assessment of disease severity in infected patients. Therefore, it is worth asking whether SARS-CoV-2 is solely responsible for damaging multiple tissues or it is the cytokine storm or the synergistic effect of both that causes multi-organ damage in the COVID-19 patients. Also, whether blocking the pro-inflammatory mediators would affect the clinical outcome of patients infected with SARS-CoV-2 is still a matter of debate.

Moreover, insufficient activation of the anti-viral cytokines viz. type I and type III interferon is found to be the crucial factor contributing to the failure of innate immune response thereby enhancing viral dissemination and persistence. Thus, the identification of molecular mechanisms responsible for reduced expression of anti-viral cytokines would be crucial for the development of directed immunomodulatory strategies for COVID-19 treatment.

Along with the cytokine storm, lymphopenia is one of the critical clinical manifestations observed in COVID-19 patients [31]. Lymphopenia is defined as the condition in which a substantial reduction in the lymphocyte counts mainly CD4$^+$ and CD8$^+$ T cells is observed in peripheral blood. A study reported in 2004, demonstrated that lymphocytes lack ACE2 expression [32]. Thus, it is reasonable to postulate the existence of an alternative mechanism through which SARS-CoV-2 compromises the T cell population. It is still an open question in the research community. Recently, terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining suggested apoptosis of lymphocytes in the secondary lymphoid organs (spleen and lymph nodes) of patients who died from COVID-19. These patients showed higher expression of FAS (death receptor) suggesting towards activation induced cell death (AICD) [33]. Apart from AICD, a study reported that T cells isolated from the circulation and lung tissue of infected patients displayed higher expression of T cells exhaustion markers such as T-cell immunoglobulin and mucin domain-3 (Tim-3) and programmed cells death receptor-1 (PD-1) [6].

Notably, a study reported that the degree of lymphopenia (lymphocyte count < 1.0 pm 10^9/L)^3 and cytokine storm were higher in severe cases of COVID-19 as compared to mild cases. Thus, we can infer from this that inflammatory cytokine levels have an inverse correlation with the T cell population. Accordingly, these parameters are indicative of disease severity. The analysis of lymphocyte level and cytokine profile in PBMCs of 40 COVID-19 positive patients revealed that the count of lymphocytes especially CD8$^+$ T cells was lower whereas, the neutrophil count was higher in severe cases as compared to mild cases [34]. Therefore, N8R (Neutrophil to CD8$^+$ T cells ratio) and NLR (Neutrophil to lymphocytes ratio) may also serve as a prognostic biomarker for the identification of severe COVID-19 cases.

5. Traditional medicine as phytotherapeutics in managing COVID-19

Traditional medicines have long antiquity in playing a central role in the prevention as well as in the management of several diseased conditions. They have a holistic concept that works by strengthening the body resistance to eradicate pathogenic factors. Recently, the significance of traditional medicines has also been proven in the management of COVID-19 pandemic. A study reported that early involvement of traditional medicine improves the recovery rate and reduces the mortality rate in SARS-CoV-2 infected patients [35]. Traditional medicines not only

work by inhibiting virus replication but also dampen the inflammatory storm by regulating the immune response [35]. Moreover, various studies have clearly specified that phytoconstituents exhibit immunomodulatory properties and are known to augment the expression level of anti-inflammatory cytokines along with reducing the expression of inflammatory cytokines such as IL-6, IL-17, and TNF-α that are produced during inflammatory conditions [36]. In the present review, we thus enlist some of the important traditional plants that exhibit both anti-inflammatory and tissues protective activities with an idea of employing these plants as a mode of phytotherapy for the treatment of COVID-19 pathologies (Figs. 3,4) & (Table 1). We have also enlisted some of the clinical trials undergoing with traditional medicines and natural compounds (Table 2).

5.1 *Withania somnifera* (Ashawagandha)

Withania somnifera belongs to Solanaceae family and is commonly known as "Indian Ginseng" or "Indian Winter cherry". It is also known as "Sattvic Kapha Rasayana" that holds a prominent place in Ayurvedic Rasayana herb [62]. It is among the most esteemed herb of the Indian Ayurvedic system which is prominently used as a Rasayana (tonic) with wide range of health benefits. The pharmacologically active components of *W. somnifera* are alkaloids, steroidal lactones, and saponins [63] that are crucial for imparting these health benefits. Withaferin (WA) is the first withanolides compound that was isolated from the leaves of *W. somnifera*. Withanolides are a group of 28 carbon-containing steroidal lactones isolated from solanaceous plant. Along with anti-microbial activity, anti-arthritic activity and anti-tumorigenic activity, these withanolides also possess hepato-protective properties [64].

5.1.1 Anti-viral potential of *Withania somnifera*

In addition to several beneficial and health promoting effects, *W. Somnifera* root extract also possesses anti-viral and immunomodulatory properties as treatment of PBMCs from HIV patients with *W. Somnifera* reduced the expression of CD38 on CD8$^+$ T cells of HIV patients. CD38 is a marker of CD8$^+$ T cells and can be used as a biomarker for monitoring HIV progression [65]. It also plays a vital role in chikungunya virus clearance from the host [66]. Recently, Balkrishna *et al*. demonstrated that withanone from the *W. somnifera* exhibits the ability to weaken the interconnections between SARS-CoV-2 S-protein RBD (receptor binding domain) and host ACE2 receptor by disrupting the electrostatic interactions between the complex [67]. Proteases are found to be the predominant target for inhibiting the viral replication. One of the best targets for coronavirus is main protease (M^{pro}). M^{pro} cleaves polyproteins required for the replication and transcription of SARS-CoV-2 and inhibition of M^{pro} will prevent viral multiplication. A study reported by Shree *et al*. via molecular docking analysis revealed that two compo-
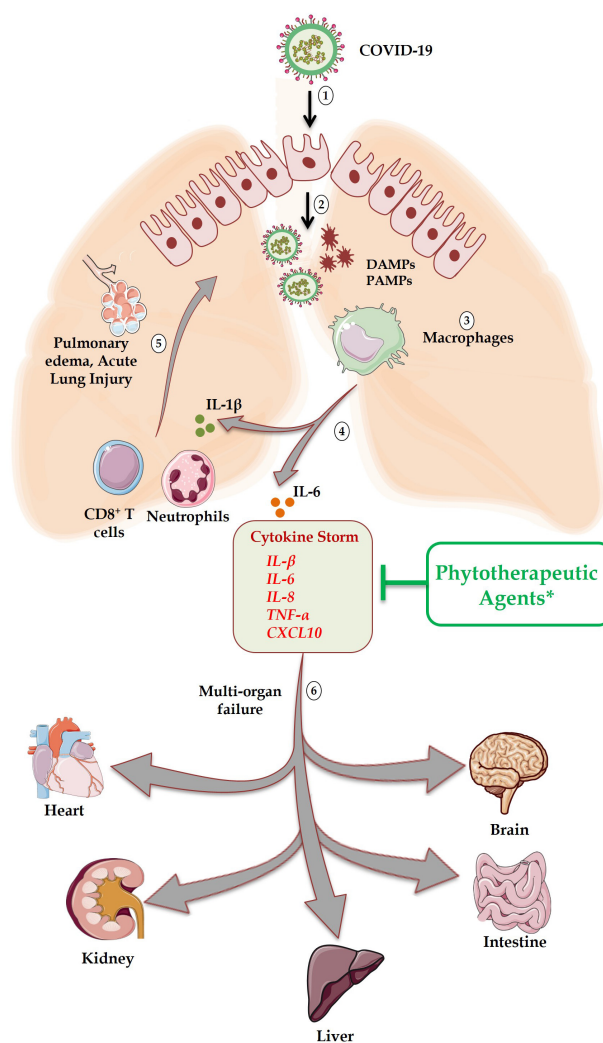

Fig. 3. Schematic representation of immune response and associated tissues toxicity in sequential manner. Step 1: Internalization of COVID-19 into target cells expressing ACE2 receptor; Step 2: After pyroptosis waning cells generate death associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs); Step 3: Virally derived DAMPs and PAMPs engulfed by macrophages in turn produce pro-inflammatory cytokines; Step 4: Interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, chemokine (CC) ligand-2 ,CCL-3 and CXCL10; Step 5: Recruitment of neutrophils and CD8+ T cells to the site of infection that further produces reactive oxygen species, ROS, MMPs, leukotriene that causes tissue injury in lung parenchyma; Step 6: "Cytokine Storm Syndrome" i.e. flooding of cytokines into circulation that leads to multi-organ failure. *All the 16 traditional medicines systematically summarized in the present review possess anti-inflammatory potential along with proven heart, liver, brain, lung, kidney, intestinal etc. protective activities. (Figure illustrated with the help of https://smart.servier.com/).

nents of *W. somnifera* viz. Withanoside V (10.32 kcal/mol) and Somniferine (9.62 kcal/mol) possess high affinity towards SARS-CoV-2 M^{pro} (main protease: a vital target for COVID-19) [68]. In consistence with this, a study observed that amongst the forty constituents of *W. somnifera*, Withanoside V is a potent inhibitor of M^{pro} involved in the

Table 1. Traditional medicines possessing anti-inflammatory and anti-viral properties.

Phytotherapeutic agents	Common names	Family	Biologically active components	Pharmacological activities	Predicted targets in COVID-19	Tissue protective activities	Ref.
Commiphora wightii	Gugal, Guggul, Indian Bdellium	Burseraceae	Guggulsteron, lignans, ketosterols, flavanones, guggulipid	Anti-inflammatory ($\downarrow$ IL-1β, IL-6, TNF-α), Anti-diabetic, Anti-arthritic, Anti-oxidant, Anti-bronchitis, Anti-viral	Cytokine storm (IL-1β, IL-6, TNF-α)	Neuroprotective, Cardiopro-tective, Hepatoprotective, Nephroprotective, Lung protective	[37]
Salvia officinalis	Sage	Lamiaceae	Alkaloids, phenolic compounds, steroids polyacetylen, essential oils	Anti-inflammatory ($\downarrow$ IL-1β, IL-6), Anti-cancer, Anti-diabetic, Anti-microbial, Anti-oxidant	Cytokine storm (IL-1β, IL-6)	Neuroprotective, Cardiopro-tective, Lung protective	[38]
Foeniculum vulgre	Fennel	Apiaceae	Coumarins	Anti-inflammatory ($\downarrow$ IL-17), Anti-oxidant	Inflammatory cytokine (IL-17)	Lung protective, Skin protective	[39, 40]
Mentha balsamea	Peppermint	Lamiaceae	Ursolic acid (triterpenoid compound), phenolic acids (rosmarinic and caffeic acids), flavones, flavanones	Anti-inflammatory ($\downarrow$ IL-1β, IL-6, TNF-α), Anti-viral, Anti-oxidant, Anti-microbial, anti-carcinogenic	Cytokine storm (IL-1β, IL-6, TNF-α)	Skin protective, Improve lung function	[41, 42]
Salvia rosmarinus	Rosemary	Lamiaceae	Carnosic acid, Carnosol,	Anti-inflammatory ($\downarrow$ IL-1β, $\downarrow$ NF-kB pathway, iNOS), Anti-oxidant, Anti-osteoporotic, Anti-carcinogenic	IL-1β, iNOS in alveolar macrophages, NF-kB pathway	Lung protective, Neuroprotective	[43, 44]
Echinacea purpurea	Cone flower	Asteraceae	Phylloxanthobilins (tetrapyrrolic compounds), caffeic acids	Anti-inflammatory, Anti-bacterial, Anti-oxidant, Anti-Diabetic, Treat upper respiratory illness, Common cold, Anti-viral, Immunomodulatory properties ($\uparrow$ CD4$^+$ and CD8$^+$ T cells)	Lymphopenia (Increased CD4$^+$ and CD8$^+$ T cells)	Lung protective, Hepatoprotective, Neuroprotective	[45–49]
Sambucus nigra	Elderberry	Adoxaceae	Phenolic acids, flavonols, flavonoids, Total phenols	Anti-inflammatory ($\downarrow$ IL-1β, IL-6, TNF-α, COX2, iNOS), Anti-viral, Treat upper respiratory illness, Anti-microbial, Anti-pyretic, diuretic agent, Anti-diabetic, Anti-oxidant properties	Cytokine storm (IL-1β, IL-6, TNF-α), iNOS and COX-2 in alveolar macrophages	Lung protective, Hepatoprotective, Nephroprotective	[50–52]
Panax ginseng	Man-root	Araliaceae	Ginsenosides, Panax notoginseng saponin (PNS)	Immunomodulatory properties ($\uparrow$humoral and cell mediated immunity), Anti-inflammatory ($\downarrow$IL-8, IL-6; inhibits NF-kB signalling pathway) Anti-diabetic, Anti-neurotoxic, Anti-angiopathy	Cytokine storm (IL-1β, IL-6, IL-8, TNF-α), NF-kB pathway	Neuroprotective, Myocardial protection, Hepatoprotective, Intestinal protection, Lung protective	[53–55]
Taraxacum officinale	Dandelion	Asteraceae	Polysaccharide, Taraxasterol	Anti-inflammatory ($\downarrow$ IL-1β, IL-6, TNF-α), Ameliorates colitis ($\downarrow$IL-6/STAT3 pathway), Anti-arthritic, Anti-viral	Cytokine storm (IL-1β, IL-6, IL-8, TNF-α), NF-kB pathway, IL-6/STAT3 pathway	Hepatoprotective, Lung protective, Neuroprotective, Nephroprotective	[56–58]
Tanacetum vulgare	Tansy	Asteraceae	Flavonoids	Anti-inflammatory ($\downarrow$iNOS and cytokine induced neutrophil chemo attractants), Anti-microbial , Anti-viral	Cytokine storm (IL-1β, IL-6, IL-8, TNF-α), iNOS	Nephroprotective, Neuroprotective	[59–61]

Table 2. Clinical trials of natural compounds for COVID-19 management and treatment.

Drug	Composition	Clinical trial phase/type of study/No. of participants	Mechanism of action	Reference identifier
ArtemiC (Micellar formulation)	Artemisinin (6 mg), Curcumin (20 mg), Frankincense (15 mg), Vitamin C (60 mg)	Phase II/ To evaluate the safety and efficacy of ArtemiC on patients diagnosed with COVID-19/50 P	Diminish IL-6 and TNF-α levels	NCT04382040
Previfenon®	Epigallocatechin-3-Gallate (EGCG) (250 mg)	Phase II/ To determine the efficacy of Previfenon® (EGCG) to prevent COVID-19/524 P	Exhibits anti-viral chemoprophylaxis of COVID-19	NCT04446065
Guduchi Ghan Vati	Giloy (500 mg)	NA/ To evaluate the safety and efficacy of Guduchi Ghan Vati for COVID-19 asymptomatic patients/18-75 years age	Immunomodulatory potential	NCT04480398
Gargles (Mouthwash)	Neem	NA/ To reduce intraoral viral load in COVID-19 infected patients/50 P	Anti-viral	NCT04341688
Omega 3 Viruxide	Neem oil & Wort oil	NA/ To study the viruxal oral and nasal spray for treating the symptoms of COVID-19/128 P	Reduce symptoms associated with COVID-19 infection	NCT04357990
Nigella sativa (Black Cumin)	Black seed (500 mg)	Phase II/ To study Nigella sativa As a treatment option for patients having upper respiratory infection caused by SARS-CoV-2/200 P	NA	NCT04401202
Nigella sativa (HNS-COVID-PK)	Cumin seed powder (1 gm)	Phase III / Role of honey and Nigella sativa in the management of COVID-19/ 30 P	NA	NCT04347382
Traditional Chinese medicine	NA	Phase III/ To evaluate the safety and efficacy of TCM as an adjuvant for the patients with SARS-CoV-2 COVID-19/50 P	NA	NCT04323332
Individualized Ayurveda	Ginger/Turmeric/Honey/Lemon	NA/ Ayurveda self-management for flu like symptoms during the COVID-19 outbreak/18-6 years age	—-	NCT04345549

NA* denotes Not Available at clinical trial government site (https://clinicaltrials.gov/).

replication of SARS-CoV-2 [69]. Furthermore, *in silico* study demonstrated that withaferin A, a pharmacological constituent of *W. somnifera* displayed strong interaction with the M^{pro} (-11.242 kcal/mol) and with the RNA Dependent RNA Polymerases enzyme (-9.27 kcal/mol) [70]. In case of SARS-CoV, it has been observed that papain like proteases (PLpro) stimulates oxidative stress by inducing ROS production and TGF-β1 signaling that further leads to lung fibrosis [71]. A study revealed that *W. somnifera* exhibits the potential of suppressing generation of oxidative stress induced due to viral infection [72]. Also, among various withanolides, withanolide_D and withanolide_G showed higher binding affinity with PLpro whereas withanolide_M showed better binding with 3CLpro and spike protein. In comparison to all these withanolides, withanolide_Q was found to modulate higher number of proteins [73]. In addition to ACE-2 receptor, SARS-CoV-2 invades human cell by recognizing Glucose-Regulated Protein 78 (GRP78) receptor through its substrate binding domain (SBD). Interestingly, it has been observed that withanolide A also showed higher binding affinity with GRP78 (-8.7 kcal/mol). Thus, these studies suggest that *W. somnifera* can be potential candidate for treating COVID-19 infected patients. But further research is needed to validate these *in silico* studies against COVID-19.

5.1.2 Anti-inflammatory and health mediated properties of Withania somnifera

Entry of SARS-CoV-2 virus into the host cells cause development of cytokine storm that involves excessive production of inflammatory cytokines which further results in pulmonary edema and acute lung injury which may results in shock and multiple organ failure eventually leading to death in COVID-19 infected patients. Of note, *W. somnifera* reported to suppress various pro-inflammatory cytokines viz. IL-2, IL-6, TNF-α, IFN-γ, IFN-γ protein 10 (IP-10): this condition is interrelated with the improvement in the health condition associated with COVID-19 infection due to cytokine storm [72]. It has also been observed that treatment with *W. somnifera* reduced the oxidative stress, improved endothelial dysfunction, suppressed inflammation and inverted the pulmonary vascular remodelling related to pulmonary hypertension [74]. In consistence with this study, it has also been found that methanolic extracts isolated from roots of *W. somnifera* exerted hepatoprotective role by suppressing inflammation induced secretion of IL-1β, TNF-α, induced nitric oxide synthase (iNOS) and cyclooxygenase-II (COX-II) [75]. Withaferin A administration also attenuated the LPS induced lung injury by reducing the infiltration of neutrophils into the lungs which is further accompanied with the lowering of inflammatory cytokines viz. IL-6 and TNF-α and oxidative stress [76]. The

anti-inflammatory properties of water extract of Ashawagandha (ASH-WEX) were investigated under both *in vitro* and *in vivo* conditions in LPS induced neuro-inflammatory rat model. It was observed that after 8 weeks of administration, water extract of Ashawagandha ameliorated the inflammatory condition by suppressing the production of inflammatory cytokines viz. IL-1β, IL-6, and TNF-α by inhibiting Nuclear factor kappa B (NF-κB), P38 and mitogen activated protein kinase (MAPKs) signaling pathway [77, 78]. WA treatment suppressed the activation of the nucleotide binding domain leucin rich repeat (NLRP3) inflammasome that further inhibited the IL-1β secretion in LPS induced macrophages and also suppressed the *Helicobacter pylori* stimulated production of IL-1β from dendritic cells by modulating NLRP-3 inflammasome and NF-κB activation in a dose dependent manner [79]. Thus, based on these studies it can be suggested that *W. somnifera* and its biological active phytoconstituents possess the ability to suppress inflammation and oxidative stress linked with various inflammatory diseases including viral diseases such as COVID-19.

5.2 *Tinospora cordifolia* (Guduchi)

Tinospora cordifolia commonly named as "Guduchi" belongs to Menispermaceae family. Across the globe, this traditional herb has gained researcher's interest because of its diverse medicinal properties e.g., antioxidant, anti-arthritic, anti-diabetic, anti-inflammatory, anti-malarial, anti-stress, anti-allergic and immunomodulatory etc. [80]. The biologically active components of Guduchi responsible for its medicinal properties are alkaloids, aliphatic, glycosides, steroids and diterpenoid lactones [81].

5.2.1 Anti-viral potential of *Tinospora cordifolia*

Recently, *in silico* study screened the anti-viral potential of chemical constituents of *Tinospora cordifolia* (e.g., berberine ($C_{20}H_{18}NO_4$), choline ($C_5H_{14}NO$), β-sitosterol ($C_{29}H_{50}O$), tetrahydropalmatine ($C_{21}H_{25}NO_4$) and octacosanol ($C_{28}H_{58}O$) against SARS-CoV-2 [82]. Among all the screened chemical constituents, molecular docking along with molecular dynamics studies revealed that berberine regulates the M^{pro} protein function and thus inhibits the viral replication [82]. Furthermore, a study by Balkrishna *et al*. demonstrated that one of the phytocompounds of *T. cordifolia* "Tinocordiside" significantly reduced the electrostatic interaction between ACE2-RBD complexes that leads to enhancement in the flexibility of the complex [83]. Thus, we can postulate that Tinocordiside could be one of the viable options for controlling the SARS-CoV-2 entry into the host cell. In consistent to this, a study reported that four natural compounds isolated from *T. cordifolia* that are Berberine, Isocolumbin, Magnoflorine and Tinocordiside showed higher binding efficacy with key SARS-CoV-2 targets that are responsible for attachment of

virus to host cell such as surface glycoprotein (6VSB) and receptor binding domain (6MoJ) [84]. In addition, these natural compounds also showed higher binding efficacy with the targets that are responsible for replication of virus into the host cell such as RNA dependent RNA polymerase (6M71) and with main protease (6Y84) [84]. Hence, these studies highlight the merit of using natural compounds isolated from *T. cordifolia* in the clinical management of infection caused by SARS-CoV-2. Interestingly, another study reported that administration of *Tinospora cordifolia* along with other ayurvedic herbs strengthens and rejuvenates the immune system of the SARS-CoV-2 exposed asymptomatic group [85]. Guduchi Ghan Vati is under clinical trials for managing and treatment of COVID-19 (NCT04480398). *Tinospora cordifolia* silver nanoparticles (AgNPs) at 250 ug/mL concentration enhanced the viability of chikungunya virus infected cells [86] and thus indicated towards the usage of this plant in AgNPs form as an anti-viral agent that could provide a plausible alternative treatment against SARS-CoV-2 which has no known antiviral therapy and vaccine available yet.

5.2.2 Anti-inflammatory and health mediated properties of Tinospora cordifolia

The anti-inflammatory properties of *Tinospora cordifolia* extract (TCE) is mediated via suppression of pro-inflammatory cytokines such as IL-1β, IL-6, IL-17 and TNF-α in LPS induced Raw 264.7 macrophages, neuro-inflammatory rat model and in arthritis model [87–89]. The polysaccharide G1-4A from *Tinospora cordifolia* shows anti-microbial activity by inhibiting the survival of both drug sensitive as well as multiple drug resistant *Mycobacterium tuberculosis* (MTB) strains under both *in vitro* and *in vivo* conditions through the modulation of the host immune system in a TLR4-dependent manner [89, 90]. Thus, these studies suggest that *Tinospora cordifolia* exhibits anti-viral and anti-inflammatory properties.

5.3 *Glycyrrhiza glabra* (Yashtimadhu)

Glycyrrhiza glabra belongs to Fabaceae family and is commonly known as Liquorice or Licorice. Since, 1950s one of the triterpene glycosides called Glycyrrhizin (GL) isolated from *Glycyrrhiza glabra* (root and rhizomes) has been studied widely because of its pharmacological properties such as anti-inflammatory, hepatoprotective, anti-carcinogenic and anti-viral properties.

5.3.1 Anti-viral potential of *Glycyrrhiza glabra*

In addition to various health promoting effects of *Glycyrrhiza glabra*, it also possesses anti-viral activities: GC7 (18β-glycyrrhetinnic acid), a primary metabolite of GL was assessed by Fu *et al*. in which they mentioned that this metabolite targets the nuclear proteins of Ebola and MARS virus [91]. As ACE2 is a part of renin-angiotensin-aldosterone-system (RAAS) and the compounds that inhibits classical ACE leads to activation

of plasma aldosterone and aldosterone receptor (MR) system. Further MR activation protects the organs from attachment of COVID-19 by reducing the ACE2 expression. Murck *et al.* study reported that a systematically active metabolite of GL i.e., glycyrrhetinic acid (GA) inhibits the 11β-hydroxysteroid dehydrogenase (11β-HSD2) and activates MR in the organs including lungs [92]. GA it's self-possesses anti-inflammatory potential by targeting toll like receptor (TLR)-4 and also found to block TMPRSS2 and thus inhibits virus uptake. Thus, this study suggested that GL reduced the severity associated with COVID-19 infection by acting at two stages: it blocks the virus entry by reducing the expression of TMPRSS2 and ACE2 and also reduced the lung inflammation independent of ACE2 [92]. Furthermore, an *in vitro* study suggested that GL potently neutralize the SARS-CoV-2 virus by inhibiting the main viral protease [93]. Thus, highlighted that GL should be investigated for COVID-19. In addition to this, clinical trials (NCT044241349, NCT043465887, NCT04487964) study suggested that glycyrrhizin showed synergistic effect with spironolactone (SP) and may be considered for COVID-19 infections [94]. Another biologically active ingredient of *Glycyrrhiza glabra* root is Glycyrrhizic acid (GA). Recently, a study revealed that glycoside moiety of GA displayed efficient binding with the HMG box protein HMGB1 that plays a vital role in the virus infection and replication [95]. Further, a study demonstrated that GA, Liquiritigenin (L) and Glabridin (G) active compounds of *Glycyrrhiza glabra* inhibits the enzymatic activity of M^{pro} by binding strongly to the active site. But in comparison to other two compounds GA showed higher binding affinity of -8.0 Kcal/mol [96]. Also, GA could be considered as the best molecule of *Glycyrrhiza glabra* that could be useful against SARS-CoV-2 [97]. Thus, various studies suggested that after consultation with the ayurvedic practitioner, Yashtimadhu can be administered as an immune booster that can play a crucial role in the prevention and management of COVID-19 [98]. Altogether, we can summarize that GL and GA can be deployed as phytotherapeutic agents in ameliorating inflammation and lung injury associated with SARS-CoV-2 infection.

5.3.2 Anti-inflammatory and health mediated properties of Glycyrrhiza glabra

Recently, it is proven that GL mediates anti-inflammatory effects by suppressing the levels of inflammatory cytokines (IL-1β, IL-6 and TNF-α) in BALF of LPS induced ALI mouse model [99]. Flow cytometry and light microscopy data also demonstrated that GL administration reduced the count/mL and percentages of infiltrated: total immune cells, neutrophils and macrophages in BALF and lung tissues as compared to LPS group by downregulating the expression of CXCR4/CXCR1 on neutrophils [99]. Similarly, a study demonstrated that GL administration reduced inflammation, pain and lung damage in ALI by

downregulating TLR2 signaling pathway [100]. Further, a study reported that GL (at 200 mg/kg) downregulated the TLR2 mediated signaling in lung tissue as well in alveolar macrophages in ischemia-reperfusion (I/R) lung injury model [101]. It has been observed that GA administration alleviated the sepsis induced ALI in rats by suppressing inflammatory reaction, oxidative stress and apoptosis in lung tissue by reducing NF-κB, JNK and MAPK signaling pathway [102]. Accordingly, we can conclude that *Glycyrrhiza glabra* has the potential to be employed as a novel phytotherapeutic agent for ameliorating the inflammation and lung damage associated with infection.

5.4 *Allium sativum* (Garlic)

Allium sativum belongs to Liliaceae family and is commonly known as "Garlic" with a well-established historical relevance as a favorable traditional medicine in the ancient years. Notably, garlic has been in use for the treatment of several conditions such as cardiovascular diseases [103], hyperlipidemia [104] and as anti-fungal [105] or anti-diabetic for impediment of nephropathy [106] etc. The biologically active ingredients of garlic that are responsible for its medicinal properties are: sulphur containing compounds like alliin, diallyl-sulfide, diallyl-disulfide, diallyl-trisulfide, S-allylcysteine (SAC), enzymes (alliinase) and the compounds produced from alliin (allicin) [107, 108]. Garlic exhibits potent anti-microbial activity due to the production of allicin in damaged garlic tissues which inhibits bacterial infection in vapor form [109]. It also exhibits anti-bacterial and anti-biofilm potential against antibiotic resistant Shiga-Toxin producing *Escherichia coli* (STEC) isolates from food sources as well as from patient samples [110]. Since no volatile antibiotic is available till date that can treat pulmonary pathogenic infections, allicin could make a valuable addition to the presently available therapies.

5.4.1 Anti-viral potential of *Allium sativum*

Recently, the anti-viral property of garlic essential oil has been investigated by a group in which they examined the anti-coronavirus activity of garlic oil by molecular docking technique and observed that some biologically active ingredients of garlic such as diallyl-disulfide and diallyl-trisulfide have the potential to suppress ACE2 host receptor and main protease PDB6LU7 of SARS-CoV-2 virus [111]. Thus, the results suggest that garlic essential oil (GEO) may act as a valuable natural anti-viral source that contributes towards the restricted entry of coronavirus into the human body. A study suggested that *Allium sativum* possess the potential of reducing inflammatory cytokines and adipose tissue derive hormone i.e., leptin having inflammatory nature and may be utilize as a preventative measure in the population before being infected with COVID-19 infection [112]. Organosulfurs and flavonoids are found to be the predominant bioactives behind the immunomod-

ulatory nature of *Allium sativum*. By forming the hydrogen bonds with the active sites of serine protease these bioactives may inhibit the COVID-19 outbreak [113]. Furthermore, a study demonstrated that alliin, SAC and other bioactive compounds of *Allium sativum*, can be employed as a potential inhibitor candidate for COVID-19 and could be beneficial in combating this pandemic [114].

5.4.2 Anti-inflammatory and health mediated properties of *Allium sativum*

Several *in vitro* and *in vivo* studies reported that water fraction of garlic exhibits anti-inflammatory properties by which it ameliorated the infiltration of inflammatory cells, mucus hypersecretion and lung based-goblet formation in allergic asthma mouse model. Moreover, water fraction of garlic enhanced the levels of Th1 cytokines (IL-12 and IFNγ) along with reducing IL-1β, IL-6 and TNF-α inflammatory cytokines in BALF [115]. Administration of SAC also protected the LPS induced acute kidney injury (AKI) in C57BL/6 strain of mice via preserving the mitochondrial integrity with simultaneous reduction in oxidative stress, inflammation and apoptosis [116]. Thus, these studies suggested that *Allium sativum* can be a potential therapeutic candidate for COVID-19 infection.

5.5 *Zingiber officinale* (Ginger)

Zingiber officinale belongs to Zingiberaceae family which is not only utilized as a spice or flavouring agent in food but also considered as a traditional medicine from ancient times. It is adapted as a traditional herb due to its potential to treat various health problems such as nausea [117], migraine [118], diabetes etc. [119, 120]. The biologically active ingredients that are responsible for its pharmacological properties are paradols, 5-acetoxy-6-gingerol, gingerdiones, gingerdiols, 6-gingerol, 10-gingerol, 12-gingerol, 6-dehydrogingerols, 6-shogaol and 3,5-diacetoxy-6-gingerdioal. Among all the two primary compounds that are found to be associated with medicinal properties are 6-gingerol and 6-shogaol [121]. It also exhibits anti-microbial [122], anti-inflammatory [123], anti-ageing [124], anti-oxidant [125], neuroprotective [126] and anti-carcinogenic [127, 128, 130, 131] properties. Both hyperoxia and inflammatory conditions cause lung injury that further leads to the progression of broncho-pulmonary dysplasia (BPD) condition.

5.5.1 Anti-viral potential of *Zingiber officinale*

Moreover, it has also been found that ginger essential oil (GEO) constituents also exhibit the virucidal activity [131]. Recently, molecular docking study revealed that rhizome extract of ginger possesses higher affinity for the SARS-CoV-2 papain-like protease (PLpro) which is essential for the survival and replication of SARS-CoV-2 [132]. Recently, *in silico* study demonstrated that phytochemical compounds of *Zingiber officinale* showed significant affinity with the S-spike protein of SARS-CoV-2 and ACE2 receptor in the host and may have a great potential in reducing the viral load along with decreasing the shedding of SARS-CoV-2 in the nasal passage [133]. Hence, it may be of interest to consider garlic for anti-viral therapy.

5.5.2 Anti-inflammatory and health mediated properties of *Zingiber officinale*

Administration of ginger at a dose 1000 mg/kg abridged the levels of inflammatory cytokines (IL-1β, IL-6 and TNF-α) and protected the lung from the damage and edema in LPS + hyperoxia mice group [134]. Different fractions of ginger also exhibited the potential to inhibit the migration and activation of monocytes, macrophages and neutrophils [123]. Hence, suggesting that *Zingiber officinale* possess the potential of treating viral infection by suppressing the inflammation induced upon viral infection.

5.6 *Curcuma longa* (Turmeric)

Curcumin belongs to curcuminoids group that accounts for the majority of fraction of curcuminoids as compared to bisdemethoxycurcumin and demethoxycurcumin. It is also known as diferuloylmethane and found to be the chief polyphenol observed in rhizome of *Curcuma longa* (Turmeric) and other curcuma species [135]. In the past 50 years, most of the beneficial properties of *Curcuma longa* are predominantly attributed to curcumin. *Curcuma longa* has traditionally been used as a medicinal herb for pathological conditions due to its anti-microbial, anti-inflammatory, anti-carcinogenic and anti-oxidant properties.

5.6.1 Anti-viral potential of *Curcuma longa*

Curcumin is also known to possess anti-viral properties against dengue virus (serotype 2) [136], human simplex viruses (HSV) [137], HIV [138], Zika and chikungunya viruses [139]. Moreover, *in vitro* and *in vivo* studies revealed that treatment with curcumin ameliorated the influenza virus associated pneumonia by attenuating the lung injury and regulating the levels of inflammatory cytokines in macrophages [140]. Recently, a study discussed the potential ways by which curcumin (poly-phenolic compound) can be employed for treating SARS-CoV-2 infection [141]. Furthermore, docking results suggest that curcumin exhibits the highest interaction with the spike protein (-141.36 kcal/mol) and with the ACE2 receptor (-142.647 kcal/mole) [142]. In consistence with this, a study suggested that curcumin also displayed significant binding with the M^{Pro} [143]. Interestingly, with the help of *in silico* approach researchers evaluated the potential of curcumin in destabilizing the structural integrity of SARS-CoV-2 in combination with hydroxychloroquine [144]. Molecular docking data displayed that binding energy of hydroxychloroquine (-24.58 kcal/mol) is greater than that of curcumin (-20.47 kcal/mol) for main protease. On the other hand, for S protein receptor binding domain, curcumin displayed higher binding energy (-38.84 kcal/mol) in comparison to hydroxychloroquine (-35.87 kcal/mol) [144]. Thus, the study sug-

gested that curcumin can also be used as adjunct drug with hydroxychloroquine for disrupting the structural integrity of the SARS-CoV-2 protein. Altogether, these studies support the potential of curcumin as a promising treatment against viral infections including COVID-19 that mediates its effects by damaging the lung tissues.

5.6.2. Anti-inflammatory and health mediated properties of *Curcuma longa*

Inflammasomes plays a vital role in maturation and secretion of inflammatory cytokines (IL-1β and IL-18) via NF-κB signaling pathway. Recently, a study proved that curcumin works as an "inflammasome silencer" [145]. It has been found that curcumin also plays a vital role in various respiratory diseases such as asthma, acute lung injury, chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis that are linked with inflammatory conditions [146, 147]. However, its low or no water solubility results in its poor bioavailability, rapid metabolism, and fast elimination thus lessening its therapeutic efficacy. Recently, it has been observed that nanoencapsulation of curcuminoids isolated from *Curcuma longa* and liposomal curcumin formulation enhanced its water solubility [148, 149]. Furthermore, a study demonstrated that loading of curcumin on large porous microparticles (LPMPs) showed promising results in the treatment of idiopathic pulmonary fibrosis [150]. Charge of the nanoparticles carrying curcumin plays a key role in regulating the efficiency and cellular uptake of nanoparticles and it was observed that the positively charged nanoparticles have a higher efficiency to enter into alveolar macrophages as compared to negatively or neutral charged nanoparticles [151]. Thus, the studies suggest that curcumin could be used as therapeutic and prophylactic agent in inhibiting the attachment of virus with the host cells.

5.7 Cinnamon (Dalchini)

Till date different cinnamon species e.g. *Cinnamomum verum*, *Cinnamomum cassia*, *Cinnamomum burmanii*, *Cinnamomum zeylanicum*, *Cinnamomum tamala*, *Cinnamomum loureirii* and *Cinnamomum cordatum* have been reported that can be used in food industries as food additives. Cinnamon belongs to Lauraceae family and recently, cinnamon has gained tremendous attention due to its medicinal properties. The pharmacologically active chemical components of cinnamon are: cinnamaldehyde, trans-cinnamaldehyde and cinnamic acid. These active components confer various health benefits when administered adequately including antioxidants, anti-microbial, anti-inflammatory, anti-gastric ulcer, anti-yeast etc. [152].

5.7.1 Anti-viral potential of Cinnamon

In most of the viral infections including SARS-CoV-2 the expression of HSPA5 protein is upregulated due to ER stress conditions [153]. Interestingly, it has been reported that SARS-CoV-2 with the aid of spike protein enters into the host cells by using more than one host cell receptor and among them one of the receptors is HSPA5 also known as Bip or GRP78 [154]. Under stress conditions, HSPA5 is exposed on the cell surface that permits pathogen entry into the cell. Surprisingly, cinnamon administration has been reported to reduce ER stress in rat obesity mouse model [155] thus it is plausible to suggest that cinnamon administration may also inhibit the translocation of HSPA5 to the cell membrane from cytoplasm and reduce the interaction between virus and host cells thereby, inhibiting virus entry. Recently, it has been demonstrated that cinnamon exhibits the potential to bind HSPA5 substrate binding domain β (SBDβ) with a binding energy -6.25 $\pm$ 1.10 and thus it might interfere with SARS-CoV-2 recognition and binding [156]. Furthermore, *in silico* data validation indicated that two compounds Pavetannin C1 (PAV) and Tenufolin (TEN) among 48 isolates compounds of cinnamon exhibits good binding efficacy with the main proteases and spike proteins of SARS-CoV-2 [157]. *Cinnamomum zeylanicum* is also one of the components of Ayiush Kwath that exhibits anti-inflammatory, anti-oxidant, anti-platelet and hepatoprotective potential that may be effective in controlling COVID-19 infection [158].

5.7.2 Anti-inflammatory and health mediated properties of Cinnamon

The bark of *Cinnamomum verum* has well established anti-inflammatory potential and it has been demonstrated that the ethanolic fraction of cinnamon showed anti-inflammatory properties by inhibiting the production of IL-1β, IL-6, TNF-α and nitric oxide (NO) molecules [159]. Also, a study reported in 2018 showed that ethanolic fraction of cinnamon inhibited the LPS induced IL-8 secretion in THP-1 monocytes via modulating TLR-2 and TLR-4 signaling pathway [160]. Thus, cinnamon can be employed as an antidote against natural and chemical toxicities.

5.8 *Moringa oliefera* (Drumsticks)

Moringa oliefera belongs to Moringaceae family and commonly known as drumstick or miracle tree, considered as nature's healthiest and nutritious plant. Its origin is in the northern side of India and its pharmacological properties lie in the different parts of tree such as leaf, bark, sap, roots and flowers that have been utilized as a traditional herb for years [161]. *M. oliefera* exhibits ethnomedicinal characteristics, attributed to various biologically active ingredients of the plant such as flavonoids, polyphenol, vitamins, tannins, isothiocyanates and saponins [162, 163].

5.8.1 Anti-viral potential of *Moringa oliefera*

Moreover, seeds of the *M. oliefera* have also been utilized as reducing and stabilizing agents for the biosynthesis of silver nanoparticles (AgNP) to fight against dengue virus (DEN-2) and its primary vector *Aedes aegypti* [164]. Further, leaves of *M. oliefera* tree facilitated the manufacturing of gold nanoparticles that further aided the cancer

cells recognition and possess anti-proliferative and apoptotic activities [165]. Recently, some evidences suggest that plants not only provide macro and micro-nutrients as food but also deliver distinct molecules with medicinal properties such as microRNAs and developed a phenomenon known as "cross-kingdom regulation" [166]. Thus, it is plausible to suggest that *M. oliefera* being nutritious plants follows this cross-kingdom regulation and modulates the expression of human genes responsible for immunomodulatory properties. Recently, a study attempted to identify the natural compounds from *M. oliefera* that exhibit the potential to inhibit COVID-19 [167]. The molecular docking results suggested that four compounds such as quercetin, kaempferol, morphine and pterygospermin displayed higher binding efficacy with M^{pro} and RNA dependent RNA polymerase (RdRp) proteins of SARS-CoV-2 [167]. Thus, these data clearly indicate that these four compounds can be a promising candidate for COVID-19 prevention. Further, *in silico* study confirmed that phytocompounds of *M. oliefera* showed strong interaction with main protease of SARS-CoV-2 and can curtail the replication of SARS-CoV-2 in host cells [168]. Moreover, a study suggested that presence of Anthraquinone phytochemical in *M. oliefera* may serve as an anti-viral agent against COVID-19 [169].

5.8.2 Anti-inflammatory and health mediated properties of *Moringa oliefera*

Several studies demonstrated that different extracts (alcoholic or aqueous) of *M. oliefera* leaves possess diverse range of biological activities such as immunomodulatory, analgesic, radioprotective, tissue protective (liver, kidney, testes, lungs and heart) and antioxidant properties [162, 170]. In comparison to moringa seed extract (MSE), extract enriched with isothiocyanate showed enhanced anti-inflammatory potential under both *in vitro* and *in vivo* conditions making it a promising phytotherapeutic agent [171]. Furthermore, one of the novel polysaccharides (MRP-1) isolated from the roots of *M. oliefera* showed enhanced anti-inflammatory properties by suppressing NO and TNF-α expression in LPS induced inflammation in macrophages. Thus, pointing towards new possible application of *M. oliefera* [172].

5.9 *Azadirachta indica* (Neem)

Azadirachta indica belongs to Mahogany family, commonly known as Muarubaini; and possess the potential to treat 40 different diseases. Due to its astonishing activities this plant is also known as Heal All, Nature's Drugstore, Village Pharmacy and Panacea [173]. United Nations has declared Neem plant as "Tree of 21st century" and various reports also suggested that this plant is meant for resolving global problems. Neem is also considered to be "storehouse" for more than 300 phytochemicals. Two foremost classes of phytochemicals are isoprenoids and non-isoprenoids. Isoprenoids class includes limonoids, C-secomeliacins, vilasinins, diterpenoids and triterpenoids. Non-isoprenoids class involves coumarin, polyphenolics, sulfur compounds, tannins, aliphatic compounds, polysaccharides, and proteins. Nimbin is a triterpenoid that accounts for the pharmacological activities of neem oil. It exhibits anti-pyretic, anti-inflammatory, antiseptic, anti-histamine, anti-microbial, anti-malarial, anti-cancer and fungicidal properties [173–175].

5.9.1 Anti-viral potential of Azadirachta indica

Recently, using computational and experimental method it has been observed that bioflavonoids of *A. indica* inhibited Dengue virus type-2 (DENV-2) infectivity by interacting with NS2B-NS3; DENV-2 serine viral protease. Further, by using molecular docking, molecular dynamics simulation and binding energy calculations, it was observed that the compounds derived from neem such as Nimbolin A, Nimocin and Cycloartanols displayed stable and efficient binding with the vital regions of E and M proteins required for the assembly of SARS-CoV-2 [176]. Moreover, a study revealed that several compounds present in the leaves of neem exhibit the potential to suppress the M^{pro} of SARS-CoV-2 [177]. Altogether, these results demonstrated that Neem exhibits multidimensional therapeutic applications and can also be a potential therapeutic option against COVID-19. Recently, a study demonstrated that *A. indica* showed significant inhibitory activity against papain like proteases PLpro of SARS-CoV-2 [178]. Among various compounds, desacetylgedunin (DCG) showed highest binding affinity against PLpro [178]. In consistent to this, a study showed that in comparison to other bioactive compounds of *A. indica*: few compounds viz. Vepnin, Epiazadiradione, Azadiradione and Nimbione compounds showed greater potential to acts as COVID-19 protease inhibitor. Thereby, it is plausible to suggest that neem may acts a potential phytotherapy in COVID-19 pandemic by inhibiting the proteases required for the infectivity and replication of SARS-CoV-2 [179], thereby highlighting the potential of *A. indica* in the development of effective drug against viruses.

5.9.2 Anti-inflammatory and health mediated properties of Azadirachta indica

Furthermore, a study revealed that treatment with neem leaf extract suppressed the infiltration of neutrophils and monocytes along with reduction of IL-6, MCP-1 and TNF-α cytokines in BALF in the lungs of LPS-induced pulmonary inflammatory mice model [180]. Moreover, a study demonstrated that treatment with nimbolide (limonoid) abrogated the difficulties associated with ARDS. Molecular docking studies suggested that nimbolide interacts with TNF-α and hence ameliorated the TNF-α-regulated NF-κB-histone deacetylases 3 (HDAC3) crosstalk in LPS induced ARDS [181]. These reports thus suggest towards the usage of neem in treating chronic pulmonary diseases. A study showed that nimbolide ameliorated colitis in Dextran Sodium Sulfate (DSS) induced mice model by suppressing

the NF-κB mediated inflammatory signalling pathway in macrophages and intestinal epithelial cells [182].

5.10 *Ocimum tenuiflorum/sanctum* (Tulsi)

Ocimum tenuiflorum belongs to Lamiaceae family and is commonly known as holy basil or Tulsi. Within Ayurveda this plant is known as "The Queen of Herbs" and "Mother Medicine of Nature". Various scientific studies till date have examined the medicinal properties of tulsi under both *in vitro* and *in vivo* conditions. These studies demonstrated that tulsi has unique blend of actions such as anti-inflammatory, anti-stress, anti-cancer, anti-microbial, anti-oxidant, anti-ulcer, anti-thyroid, adaptogenic, anti-cataract etc. [183].

5.10.1 Anti-viral potential of *Ocimum tenuiflorum/sanctum*

Furthermore, it has been found that different fractions of *O. tenuiflorum* (crude extract, polyphenol and terpenoid) exhibited anti-viral properties against avian influenza H9N2 infection [184]. Molecular docking studies have proved that several phytochemicals isolated from *O. sanctum* showed anti-viral activity by interacting with proteins involved in viral replication and metabolic pathways of H1N1 influenza virus [185]. Anti-viral based cytopathic effects (CPE) studies showed that methanolic extracts of *O. sanctum* inhibited the cell death of Vero E6 cells infected with DENV-1 serotype [186]. Moreover, molecular modelling studies revealed that natural products derived from *O. sanctum* leaves possess inhibitory activity against ribonuclease-H and DNA polymerase activity of Reverse Transcriptase (RT) enzyme of HIV [187]. Recently, a study via *in silico* approach showed that flavonoids and polyphenolic compounds predominantly luteolin-7-O-glucuronide and chlorogenic acid, exhibits the ability to covalently bind to the main protease of SARS-CoV-2 and results in irreversible inhibition of viral enzyme [188]. Moreover, a study suggested that *Ocimum sanctum* extract bioactive compounds viz. tulsinol showed significant interaction with the ACE2 receptor, main proteases and papain like proteases [189]. Thus, these studies suggests that *Ocimum sanctum* can be employed as a preventative measure against COVID-19 due to its inherent potential to inhibit virus entry, virus replication etc.

5.10.2 Anti-inflammatory and health promoting properties of *Ocimum tenuiflorum/sanctum*

A study revealed that leaf extract of *O. tenuiflorum* and its phenolic compound eugenol attenuated the activation of human monocyte THP1 cells by suppressing the LPS induced IL-6, MIP-1α, MCP-1 and TNF-α secretion and also block the NF-κB translocation from cytoplasm to nuclei [190]. *O. sanctum* also showed lung and brain protective effects against smoke aggravated pulmonary and brain damage in rats by suppressing smoke induced oxidative stress [191, 192].

5.11 *Camellia sinensis* (Green tea)

Camellia sinensis belongs to Theaceae family and is commonly known as green tea. Tea is one of the widely used beverages worldwide and mainly comprises of minerals, vitamins, carbohydrates, polyphenols, caffeine, and theanine [193]. Among other polyphenols, catechins and flavonols are found to be the predominant constituents. Further, catechins include epicatechin (EC), epigallocatechin (EGC), gallocatechin (GC), epicatechin gallate (ECG), gallocatechin gallate (GCG), and epigallocatechin gallate (EGCG). Green tea exhibits various health benefits against different diseases such as diabetes, obesity, cancer, cardiovascular diseases, neurodegenerative disorders etc. [193, 194].

5.11.1 Anti-viral potential of *Camellia sinensis*

Furthermore, Zhou *et al.* stated that SARS-CoV-2 infected patients are prone towards secondary infections that lead to multi-organ failure [3]. Interestingly, a study showed that administration of L-theanine alleviated the organ damage in sepsis induced liver and kidney injury mice model in a dose dependent manner [195]. Catechin polyphenol also known to exhibit anti-viral properties against HIV, influenza virus, herpes simplex virus type-1 and hepatitis B and C viruses [155, 196]. In order to investigate the anti-viral potential of *Camellia sinensis* against coronavirus, a recent study demonstrated that EGCG displayed higher binding energy (-8.3 kcal/mol) with M^{pro} of SARS-CoV-2 in comparison to remdesivir (-7.1 kcal/mol) and chloroquine (-5.8 kcal/mol) [197]. Further, molecular docking analysis revealed that five bioactive polyphenols of *Camellia sinensis* viz. theaflavin, epigallocatechin 3-gallate, genistein, 1-O-caffeoylquinic acid and ethyl transcaffeate showed affinity against matrix metalloproteinase (MMPs) against SARS-CoV-2 main protease [198]. Among these five polyphenolic compounds, theaflavin and epigallocatechin 3-gallate showed strong affinity and good drug likeness score and could be beneficial option in the prophylaxis of COVID-19 outbreak [198]. In consistent to this, a similar study suggested that EGCG and theaflavin mainly theaflavin-3, 3'-digallate (TF3) showed significant interaction with the receptor binding domain of SARS-CoV-2 [199]. Also, tea component Thearubigins showed strong affinity against SARS-CoV-2 3CL^{pro} protease and it suggests that *Camellia sinensis* can halt replication cycle and thus, can be a potential therapeutic option against SARS-CoV-2 infection [200]. Furthermore, a study suggested that *Camellia sinensis* is a vital source of nutritional immunity which can increase innate immunity and mitigate the COVID-19 pandemic and disease progression [201].

5.11.2 Anti-inflammatory and health mediated properties of *Camellia sinensis*

Remarkably, various animal and human studies showed that EGCG (predominant catechins); possess anti-

inflammatory potential [202, 203]. A study reported that pre-treatment with theanine (20 mg/kg/day) (bioactive component of green tea leaves) suppressed the LPS induced secretion of IL-1β, IL-6, and TNF-α along with enhancing the IL-10/IFN-γ ratio in the liver of mice [204]. Furthermore, administration of theanine also alleviated the LPS induced C-reactive proteins and iNOS in liver tissues [204]. Thus, ameliorated inflammation in LPS induced acute liver injury mice model. Recently, a study reported that treatment with green tea extract attenuated inflammation in the colon tissues by supressing NF-κB signaling pathway and restored the gut-integrity in DSS induced colitis mice model [205]. It also exhibits pre-biotic properties and administration of green tea extract enhanced the abundance of beneficial bacteria (*Bifidobacterium* and *Faecalibaculum*) along with reducing the abundance of harmful bacteria (*Mucispirillum* and *Bacteroids*) in colitis model [205].

5.12 *Astragalus membranaceus* (Huangqi)

Astragalus is an important traditional herb in Chinese medicine. Primarily, it is used as a lung protective tonic that enhances resistance against pulmonary infections. From *in vitro* studies, it was observed that treatment with *Astragalus* augmented the cytotoxic T cells function; B cells proliferation, activation and antibody mediated responses [206]. Various studies till date have reported anti-viral properties of *Astragalus* polysaccharide (APS) against viruses [207, 208].

5.12.1 Anti-viral potential of *Astragalus membranaceus*

A study reported that in case of COVID-19, endoplasmic reticulum (ER) stress plays a crucial role in the upregulation of receptors required for SARS-CoV-2 adherence to the host cells. Remarkably, it has been observed that APS attenuated porcine circovirus type 2 (PCV2) infections by inhibiting ER stress both *in vitro* and *in vivo* [209] thereby highlighting the significance of APS consumption in limiting virus entry into the host cells through the inhibition of ER stress. These studies therefore clearly highlight the potential of *Astragalus* in the management of SARS-CoV-2 mediated pathologies. Recent studies have shown that multiple organ failure that occurs during COVID-19 infection results from the enhancement in inflammatory cytokine storm and accumulation of free radicals. A study revealed that *Astragalus membranaceus* exhibits anti-inflammatory property and suppressed the activation of MAPK/NF-κB signaling pathway and downregulated the levels of inflammatory cytokines such as IL-6, IL-8 and TNF-α and thus, reduced the inflammatory response. One of the biological active compounds of *Astragalus membranaceus* i.e. *Astragaloside IV* activated the PI3K/Akt signaling pathway and enhanced the levels of superoxide dismutase (SOD) and protected the body.

5.12.2 Anti-inflammatory and health mediated properties of *Astragalus membranaceus*

A study showed that treatment with APS suppressed the replication of avian infectious bronchitis coronavirus in chicken embryo kidney (CEK) cells by reducing the expression of inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α) [207]. Further, it has been reported that APS promoted immunity and exerted anti-tumorigenic property by modulating TLR4 mediated MyD88 dependent signalling pathway [210, 211]. Recently, a study revealed that it ameliorated the *Salmonella typhimurium* induced inflammation in diarrhea mice model by balancing the GUT flora of mice that maintains the intestinal integrity by enhancing the tight junction proteins viz. Claudin-1 and Occludin [212]. Moreover, a study demonstrated that total flavonoid astragalus (TFA) extracts attenuated LPS elicited inflammation in Raw 264.7 macrophages by reducing MAPK and NF-κB signalling pathway [213]. A study has reported that treatment with astragaloside, an active component of *Astragalus membranaceus* inhibited the IL-1β induced generation of inflammatory mediators such as prostaglandin E2 (PGE2), IL-6, TNF-α and MMP-13 in patient derived chondrocytes and osteoarthritis mouse model [214]. Thus, we can propose that astragaloside may act as a potential therapeutic agent in the treatment of various inflammatory diseases. Moreover, it has been shown that consumption of dried root of *Astragalus* protected various organs such as kidney, liver, heart, lungs, intestine and brain from oxidative stress mediated injury in various mice models [215, 216]. Recently, few studies reported that usage of *Astragalus membranaceus* with other anti-oxidative compounds enhanced the immunomodulatory potential of *Astragalus* [217–219].

5.13 *Piper longum* (Pippali)

Piper longum belongs to Piperaceae family, commonly known as long pepper (pippali). Piperlongumine (PL) an amide compound extracted from the roots of *P. longum*, is a biologically active component known for its medicinal properties. It possesses various physiological and pharmacological properties such as anti-tumorigenic, anti-inflammatory, anti-depressant, analgesic, sedative etc. [220–222].

5.13.1 Anti-viral potential of *Piper longum*

Recently a study demonstrated that piperolactam A from *P. longum* shows higher affinity for M^{pro} and ACE2 receptor [223]. It has been observed that by targeting these proteins, piperolactam A blocks the replication and entry of virus into the host cells [223].

5.13.2 Anti-inflammatory and health mediated properties of *Piper longum*

Recently, a study revealed that pre-treatment with PL suppressed the OVA induced airway inflammation in asthma mouse model. PL administration inhibits inflam-

matory reaction in both BALF and lung tissue by suppressing the infiltration of inflammatory cells and T_H2 cytokine levels involved in IgE production by reducing NF-κB mediated inflammatory pathway in asthma model [224, 225]. In continuity to this, a study reported that treatment with PL significantly reduced the lipopolysaccharide (LPS) induced inflammatory genes expression (IL-6, TNF-α, iNOS) in BV2 microglial cells by inhibiting NF-κB signaling pathway [226]. Thus, these evidences suggest that PL could be a potential agent in treating various inflammatory diseases. Generally, macrophages are categorized under two extremities: M1 macrophages (pro-inflammatory) and M2 macrophages (anti-inflammatory) and dramatic shifts in the cell metabolism pathways regulate the phenotype and functions of M1 and M2 macrophages [227]. Interestingly, a study demonstrated that PL exhibits the potential to suppress glycolysis via suppression of hexokinase activity [228]. It also reduces the glucose levels, influx of lymphocytes, macrophages, and neutrophils in BALF and attenuates both systemic and pulmonary inflammation [229]. A study reported that hypoxia condition can potentiate the activity of PL [230]. Thus, these findings suggest that PL exhibits the potential to eradicate viral infection by modulating the inflammatory potential of alveolar macrophages via altering the metabolic profile of these cells under hypoxic conditions observed in case of COVID-19 patients.

5.14 *Phyllanthus emblica* (Amla)

Phyllanthus emblica or *Emblica officinalis* belongs to Phyllanthaceae family and is commonly known as Indian gooseberry. The fruits are utilized widely in Ayurvedic medicine as a potent "Rasayana" and also found to be the major component of the Ayurvedic preparation "Chyawanprash" [231, 232]. Increasing evidences suggest that *P. emblica* extract (PEE) possess lung protective activities.

5.14.1. Anti-viral potential of *Phyllanthus emblica*

Recently, a study demonstrated that various chemical constituents of *Phyllanthus emblica* such as phyllaemblicin-B, phyllaemblinol and phyllaemblicin G7 exhibited higher binding affinity against helicase and spike proteins of SARS-CoV-2 [233]. In case of SARS, MERS and SARS-CoV-2 virus, 3-chymotrypsin like cysteine proteases ($3CL^{pro}$) enzyme regulates their replication and life cycle. A study demonstrated that (2S)-Eriodictyol 7-O-(6″-O-galloyl)-beta-D-glucopyranoside phytochemical from *Phyllanthus emblica* displayed strong binding affinity with $3CL^{pro}$ (-19.47 kcal/mol) enzyme. Thus, altogether these studies prove that *Phyllanthus emblica* may be a potential therapeutic candidate for COVID-19 treatment [234].

5.14.2 Anti-inflammatory and health mediated properties of *Phyllanthus emblica*

Studies showed that administration of PE extract protected the lung from the inflammatory injury by altering the IL-1β/miR-i101/Lin28B signaling pathway [235]. It also inhibited the benzopyrene induced pre-cancerous lung lesions by downregulating the pro-inflammatory cytokine expression viz. IL-1β, IL-6, TNF-α and MIP-2 in lung tissues. It also suppressed edema in rats in a dose dependent manner [236].

6. Concluding remarks and future outlook

In the present review, we have summarized the pharmacological potential of various traditional medicines that can be employed for the management and treatment of cytokine storm induced in COVID-19. Phytotherapeutic agents play a vital role in the prevention and treatment of several diseases including viral diseases. Traditional plants having medicinal properties are used as foremost resources for alternative medicine including several modern medicines for the treatment of various human disorders including chronic inflammatory conditions. The traditional medicines are also found to be effective in treating various viral infections. The scientific society has already proven the efficacy of various plants harboring anti-viral potential for such conditions and also accomplished relevant position for them in the health care system across the globe for both human and animals. Currently, there are no proven treatment options available for the deadly acute respiratory distress syndrome caused by SARS-CoV-2 virus. Various countries including India and China have already resorted to their respective traditional medicine for the management of COVID-19 pandemic which has been of great help in alleviating various symptoms leading to reduced mortality associated with the viral infection. In April 2020, China approved the usage of three traditional herbs (Liahuaqingwen, Jinhuaqinggan and Xuebijing) in treating mild and severe cases of COVID-19 [237]. However, when we employ them with antibiotics, anti-virals and immunosuppressive drugs; safety should be cautiously monitored. Several *in silico* studies have also proven the relevance of traditional medicines in inhibiting the viral entry, virus replication and assembly (Figs. 4,5). A study demonstrated that EGYVIR (herbal drug comprised of black pepper and curcumin) antagonize the NF-κB signaling pathway and abrogated the release of inflammatory cytokines viz. IL-6 and TNF-α under SARS-CoV-2 infected Huh-7 cell line [238]. Taken together, more evidences and clinical trials are further warranted for the judicious use of traditional herbs in the treatment of COVID-19.
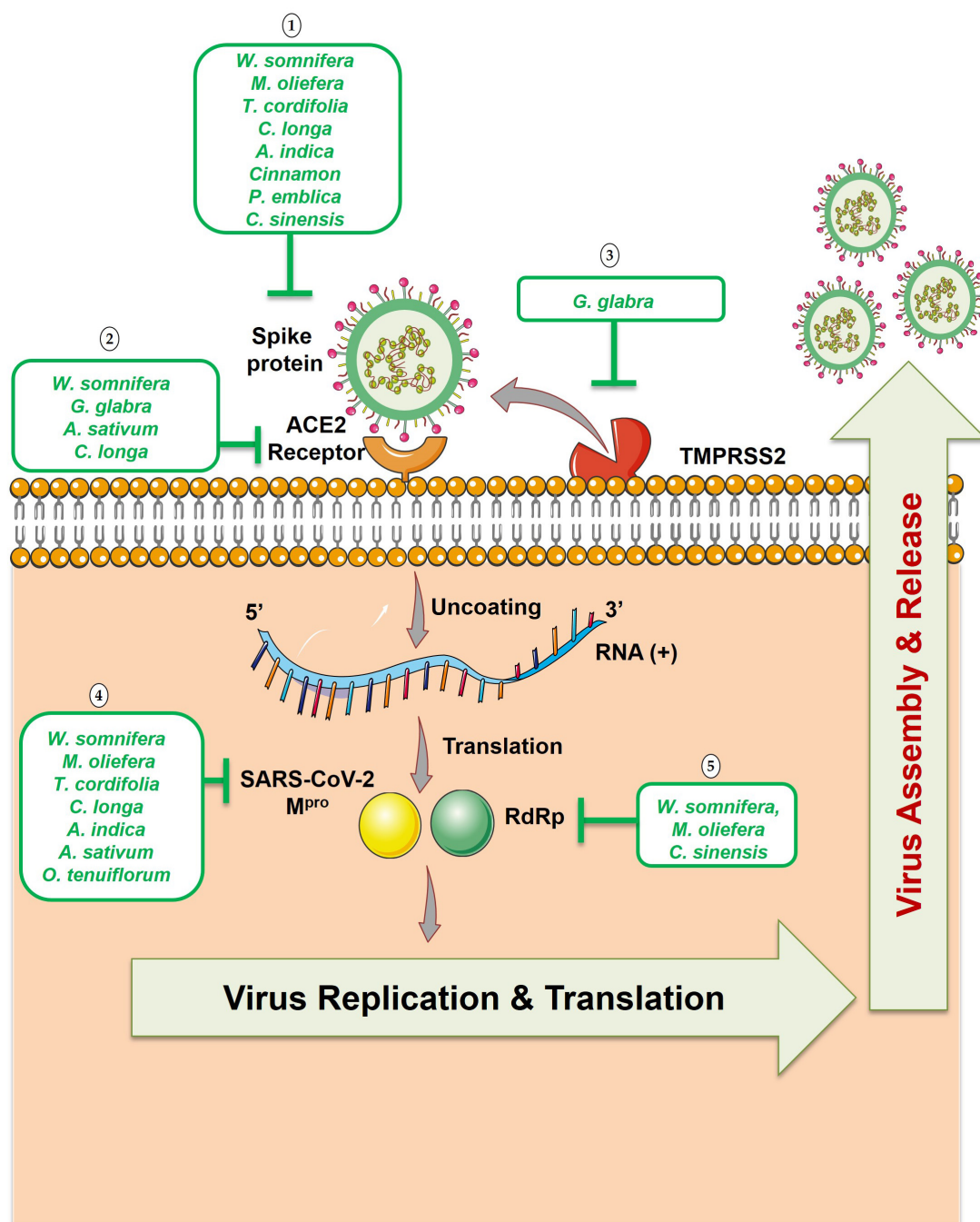
Fig. 4. Potential phytotherapeutic approaches against SARS-CoV-2. (1) Natural compounds that targets spike proteins could block SARS-CoV-2 from interacting with the ACE2 receptor. (2) Natural compounds that targets ACE2 host receptor could block SARS-CoV-2 attachment to the cells. (3) Natural compounds against the serine protease (TMPRSS2) prevent the spike protein cleavage which is required for the viral fusion to the host cells. (4) Natural compounds that targets M^{pro} Main protease) could block the replication and translation of viral genome. (5) Natural compounds that hinders RdRp (RNA Dependent RNA Polymerase) activity leads to blockage of viral positive sense (+) single stranded RNA replication (Figure illustrated with the help of https://smart.servier.com/).

7. Author contributions

RKS conceptualized and wrote the manuscript. LS drafted and revised the manuscript. AB, ZA, DM, BV and SR provided valuable suggestions during manuscript preparation and critically revised the manuscript. RKS suggested and LS created the illustrations.

8. Ethics approval and consent to participate

Not Applicable.
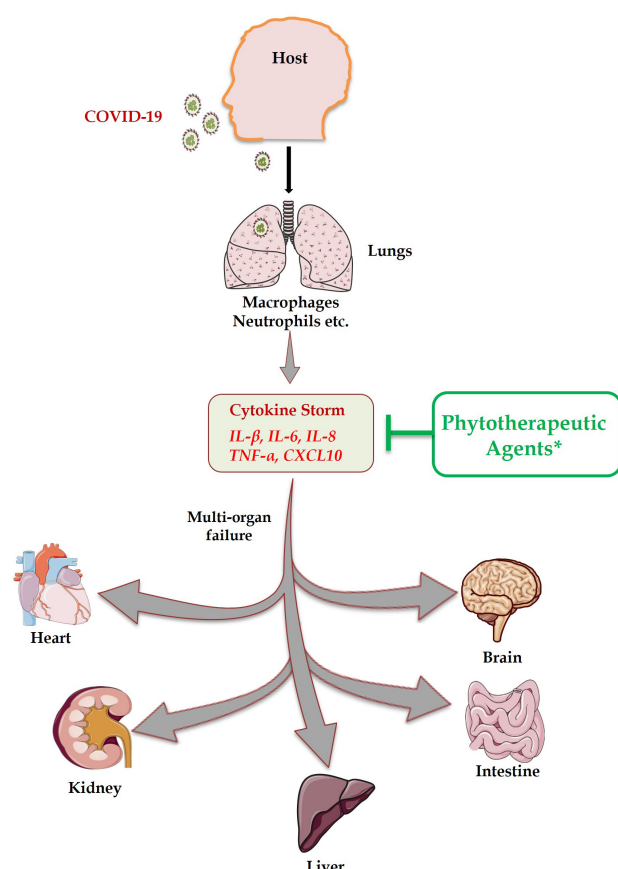
Fig. 5. Transmission of COVID-19 occurs mainly from one person to other through droplets during sneezing and coughing, touching contaminated surfaces, personal contacts etc. After entering host, it attacks the lung tissue and results in massive production of inflammatory cytokines (Cytokine Storm Syndrome) that in turn causes multi-organ failure. Phytotherapeutic agents exhibit the potential to suppress inflammatory cytokines along with tissue protective properties.

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11. Conflict of interest

The authors declare no conflicts of interest.

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