

# Phytochemicals: A Novel Approach for the Management of Coronavirus Disease 2019

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## Shivatare *et al.*: Phytochemicals in the Management of Coronavirus Disease 2019

The severe acute respiratory syndrome coronavirus 2, formerly known as 2019 novel coronavirus, the causative pathogen of coronavirus disease 2019 is a major source of disaster in the 21<sup>st</sup> century. In the second meeting of the Emergency Committee, the World Health Organization declared that coronavirus disease 2019 is a “public-health emergency of international concern” on 30 January, 2020. Coronavirus is transmitted *via* airborne droplets from human to human or human to animal. Through membrane angiotensin-converting enzyme 2 exopeptidase receptor coronavirus enters in human cell. For the treatment of this sudden and lethal disease during coronavirus disease 2019, there are no specific anti-virus drugs or vaccines. Still, the development of these medicines will take months, even years. Currently there is need of supportive care and non-specific treatment to improve the symptoms of coronavirus disease 2019 infected patient. For this specific indication, rapid performance of herbal medicine or phytochemicals can contribute as an alternative measure. Phytochemicals are a powerful group of chemicals that are derived from plants origin hence causing fewer side effects because of less use of additives, preservatives or excipients. Hence, this review will focus on some phytochemicals which may control and prevent severe acute respiratory syndrome coronavirus 2. Further, the existing healing options, drugs accessible, ongoing trials and current diagnostics to treat severe acute respiratory syndrome coronavirus 2 have been discussed. We suggested phytochemicals extracted from herbal plants are potential novel therapeutic approaches, completely targeting severe acute respiratory syndrome coronavirus 2 and its pathways.

**Key words:** Severe acute respiratory syndrome coronavirus 2, phytochemicals, herbal medicine, coronavirus disease 2019

Coronaviruses (CoVs) classified to the subfamily Orthocoronavirinae in the family Coronaviridae and order Nidovirales. The subfamilies Orthocoronavirinae again contain four genera, namely Alphacoronavirus ( $\alpha$ -CoV), Betacoronavirus ( $\beta$ -CoV), Gammacoronavirus ( $\gamma$ -CoV) and Deltacoronavirus ( $\delta$ -CoV). From that,  $\alpha$  and  $\beta$ -CoV genera are known to infect mammals, whilst  $\delta$  and  $\gamma$ -CoVs are identified to infect birds. Coronavirus Disease 2019 (COVID-19) is not the first severe respiratory infection epidemic originated by the corona virus. In the past few decades, CoVs have caused three outbreak infections, namely, COVID-19, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)<sup>[1,2]</sup>. This article gives a bird's eye view about this new virus i.e. COVID-19 and phytochemicals which may be effective in the treatment of COVID-19 as given in fig. 1. In view of the fact that awareness about this new virus is speedily developing,

readers are urged to modernize themselves repeatedly.

## HISTORY

Novel Coronavirus (nCoV)-precipitated pneumonia, which was named by the World Health Organization (WHO) on the February 11, 2020 as COVID-19, has swiftly accelerated in epidemic scale since it first appeared during December 2019, inside Wuhan city, China. The international virus classification commission, on the same day, declared that the nCoV was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Right now, the

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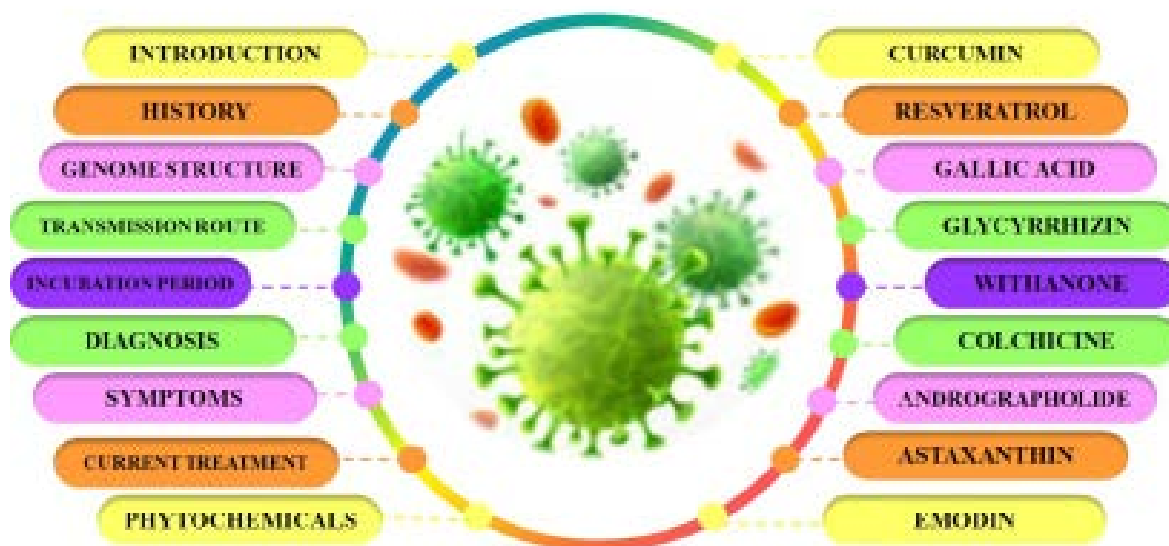
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**Fig. 1: Information about COVID-19 and phytochemicals used for the treatment of COVID-19**

COVID-19 cases have been found in many countries around the world including United States of America (USA), India, Germany, Brazil, France etc.<sup>[3]</sup>.

#### Genome structure:

COVID-19 is a sphere-shaped or pleomorphic enclosed particles surrounding single-stranded (positive-sense) Ribonucleic Acid (RNA) linked with a nucleo-protein within a capsid comprised of matrix protein. The envelope bears club-shaped glycoprotein protrusions. A few CoVs also enclose a Hemagglutinin-Esterase (HE) protein. A typical CoV have minimum six Open Reading Frames (ORFs) in its genome. Apart from  $\gamma$ -CoV that takes non-structural protein 1 (nsp1), the primary ORFs (ORF1a/b) constitute about two-thirds of the entire genome length, encoding sixteen nsps (nsp1-16). ORF1a and ORF1b fit in a frame shift among which it creates two polypeptides: Protein phosphatase (pp)1a and pp1ab. These polypeptides are progressed *via* virally encoded 3-Chymotrypsin Like protease (3CLpro) or Main protease ( $M^{pro}$ ) and one or more papain-like protease into 16nsps. All the structural and accent proteins are translated from the single guide RNAs (sgRNAs) of CoVs<sup>[4]</sup>. Four main structural proteins contain Spike (S), Membrane (M), Envelope (E) and Nucleocapsid (N) proteins are encoded by ORFs on the one-third of the genome near the 30-terminus. In addition to these four main structural proteins, different CoVs instruct particular structural and accessory proteins, such as 3a/b protein, HE protein and 4a/b protein. These established proteins are responsible for

numerous vital functions in genome safeguarding and virus reproduction. There are 3 or 4 viral proteins in the coronavirus membrane. The most enough structural protein is the membrane (M) glycoprotein; it extends the membrane belayed 3 times, parting a short Amine ( $NH_2$ )-terminal area outdoor the virus and a long Carboxyl ( $COOH$ ) terminus (cytoplasm domain) inner the virion. The spike protein (S) as a kind of membrane glycoprotein constitutes the peplomers. In fact, the primary inducer of neutralizing antibodies is S protein. Between the envelopes proteins there exists a molecular interplay that probably determines the formation and composition of the corona viral membrane. M performs a predominant function in the intracellular formation of virus particles except requiring S. In the existence of tunicamycin, CoV develop and generate spikeless, noninfectious virions that incorporate M but devoid of S<sup>[5]</sup>.

#### Symptoms:

The signs and indications of COVID-19 contamination come out later than an incubation length of about 5.2 d. The time from the onset of COVID-19 symptoms to finish ranged from 6 to 41 d with a center of 14 d. This duration is dependent on the age of the affected person and repute of the patient's immune system. It was once shorter among sufferers >70 y old in contrast with those under the age of 70. The most frequent signs and symptoms at onset of COVID-19 illness are fever, cough and fatigue, while other signs consist of sputum production, headache, haemoptysis, diarrhoea,

dyspnoea and lymphopenia. Clinical facets published with the aid of a chest Computed Tomography (CT) scan introduced as pneumonia; however, there were bizarre facets such as RNAemia, acute respiratory distress syndrome, acute cardiac injury and occurrence of ground-glass opacities that led to death. In some cases, the couple of peripheral ground-glass opacities were observed in subpleural regions of each lung that in all likelihood precipitated both systemic and localized immune response that led to extended inflammation. Regrettably, treatment of some instances with Interferon (IFN) inhalation showed no scientific effect and rather appeared to irritate the circumstance by using progressing pulmonary opacities<sup>[6,7]</sup>.

### Transmission route:

Transmission of the virus is primarily *via* inhalation of suspended respiratory secretions, i.e., droplets generated when an infected individual coughs, sneezes or speaks, or through direct contact with an infected patient. There is a possibility that viral RNA may also be transmitted through microparticles of saliva, e.g. in exhaled air or when speaking, although this remains to be confirmed. Viral load in saliva peaks at presentation and remains high for at least the 1<sup>st</sup> w of symptomatic illness, gradually declining thereafter but remaining detectable for 20 d or more.

The virus can also be transmitted *via* fomites. It remains viable for up to 24 h on cardboard and for up to 72 h on plastic and stainless steel. Infectious droplets and body fluids can also contaminate the human conjunctival epithelium, producing ocular complications that may then progress to respiratory infection. At later stages of infection, viral persistence has been detected in anal swabs, blood and serum, suggesting additional shedding mechanisms and the potential for transmission *via* the oral-fecal or body fluid routes<sup>[4,8]</sup>.

### Incubation period:

The mean incubation period of SARS-CoV-2 is estimated to be 3-7 d (range, 2-14 d), indicating a long transmission period of SARS-CoV-2. It is estimated that SARS-CoV-2 latency is consistent with those of other known human CoVs, including non-SARS human CoVs (mean 3 d, range 2-5 d), SARS-CoV (mean 5 d, range 2-14 d) and MERS-CoV (mean 5.7 d, range 2-14 d). Moreover, it has been reported that asymptomatic COVID-19 patients during their incubation periods can effectively transmit SARS-CoV-2, which is different from SARS-CoV because most SARS-CoV cases are

infected by 'superspreaders' and SARS-CoV cases cannot infect susceptible persons during the incubation period. Taken together, these data fully support the current period of active monitoring recommended by the WHO of 14 d<sup>[9,10]</sup>.

### Diagnosis:

Quick and precise detection of SARS-CoV-2 is important to manage the outbreak of COVID-19. Nucleic acid detection may be a major technique of laboratory designation. Reverse Transcription quantitative Polymerase Chain Reaction (RT-qPCR) may be a molecular biological analysis technology based on nucleic acid sequences. The entire SARS-CoV-2 genome sequences are existing in GenBank. Thus, the nucleic acid of SARS-CoV-2 is often identified by RT-qPCR or through viral gene sequencing of nasopharyngeal and oropharyngeal swabs, sputum, stool or blood samples. However, assortment of these specimen arrange by healthcare workers involve close contact with patients, that poses a possibility of scattering the virus to healthcare workers. Furthermore, gathering of nasopharyngeal or oropharyngeal specimens could cause bleeding, particularly in patients with blood disease. Significantly, To *et al.* establish that SARS-CoV-2 may be effectively detected within the saliva samples of infected patients, signifying that saliva may be a promising non-invasive specimen form for analysis, monitoring and infection control of COVID-19 patients<sup>[11,12]</sup>.

Further RT-qPCR, Zhang *et al.* explained a protocol by means of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based Specific High-sensitivity Enzymatic Reporter UNLOCKing (SHERLOCK) method for the finding of SARS-CoV-2. With artificial SARS-CoV-2 virus RNA fragments, the authors established that this technique is able to constantly detect target sequences of SARS-CoV-2 in a range between 20 and 200 attometer (am) (10-100 copies per microlitre of input). This test will be read out by a dipstick in <1 h, without requiring complicated instrumentation. As compared to RT-qPCR, the SHERLOCK technique is more precise and also the detection time is reduced by one-half. Therefore, utilization of the SHERLOCK technique for the finding of SARS-CoV-2 in clinical patient samples is estimated<sup>[13-15]</sup>.

### Current treatment:

The person-to-person communication of COVID-19 contamination led to the segregation of patients that

were administered a range of treatments. Currently, there are no definite antiviral drugs or vaccine to treat COVID-19 infection for potential treatment of humans. The sole alternative accessible is using broad-spectrum antiviral drugs similar to nucleoside analogues and moreover Human Immunodeficiency Virus (HIV)-protease inhibitors that might attenuate the infection until the precise antiviral becomes existing. The treatment that has been so far used proved that 75 patients were administrated existing antiviral drugs. The track of treatment enclosed double on a daily basis oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and therefore the intravenous administration of 0-25 g ganciclovir for 3-14 d. One more information showed that the broad-spectrum antivirals remdesivir and chloroquine are extremely effective within the management of 2019-nCoV infection *in vitro*. These antiviral compounds are utilized in human patients with a security record. Hence, these therapeutic agents are thought to treat COVID-19 infection. Additionally, there are varieties of alternative compounds that are in development. These contain the clinical applicant Molnupiravir (EIDD-2801) that has exposed high therapeutic potential against seasonal and epidemic contagion virus infections and this shows another potential drug to be considered for the management of COVID-19 infection. Beside those lines, until additional precise therapeutics become existing, it is sensible to judge more broad-spectrum antivirals that offer drug treatment alternative for COVID-19 infection which contain neuraminidase inhibitors, peptide (EK1), lopinavir/ritonavir and RNA synthesis inhibitors. It is still obvious, that additional analysis is desperately required to spot novel chemotherapeutic medicines for treating COVID-19 infections. So as to develop pre and post exposure prevention against COVID-19, there is an urgent requirement to set up an animal model to reproduce the severe disease presently ascertained in humans. Several teams of scientists are presently operating and exhausting to build up a non-human primate model to learn COVID-19 infection to determine fast track novel therapeutics and for the testing of possible vaccines in addition to providing a superior understanding of virus-host interactions<sup>[16,17]</sup>.

### Importance of phytochemicals:

Medicines originated from herbals include Ayurveda, Siddha and Unani that are effectively accomplished for treating various diseases. These came into continuation 5000 y ago and these systems are seen and scripted in olden literature. The phytochemicals are created

by plants to shield themselves against environmental hazards like water changes and microorganisms and to relinquish them their specific color, aroma, flavor and texture. Additionally, recent analysis demonstrated that they also need significant effects on human health nonetheless they never thought of essential nutrients. Research facility studies have exposed that these phytochemicals have the capability to stop certain compounds in drink, food and breathe from changing into carcinogens. It will moreover, decrease the swelling that triggers cancer growth. Besides, the phytochemicals reduce the oxidative damage to cells which will cause a variety of diseases and help in hormonal regulation. Researchers predicted that there are about 4000 phytochemicals that have been recognized so far, but only a little fraction of them have been studied strongly. These phytochemicals are frequently found in an extensive range of plants and are mainly present in consumed foods such as vegetables, fruits, green tea, coffee, grains, beans and so on. Phytochemicals are usually unnoticed in research and development of current drugs because their translational potentials are frequently belittled<sup>[18,19]</sup>. In spite of the fact that these medicines are ambiguous, there is wide background for their utilization in non-Western medical technology. A single herb may contain numerous phytochemical constituents that work alone or in combination with other compounds to deliver the specified pharmacological impact. The seek for new compounds with antiviral action has regularly been unsuitable due to viral resistance together with viral inactivity and repetitive contamination in immune-compromised patients. Among antiviral therapeutic technique, the bulk of them are non-specific for viruses. The progressions in creating antiviral agents are the major spotlight in medical research. The antiviral impacts of phytochemicals have played a huge part at diverse stages of viral development<sup>[20]</sup>. Phytochemicals derived pharmacological formulations stamped a major commitment for viral contaminations. Based on the accessibility of reasonable, proficient and fast bioassay systems, the antiviral compounds have been utilized for quick screening from plant extracts and fractions. Rather than synthetic antiviral drugs, phytochemicals convey fundamental raw materials for significant antiviral drugs. Synthetic drugs have been supplemented by phytochemicals, as life-saving drugs in a variety of viral diseases. Shockingly, the usage of this medicine has been passed down to eras by word of mouth and most of them have been misplaced over time, due to the need of appropriate documentation.

Research on these phytochemicals may offer assistance to advance their utilization in clinical settings to avoid or treat different ailments. Since numerous Indian medicinal plants display anti-inflammatory, antiviral and antioxidant properties, it could be favorable to believe them for the treatment of COVID-19. It is obvious that standard clinical trials ought to be carried out to logically demonstrate its adequacy<sup>[21,22]</sup>.

## PHYTOCHEMICALS IN THE MANAGEMENT OF COVID-19

### Curcumin:

In recent times a molecular docking study indicated that curcumin have higher binding capability to the receptors and should restrain the entry of COVID-19 virus. Angiotensin Converting Enzyme 2 (ACE2) is the receptor that connects with SARS-CoV-2 spike glycoprotein which supports the membrane fusion and virus infection happens through endocytosis. Hence, spike glycoprotein could be a potential candidate for drug targeting to restrain the entry of virus, that *in silico* docking studies exposed that curcumin may possibly restrain ACE2 to suppress COVID19 passage to the cell<sup>[23]</sup>.

Wen *et al.* have examined the impact of curcumin on viral replication by measurement of the amount of spike proteins that show in cultures of Vero E6 cells infected with SARS-CoV. Their result is incontestible that the inhibitory result of curcumin in EC50 values was higher than 10  $\mu$ M on SARS-CoV replication<sup>[24]</sup>.

Khaerunnisa *et al.* inspected the part of many phytochemical compounds like curcumin that will have the potential to repress the COVID-19 disease by molecular docking. Curcumin appeared generally with low binding energies and inhibition constants. They recommended that curcumin may have a latent inhibitory consequence on COVID-19 M<sup>pro</sup> and might potentially act as a therapeutic agent<sup>[25]</sup>.

There is growing proof on the repressive actions of curcumin on inflammatory cytokines. Curcumin obstructs the vital signals, directing the expression of different pro-inflammatory cytokines together with Nuclear Factor-Kappa B (NF- $\kappa$ B) and Mitogen-Activated Protein Kinase (MAPK) pathways. Curcumin have anti-inflammatory and anti-fibrotic impacts by diminishing the expression of vital chemokines and cytokines included in lung infection such as Interferon gamma (IFN- $\gamma$ ), Monocyte Chemoattractant Protein-1 (MCP-1), Interleukin (IL)-6 and IL-10. Curcumin has

an inhibitory impact against the human Respiratory Syncytial Virus (RSV) contamination by avoiding RSV replication, the discharge of Tumour Necrosis Factor alpha (TNF- $\alpha$ ) and down regulation of phospho-NF- $\kappa$ B<sup>[26]</sup>.

### Resveratrol:

Lin *et al.* illustrated conceivable antiviral mechanisms for resveratrol. Resveratrol has been reported to stimulate Extracellular Signal-Regulated Kinase 1/2 (ERK1/2) signaling pathway and support cell proliferation and improve Sirtuin 1 (SIR1) signaling, both of which are connected to cellular survival and Deoxyribonucleic Acid (DNA) restore in response to DNA harm. On the other hand, resveratrol may neutralize the MERS-CoV-induced apoptosis by down-regulating Fibroblast Growth Factor-2 (FGF-2) signaling. In addition, MERS-CoV infection might lead to the generation of inflammatory cytokines while resveratrol could decrease the inflammation *via* interfering with the NF- $\kappa$ B pathway. In their experiment, the levels of cleaved caspase 3 were decreased by resveratrol later than MERS-CoV infection. These modifications may be consequences of direct inhibition of caspase 3 cleavage by reversion of cell survival and the decrease of virus-induced apoptosis by resveratrol or restraint of an upstream incident that is required for caspase 3 cleavage<sup>[27]</sup>.

Resveratrol-treatment curbed the TNF- $\alpha$  generation, showing that the anti-retroviral action of resveratrol may be accomplished by lessening the inflammatory response. The IFN- $\gamma$  level was prominent in the dose of 10 mg/kg/d resveratrol treated cluster as well as 30 mg/kg/d resveratrol-treated set after RV infection. The proportion of Cluster of Differentiation (CD) 4<sup>+</sup>/CD8<sup>+</sup> in resveratrol-treated sets were the similar as that in mock infected cluster, signifying that resveratrol may maintain the immune function in Rotavirus-infected piglets. It was found that resveratrol might reduce diarrhea stimulated by Rotavirus infection<sup>[28]</sup>.

Zhao *et al.* examined the antiviral action of resveratrol against Pseudorabies Virus (PRV) and its mechanism of action. The consequences proved that resveratrol potently repressed PRV replication in a dose-dependent manner. The inhibition of virus reproduction in the existence of resveratrol was not credited to straight inactivation or inhibition of viral entrance into the host cells but due to the inhibition of viral reproduction in host cells. Additional studies illustrated that resveratrol may be a strong inhibitor of both NF- $\kappa$ B activation and NF-



$\kappa$ B-dependent gene expression through its capacity to restrain Inhibitor of NF- $\kappa$ B (I $\kappa$ B) kinase activity, which is the key controller in NF- $\kappa$ B actuation. Therefore, the inhibitory impact of resveratrol on PRV-induced cell passing and gene expression may be due to its capacity to restrain the degradation of I $\kappa$ B kinase<sup>[29]</sup>. In spite of the fact that there are no information for utilizing resveratrol in peoples infected with SARS-CoV-2, the above results illustrate that this compound might be an adjunctive antiviral agent to believe, particularly based on the information distributed by Linn *et al.* showing activity against MERS-CoV *in vitro*.

### Gallic acid:

Gallic acid interfered with different intra-cellular inflammatory pathways that actuate ulcerative colitis. The compound hinders the expression of nuclear transcription variables, such as NF- $\kappa$ B and Signal Transducer and Activator of Transcription 3 (STAT3), and down-regulates their inflammatory downstream objectives. It too decreases the expression and/or action of pro-inflammatory cytokines and inflammatory proteins, including INF- $\gamma$ , TNF- $\alpha$ , IL-1 $\beta$ , IL-17, IL-6, IL-23, IL-21, inducible Nitric Oxide Synthase (iNOS) and Cyclooxygenase (COX)-2, and diminishes the expression and invasion of neutrophils and CD68<sup>+</sup> macrophages into the colon<sup>[30,31]</sup>. Gallic acid is able to quench the flames of inflammation by means of distinctive mechanisms. It diminishes the expression and discharge of pro-inflammatory and inflammatory mediators, such as substance P, bradykinin, COX-2, NF- $\kappa$ B, IL-4, IL-2, IL-5, TNF- $\alpha$  and IFN- $\gamma$ . The compound moreover represses the phagocyte or Polymorphonuclear (PMN) mediated inflammatory reactions by scavenging Reactive Oxygen Species (ROS) and diminishing the Myeloperoxidase (MPO) action<sup>[32]</sup>.

Gallic acid is able to restrain HIV-1 integrase, HIV-1 protease dimerization, HIV-1 transcriptase, Hepatitis C Virus (HCV) replication, HCV attachment and penetration, the Herpes Simplex Virus (HSV)-1, HCV serine protease and HSV-2 attachment and diffusion. It as well causes disturbance in *Haemophilus influenzae* A and B particles<sup>[32,33]</sup>.

Phenolic compounds through their phenol rings interaction with viral proteins and/or RNA, or *via* its modifiable MAPK signaling in host cell defense, act as antiviral activity against many viruses such as HCV and HIV. Gallic acid polyphenols executed hydrogen bonds with 1 or 2 of the Nucleoside Triphosphate (NTP)

entry channels amino acids in COVID-19 polymerase. Polyphenols binds with NTP of COVID-19 polymerase could influence in the access of the substrate and divalent cations into the central active site cavity, repressing the enzyme activity. It shows promising result that gallic acid displayed high binding resemblance than ribavirin to COVID-19 polymerase and show good drug resemblance and pharmacokinetic properties. Thus, gallic acid may be considered as a potential treatment option for COVID-19<sup>[34]</sup>.

### Glycyrrhizin:

As the host cell receptor is significant for virus access, focusing on ACE2 could be a promising potential approach for avoiding SARS-CoV-2 contamination and more valuably, repressing the virus from diffusing out of the contaminated cell and attaching to and entering new permissive target cells. Glycyrrhizin has newly been shown to have the potential to attach with ACE2. Even though this investigation was performed *in silico* by means of molecular docking and the *in vitro* exhibition of an interaction remains to be confirmed, glycyrrhizin may still be considered as a latent treatment for COVID-19 because it has an antiviral outcome on SARS-CoV<sup>[35]</sup>.

In addition, glycyrrhizin has been reported to produce endogenous IFN. IFN is suggested in all 7 descriptions of the diagnosis and treatment of pneumonia contaminated by nCoV issued by the National Health Commission of China, maybe because of the current experience of clinical practice on COVID-19 and earlier settlement in management of severe MERS-CoV infection. While IFN is a broad-spectrum antiviral, it would restrain spreading of infection by restraining replication of both DNA and RNA infections at diverse stages of their replicative cycles and by actuating immune cell populations to clear virus infections. For that reason, glycyrrhizin may too play an indirect part in treatment of COVID-19. In the absence of a pathogen-specific antiviral or a targeted vaccine, numerous drugs with antiviral potential have been explored as of late for the treatment of COVID-19. Drug-producing liver injury has become a severe health problem. Glycyrrhizin, with its recognized liver-protection actions, could play a supporting role in COVID-19 treatment<sup>[36]</sup>.

Since ROS play an essential role in inflammatory reaction, antioxidants can also be efficient for the management of cytokine storm stimulated by infection. Glycyrrhizin may be able to inhibit the accumulation

of intracellular ROS caused by virus contamination. Inhibition of ROS development through glycyrrhizin can also decrease the activation of c-Jun N-terminal Kinase (JNK), NF- $\kappa$ B, p38 and redox-sensitive signaling procedures that are known to be appropriate for virus reproduction, by this means of suppressing virus reproduction. In expansion, a steady inflammatory or cytokine storm reaction caused by SARS-CoV-2 can result in enactment of coagulation and complement cascades, which may lead to several organs failure. Records appeared that glycyrrhizin could be a specific inhibitor of thrombin. These results indicate that glycyrrhizin has significant therapeutic benefits for COVID-19 through multisite mechanisms<sup>[37,38]</sup>.

### Withanone:

Kumar *et al.* inspected the binding potential of withanone (active withanolides extracted from Ashwagandha) to an extremely conserved protein, M<sup>pro</sup> of SARS-CoV-2. They established that withanone attach to the substrate-binding pocket of SARS-CoV-2 M<sup>pro</sup> with adequacy and binding energies corresponding to a previously claimed N3 protease inhibitor. Comparative to N3 inhibitor, withanone were binding with the extremely preserved residues of the proteases of CoVs. The interacting stability of these molecules was further evaluated by means of molecular dynamics replication. The interacting free energies deliberated *via* Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) for N3 inhibitor. Information at this point predicted that these natural compounds may have the potential to repress the efficient activity of SARS-CoV-2 protease (a crucial protein for virus endurance) and therefore may save time and cost required for designing/development and early screening for anti-COVID drugs; may propose few therapeutic value for the management of original deadly coronavirus disease; warrants prioritized advance approval within the research facility and clinical tests<sup>[39]</sup>.

Balkrishna *et al.* reported that withanone, docked exceptionally well in the binding border of ACE2-Receptor Binding Domain (RBD) complex and were found to shift somewhat towards the interface middle on simulation. Withanone altogether diminished electrostatic component of interacting free energies of ACE2-RBD complex. Two salt bridges were moreover distinguished at the interface; inclusion of withanone destabilized these salt bridges and diminished their occupancies. They hypothesize, such an intrusion of electrostatic interactions between the RBD and ACE2

would obstruct or deteriorate COVID-19 access and its subsequent contamination<sup>[40]</sup>.

### Colchicine:

Colchicine interacts to unpolymerized tubulin heterodimers, producing a constant compound that successfully restrains microtubule dynamics upon interacting to microtubule ends. Besides, colchicine may be a non-selective inhibitor of Nod-Like Receptor Protein 3 (NLRP3) inflammasome. Whereas firstly it has been thought of just as an inhibitor of microtubule polymerization and leucocyte invasion, it is presently assumed that a considerable part of colchicine is recognized to restraint of the NLRP3 inflammasome. Colchicine represses inflammasome on two levels: it restrains P2X Purinoceptor 7 (P2X7) receptor enactment and Apoptosis-associated Speck-like protein containing a Caspase-activation and recruitment domain (ASC) polymerization, in that way hindering interaction among pyrin-like domains<sup>[41]</sup>. Moreover, colchicine smoothen the transport of mitochondria and consequent approximation of ASC to NLRP3, showing that microtubules mediated the transfer of mitochondria to produce best sites for enactment of the NLRP3 inflammasome. Colchicine has been appeared to constrain IL-1 $\beta$  production as a response to diverse NLRP3 inflammasome inducers in a dose-dependent manner. For instance, in the situation of acute coronary syndrome, colchicine was useful in stifling IL-1 $\beta$ , IL-6 and IL-18, which was credited to inflammasome inhibition<sup>[42,43]</sup>.

The Greek Study in the Effects of Colchicine in COVID-19 complications prevention (GRECCO-19) will be a planned, open-labeled, randomized, controlled study to evaluate the effects of colchicine in COVID-19 complications anticipation. Patients with research lab established SARS-CoV-2 infection (beneath RT-PCR) and clinical picture that includes temperature more than 37.5° and at least 2 out of the below will be included: Sustained throat; sustained coughing pain; fatigue/tiredness; anosmia and/or ageusia; Partial pressure of oxygen (PaO<sub>2</sub>) < 95 mmHg. Patients will be randomized (1:1) in colchicine or control set<sup>[44]</sup>.

### Andrographolide:

Andrographolide is a laboratory diterpenoid derived from *Andrographis paniculata* stem and leaves. Andrographolide hindered IFN- $\gamma$ , IL-2 and IL-6 expression, diminishing the cellular and humoral adaptive immune reaction in T cells. Andrographolide

diminished the antigen presenting potential of dendritic cells to T cells. The andrographolide administration decreased the serum immunoglobulin, IL-4, IL-13, IL-5 and T helper type 2 (Th2) cytokine, in an ovalbumin-induced asthma rat model. Andrographolide signifying its role in angiogenesis by decreasing migration and invasion, adhesion molecule Intercellular Adhesion Molecule 1 (ICAM-1) and endothelial cell proliferation<sup>[45]</sup>. The andrographolide hindered NF- $\kappa$ B interacting to DNA and hence diminishing pro-inflammatory proteins expression like iNOS and COX-2<sup>[46]</sup>. Zhang *et al.* carried out an experiment to conclude the effect of andrographolide on insulinoma tumor growth. Andrographolide restrain the development of insulinoma tumor by focusing the Toll-Like Receptor 4 (TLR4)/NF- $\kappa$ B signaling pathway<sup>[47]</sup>. In neutrophils, the generation of ROS was restrained by andrographolide. Andrographolide directed the generation of components such as IFN- $\gamma$ , Natural Killer (NK) cells, IL-2 and TNF- $\alpha$ . The andrographolide enhanced the expression of CD markers and generation of TNF- $\alpha$ , as a result increasing the cytotoxic potential of lymphocytes<sup>[48]</sup>. Enmozhi *et al.* assessed andrographolide as a potential inhibitor of the M<sup>pro</sup> of SARS-COV-2 through *in silico* studies such as target analysis, molecular docking, Absorption, Distribution, Metabolism and Excretion (ADME) prediction and toxicity prediction. Andrographolide was docked effectively in the binding position of SARS-CoV-2 M<sup>pro</sup>. This molecule moreover complies with the Lipinski's rule, which makes it a promising compound to seek after assisting biochemical and cell based assays to investigate its potential for utilization against COVID-19<sup>[49]</sup>.

### Astaxanthin:

Astaxanthin is a xanthophyll carotenoid, which is present in *Haematococcus pluvialis*, *Chlorella zofingiensis*, *Chlorococcum* and *Phaffia rhodozyma*. Astaxanthin essentially constrict pathological elevation, inflammatory cell signaling NF- $\kappa$ B pathway together with *in vitro* and *in vivo* study and diminish TNF- $\alpha$  in humans, ensuring reduction in numerous pro-inflammatory cytokine level, which might show potential in maintaining lung health and reducing the impact of SARS-CoV-2 infection. Astaxanthin moreover identified to notably decrease other significant mediators of inflammation, including IL-1 $\beta$ , IL-6, C-Reactive Protein (CRP), COX-2, iNOS, Prostaglandin E2 (PGE2) and Nitric Oxide (NO)<sup>[50]</sup>. Miyachi *et al.* studied that treatment with astaxanthin show localization of NF- $\kappa$ B/p65 and the level of inflammatory cytokines (TNF- $\alpha$ ,

IL-6) tend to decrease and considerable enhancement of cell proliferation *in vitro*. Astaxanthin moreover reported to hinder apoptosis in alveolar epithelial cells. Furthermore, to the restraint of NF- $\kappa$ B pathway activation, reduction in the M1/M2 macrophage phenotype proportion is significant in diminishing levels of inflammatory cytokines<sup>[51]</sup>. These molecules also modulate the generation of Th1 cytokines, such as IFN- $\gamma$  and IL-2, without causing considerable cytotoxic effects in primary cultured lymphocytes. Astaxanthin applies regulatory activities on the immune system and specifically upgrades the immune response by improving multiplication and development of NK cells, granulocytes, T and B lymphocytes and monocytes<sup>[52]</sup>.

Immunomodulation by natural bioactive molecules is able to give additional therapeutic support to conventional chemotherapy for a range of diseases together with COVID-19, particularly when discriminating immunosuppression is required for autoimmune disorders. Dietary astaxanthin regulate immune response; protect oxidative damage and inflammation simultaneously in human model. Astaxanthin enhanced both cell-mediated and humoral immune responses. Considerable increase of immune markers including B-cell and T-cell mitogen-induced lymphocyte proliferation, Leukocyte Function-associated Antigen-1 (LFA-1) expression and IFN- $\gamma$  and IL-6 production were reported<sup>[53]</sup>. With the viral disease of respiratory epithelial cells, dendritic cells phagocytose the virus and given antigens to T cells. Effector T cells worked by killing the infected epithelial cells and cytotoxic CD8<sup>+</sup> T cells create and free pro-inflammatory cytokines which bring cell apoptosis. Both the cell apoptosis and pathogen activate and intensify the host innate immune response. Characteristics of COVID-19 recommend a reduced level of lymphocytes, neutrophils, CD8<sup>+</sup> T and CD4<sup>+</sup> T cells in peripheral blood specify disease severity<sup>[50]</sup>.

### Emodin:

Emodin may show its antiviral activity by restraining casein kinase 2, which is broken by many viruses for the phosphorylation of proteins that are crucial for their life cycle<sup>[54]</sup>. Emodin also interrupted the lipid bilayer, resulting in the inactivation of enclosed virus<sup>[55]</sup>. Ho *et al.* demonstrated that emodin was able to block the SARS-CoV S protein and ACE2 interaction. Preincubation of S protein or S protein-pseudo type retrovirus with emodin also eliminated the SARS-CoV and Vero E6 cell interaction. These conclusion recommended that in



addition to disrupting the viral envelope, emodin might stop SARS-CoV infection by opposing the interacting site of S protein with ACE2<sup>[56]</sup>. Promazine is a phenolic compound consisting of three cyclic rings which has been considered to show anti-SARS-CoV effect. Emodin along with promazine inhibited the S protein and ACE2 in a dose-dependent manner. This outcome suggested that the side chains except the anthraquinone skeleton have an immense impact on the S protein and ACE2 binding. These conclusions also point out that promazine shown anti-SARS effect by restraining both the virus access and protein processing<sup>[56,57]</sup>. Schwarz *et al.* observed that emodin capable of restraining the 3a ion channel of coronavirus SARS-CoV and Human Coronavirus OC43 (HCoV-OC43) plus virus discharge from HCoV-OC43 with a K<sub>1/2</sub> value of about 20 μM. They propose that viral ion channels could be an excellent target for the development of antiviral agents<sup>[58]</sup>.

### Some other phytochemicals used in the treatment of COVID-19:

A product of the plant *Artemisia annua*, artemisinin is a class of antimalarial medicines that have been marketed is used in the treatment. Increasing the severity of SARS-CoV-2 infection is associated with the development of pulmonary fibrosis, which is mediated by IL-1. There have been many studies that indicate that oxidative stress is linked with pulmonary illnesses and it is probable that the intake of natural antioxidants is beneficial in the treatment of lung fibrosis. The antioxidant activity of *Artemisia annua* extract is considerable, which is most likely owing to the high phenolic content of the extract. A derivative of *Artemisia annua* is artesunate, has shown promising effect in the treatment of pulmonary fibrosis. It works by blocking pro-fibrotic molecules linked with the disease<sup>[59]</sup>. Artemisinin and its derived molecules demonstrated an additional mode of interaction by binding to the Lysine (Lys) 353 and Lys31-binding hotspots of the SARS-CoV-2 spike protein and producing a better Autodock Vina score than hydroxychloroquine. Artemisinin and its derived molecules were found to have a higher Autodock Vina score than hydroxychloroquine. The findings of the research also showed that the complexes produced interfered with the SARS-CoV-2 Spike protein receptor site and stayed stable on the receptor site. Additionally, *Artemisia* has a high concentration of zinc, which has been shown to be beneficial for the immunomodulation impact of the host response as well as an increase in CD4 cell count<sup>[60]</sup>.

Betulinic acid (Bet) is a naturally occurring product with a pentacyclic triterpene nucleus that exhibits a broad spectrum of biological and pharmacological activities including antiviral, anti-HIV, antibacterial, anti-inflammatory, anthelmintic, anticancer and antimalarial properties. Bet is found in plants and has a pentacyclic triterpene nucleus. Bet (A8) interacts with Glycine 274 (GLY 274), Leucine 287 (LEU 287), Methionine 276 (MET 276) and LEU 286 amino acids and forms two hydrogen bonds with each of these amino acids, which represents the majority of sulfhydryl groups in the amino acid. Despite this, Bet (A3) and Bet (A4) were the most often suggested possible inhibitors of COVID-19's primary protease<sup>[61]</sup>.

Luteolin substantially increases the amount of CD4<sup>+</sup> CD25<sup>+</sup> regulatory T-cells in murine splenic CD4<sup>+</sup>-T cells that have been activated with anti-CD3/anti-CD28 antibodies, as shown in this study. Luteolin also shown immunomodulatory action, reducing the amount of immune cells such as CD19<sup>+</sup> B, CD4<sup>+</sup> T, CD3-C-C chemokine receptor type 3<sup>+</sup> (CCR3<sup>+</sup>) and CD11b<sup>+</sup> Granulocyte-1 (Gr-1<sup>+</sup>) in the lungs of an inflamed airway mouse model with inflamed airways. Luteolin also has anti-inflammatory properties, since it inhibits the NF-κB pathway, lowers TNF-α, IL-6 and IL-1α levels and substantially decreases MPO activity in the blood. Additionally, luteolin had a protective effect against the Lipopolysaccharide (LPS)-induced Acute Lung Injury (ALI), mice model by inhibiting MAPK pathways, which resulted in the suppression of the NF-κB pathway and the degradation of IκB protein. By inhibiting microsomal PGE synthase 1 and 5-lipoxygenase, caflanone has anti-inflammatory action on the body.

It is widely known that flavonoids are phenolic natural compounds that are used in the treatment of a variety of illnesses, including viral infection, in both traditional and contemporary medicine. CoVs, particularly the current pandemic epidemic caused by the SARS-CoV-2 and identified as COVID-19, have been shown to be susceptible to flavonoids potential inhibitory action against them. All flavonoids were found in *in silico* as possible SARS-CoV-2 inhibitors. Specifically, it has been determined that M<sup>pro</sup> is needed for the replication of the SARS-CoV<sup>[62]</sup>. Further investigation revealed that the M<sup>pro</sup> of SARS-CoV-2 and SARS-CoV are very similar. A dose-dependent antiviral activity against the HSV-1 and HSV-2 was also shown in cell cultures using quercetin. In cultured cells, it has been shown to suppress a number of different respiratory viruses.

Several rhinovirus, echovirus (type 7, 11, 12 and 19), coxsackievirus (A21 and B1) and poliovirus serotypes are inhibited in their cytopathic effects by this substance (type 1 Sabin). Antiviral action against the Canine distemper virus is shown by the fact that it reduces viral expression while increasing cellular survival. This compound has been investigated in different kinds and models of viral infection because of its potential antiviral actions on polymerases, proteases, reverse transcriptase, decreasing DNA gyrase and binding viral capsid proteins. 3CLpro was shown to be inhibited by this compound, which was discovered as one of the components of *Pichia pastoris*. Phytochemical studies have shown that quercetin-3-O-galactoside binds to SARS-CoV 3CLpro and inhibits its proteolytic activity<sup>[63]</sup>. Chrysin has the ability to inhibit the NF- $\kappa$ B, which regulates the production of genes encoding pro-inflammatory cytokines such as COX-2 and iNOS. Furthermore, it is an agonist of the Peroxisome Proliferator-Activated Receptors (PPAR) receptor, which inhibits the expression of COX-2, MPO and iNOS. The pre-treatment of mice with chrysin before they were exposed to cigarette smoking to induce inflammation of airway epithelial cells alleviated the inflammation by suppressing the release of TNF- $\alpha$ , IL-1 $\alpha$ , IL-8 and MPO expression in the lung tissue, as well as the expression of MPO in the lung tissue. Chrysin also has the additional effect of inhibiting ERK and p38 phosphorylation. The immunomodulatory effect of chrysin on rat peritoneal macrophages was investigated in another study. Chrysin was found to stimulate macrophage lysosomal activity, which was involved in killing and digesting the microbial pathogens, as well as inhibiting the production of NO in this study. A docking research revealed that chrysin may bind poorly to COX-1 enzymes but strongly to COX-2 enzymes, suggesting that it has relative selectivity for COX-2 enzymes and as a result, lowers the likelihood of unwanted Gastrointestinal (GIT) side effects. Similar results were obtained when apigenin was administered prior to the induction of inflammation in human macrophages<sup>[62,63]</sup>.

Apigenin was shown to significantly decrease IL-6 production as well as the stability of IL-6 messenger RNA (mRNA). HCoV-Netherlands 63 (NL63) replication was shown to be inhibited by tryptanthrin, which was discovered to be the most active component in *Strobilanthes cusia* leaf methanol extract in a cell-type-independent manner. Intriguingly, tryptanthrin has a higher antiviral activity against HCoV-NL63 than indigodole B (5aR-ethyltryptanthrin), which has an additional ethyl moiety at C5a instead of the double

bond in tryptanthrin. This demonstrates that the double bond in the quinazoline ring of the tryptanthrin skeleton is the active contributor to the antiviral tryptanthrin which also changes the antigenic structure of viral spike proteins and reduces the cleavage activity of Proteolipid Protein 2 (PLP2), which is linked with virucidal activity and inhibits the post-entry stage of HCoV-NL63 replication, in addition to other effects. Our particular interest is that the spike protein from HCoV-NL63 has significant sequence and structural similarities with the viruses that cause SARS and COVID-19, indicating that all of these viruses use the ACE2 receptor<sup>[64]</sup>. This is consistent with the fact that all of these viruses use the ACE2 receptor. Lycorine is a phenanthridine alkaloid from the Amaryllidaceae family that was discovered in the bulbs of the plant *Lycoris radiata*. Several CoV infections, including the SARS-CoV infection and four additional CoV infections, such as the HCoV-OC43 infection, the MERS-CoV infection, the Mouse Hepatitis Virus strain A59 (MHV-A59) infection, and the HCV-OC43 infection, have been shown to be inhibited by lycorine. Lycorine has been shown to inhibit viral RNA replication as well as viral protein synthesis in the presence of poliovirus, Enterovirus 71 (EV71) and H5N1 avian influenza virus. Recently, it was proposed that lycorine may block Zika virus viral RNA production and bind to the Zika RNA-dependent RNA polymerase (RdRp) protein, thus preventing the virus from spreading. According to the findings, lycorine forms hydrogen bonds with RdRp at the amino acid residues Aspartic acid 623 (Asp623), Asp691 and Serine 759 (Ser759), which is comparable to remdesivir<sup>[65]</sup>.

## CONCLUSION

nCoV (COVID-19) is causing an increasing number of cases of pneumonia and was declared a Public Health Emergency of International concern by the World Health Organization.

According to WHO, major concern among public health throughout the world and many countries have taken precautionary measures against the virus and Government officials in all countries continue to make hard work to diminish person to person contact by facilitating area wise shutdowns of public places plus a variety of steps have been instigated to ensure the security of the public, similar to social distancing and self-quarantine which limits our social interactions.

Although a large number of review articles have been published since the COVID-19 epidemic, the

significance of natural products in the prevention and treatment of SARS-CoV-2 has received little attention. However, there is a body of research describing a variety of naturally occurring chemicals that have strong anti-SARS-CoV and anti-MERS-CoV action. Unquestionably, there is a high degree of sequence similarity between SARS CoV-2 and either SARS-CoV or MERS-CoV. The use of computational methods to repurpose these anti-SARS-CoV or anti-MERS-CoV natural compounds may lead to the identification of candidates for the development of COVID-19 medication that is both safe and cost-effective.

Herbal medicines have gathered thousand-of-year's experiences in the treatment of pandemic and endemic diseases. Providing complementary and alternative treatments are still urgently needed for the management of patients with SARS-CoV-2 infection, experiences in herbal medicine is certainly worth learning. Fighting against existing pandemic also give an opportunity to test the true significance of phytomedicine in treating promising infectious diseases. Numerous phytochemicals have revealed inhibitory activity against HIV proteases which also have immunomodulatory activity and these molecules can be promising drugs for COVID-19. These phytochemicals can be used to ameliorate the symptoms of COVID-19. Though many phytochemicals have been identified, a lot of research has to be carried out for the development of drug specific to SARS-CoV-2. Therefore, it is important to explore the effect of these prescribed phytochemicals on SARS-CoV-2.

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The authors declared no conflict of interest.

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