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## THE ROLE OF PHYTOCOSTITUENTS IN COVID-19 MANAGEMENT

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### ABSTRACT

**Background:** One of the most lethal contagious diseases is COVID-19, a devastating global pandemic brought on by the SARS-CoV-2 virus. The discovery of therapeutic alternatives has become crucial because to the significant threat to global public health, and a worldwide race to find a cure has mobilised researchers from many disciplines.

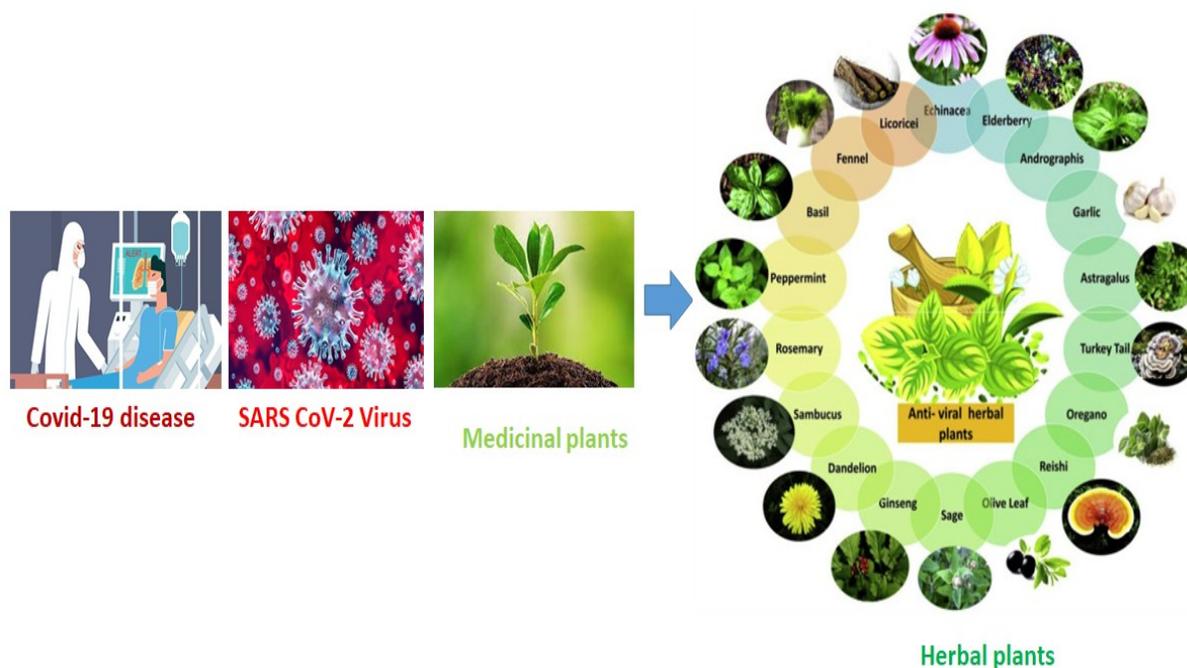
**Scope and approach:** The purpose of this study is to assess the therapeutic potential of a number of secondary metabolites like terpenoids, phenolic compounds, alkaloids, glycosides and sulphur-containing compound derived from medicinal plants as inhibitors of SARS-CoV-2 therapeutic targets or as blockers of viral particle entry via host cell receptors. Utilising medicinal plants with specific phytoconstituents may offer the populace a long-term, safer alternative with fewer side effects.

**Key Findings and Conclusions:** Despite the pricey and tedious nature of drug discovery, therapeutic repurposing of current medications was investigated as a therapy option in COVID-19; however, some compounds were withdrawn as therapeutics as a result of either no favourable outcomes or significant adverse effects. These consequences need the investigation of alternative therapy approaches that are both therapeutically effective and safe. Bearing this in mind, phyto-pharmaceuticals produced from medicinal plants might be investigated as essential resources in the development of COVID-19 therapy, since their function in the treatment of viral infections like as HIV, MERS-CoV, and influenza has been extensively documented in the past. Regarding this, many plant-based components, including flavonoids, alkaloids,

tannins, and glycosides, among others, have been assessed in this work for their potential to inhibit SARS-CoV-2.

**Keywords:** Antiviral; Coronavirus; Covid-19; Medicinal; Phytoconstituents; SARS-CoV-R

### Graphical Abstract



## 1. INTRODUCTION

SARS-CoV-2 has been proclaimed a global outbreak by the World Health Organization (WHO). It began in China and will primarily impact the respiratory system in 2019 [1]. The coronavirus has transmitted by droplets, physical contact with infected people, contaminated surfaces, and maybe through the oral-fecal pathway [2, 3]. The betacoronavirus known as SARS-CoV-2, which is 79% similar to the original SARS-CoV and is an encapsulated RNA virus from the Coronaviridae family. The SARS-CoV-2

virus shares 50% of its genetic makeup with the Middle East respiratory syndrome coronavirus MERS-CoV, 88% of its genetic makeup with two bat-derived (SARS-like) coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21 [4] and 96.2% of its genetic makeup with the bat CoV RaTG13 [5]. The SARS-CoV2 variant Wuhan-Hu-1 coronavirus (WHCV), which has a genomic size of 29.9 kb, was first discovered in a pneumonia patient in Wuhan [6]. Open reading frames are distributed differently

across the whole genome [7]. 16 non-structural proteins (NSP) are encoded by viral RNA in the ORF1 region, whereas structural proteins are encoded by the ORF at the end. The four main structural proteins of the corona virus are the spike (S) protein, the envelope (E) protein, the membrane (M), and the nucleocapsid (N) protein [8]. A crucial stage for viral entry is the interaction of the SARS-CoV-2 S glycoprotein with the host mobile receptors, angiotensin-changing enzyme 2 (ACE2). Ayurveda, Yoga, Unani, Siddha, and the homoeopathic system (AYUSH), which is being practised today, are just a few of the alternative medical practises with a long history in India [9]. Additionally, it is anticipated that 70–80% of people in poor nations get all of their basic care from natural remedies [10]. Viral infections have traditionally been treated using conventional herbs having antiviral qualities [11]. The secondary metabolites that the plant produces are often what provide plant products their advantageous medicinal effects. Alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides, among other phytochemicals derived from plants, have been demonstrated to have antiviral effects in humans [12]. The world has started

looking at conventional pharmaceuticals for the treatment of viral infections that are easily accessible, substantially less expensive, and have a lower risk of toxicity and adverse effects [13]. It is possible to examine the therapeutic potential of conventionally used medicinal plants using computational and structural biology technologies, making the creation of new medications quicker, less expensive, and safer [14]. Receptors and enzymes implicated in different stages of the SARS-CoV-2 life cycle are being used as therapeutic targets. As observed in the situations of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections, viral proteases have long been shown to be efficient targets of antiviral treatment approaches. Proteases are crucial targets for preventing viral replication, and coronaviruses have a well-known pharmaceutical target in the main protease [15]. The enormous number of persons inflamed globally as a result of the rapid spread in a brief period of time presents a substantial challenge to healthcare systems. COVID-19 has an age-related skewed distribution of morbidity and an average lethality, despite the fact that the numbers are rising as the illness progresses [16].

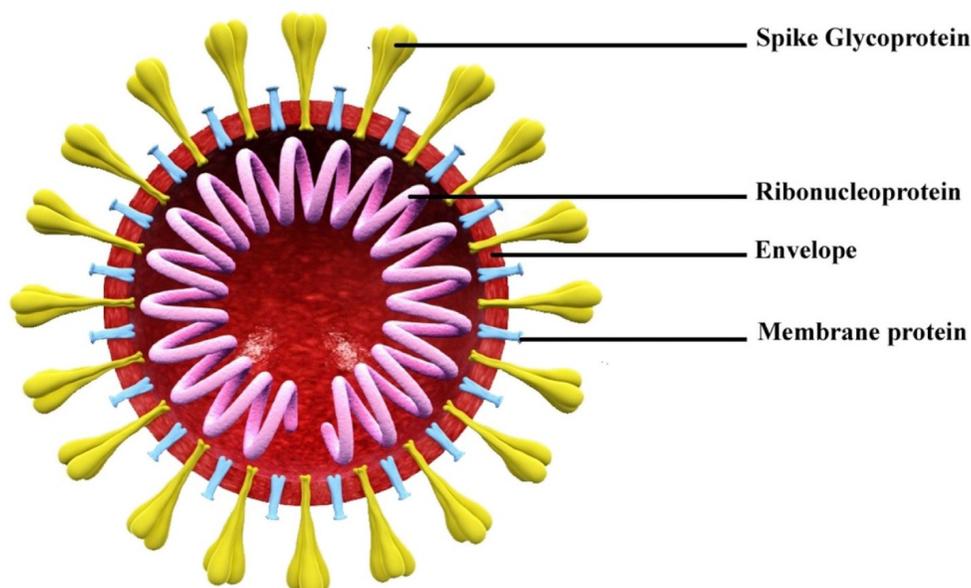


Figure 1: Schematic diagram of SARS-CoV-2 structure [29]

Herbal drugs have additionally helped to relieve the outcomes of infectious sicknesses which includes SARS-CoV-2. Evidence helps that natural medicinal drug can be powerful in decreasing and dealing with the danger of COVID19. The use of natural medicinal drug as an opportunity treatment for COVID-mixture with cutting-edge medicinal drug, and has launched numerous tips on natural therapy [17]. Meanwhile, numerous herbal preparations show potential against virus, the usage of natural medicinal drug for healing tenacities must now no longer be underestimated. Currently, various natural drugs hits viral genome that's getting used to conquer SARS-CoV-2 [18]. Herbal drugs are somehow safe, effective, and feature fewer facet effects as compared to allopathic drugs [19]. India is a country rich

in medicinal plants that are used to treat a variety of human ailments. *Tinospora cordifolia*, also known as amrita, guduchi, shindilkodi, and giloy, is widely used in indigenous Indian medical structures [20]. *T.cordifolia's* chemical constituents are classified into many groups, including terpenoids, alkanoids, glycosides, ligandans, and steroids [21]. *Tinospora cordifolia* natural phytochemicals have been shown to have antiviral activity against a variety of viral infect [22]. Curcumin, a component of turmeric, has been shown to have several properties in preventing or treating illnesses such as cancer and viral infections [23]. Curcumin has also been shown to be an antiviral agent, exhibiting activity against viruses such as dengue virus (serotype 2), herpes simplex virus, and human

immunodeficiency virus [24]. Thus, the purpose of this review is to identify possible phytochemicals and plant sources that may be exploited as inhibitor compounds targeting either the host cell or SARS-CoV-2 therapeutic receptors in order to provide a safer and longer-term solution for the population with fewer adverse effects.

## 2. Coronavirus infection mechanism

The SARS-CoV-2 and SARS-CoV segmented some sequence homology, however they exhibit differing infection ranges and transmission potential [25]. It is thought that the persisting COVID-19 sickness, which has no known cure, is more dangerous and may be caused by particular functional changes in the SARS-CoV-2. The absence of 8a, longer 8b and shorter 3b segments, as well as altered Nsp-2 and -3 proteins, are the main variations seen in SARS-CoV-2. Along with them, some locations, such as in ORF8 and ORF10, have different open reading frames [26].

The virus attached to the cell surface receptor of host cells to pass the viral genome within cell membrane. Further, initiation of infection gets to start which to build relationship between virus and host cell. The presence of S-primary protein of coronavirus gets fused with cell membrane of host. Moreover, SARS-CoV-2 has binds to

angiotensin converting enzyme receptors in the epithelium of respiratory. Further, structural modification to the spike protein that's affected by two factors cleavage of protein activation and acidification of pH [25-29]. Each subunit of the S-protein has two domains: S1, which binds to receptors, and S2, which allows membrane fusion and viral entrance into the host cell. The fundamental trait of Class I viral fusion proteins is that they cleave after fusion, which is the crucial event in the following infection process [30]. Proteases divide the S protein into two domains, S1 and S2, the latter of which is critical for allowing fusion proteins to breach the host cell's membrane and, as a result, increasing viral entry [31]. Other coronaviruses, such as MHV-2 and SARS-CoV, do not require the cleavage of the spike protein in order to enter the cell. However, in the presence of exogenous proteases, they can enter the cell directly, a mechanism that is 100-1000 times more effective than the endosomal route. Two proteases that produce SARS-CoV-2 fusion are human airway trypsin-like protease (HAT) and transmembrane protease/serine family (TMPRSS) [32-35]. Once the fusion occurs and the fusion protein reaches the host cell, angiotensin I is converted to angiotensin II, a negative regulator of the renin-

angiotensin pathway, and this decreased ACE-2 is to blame for respiratory damage and illness [36]. Once the viral protein is translated into cellular material, multiple pathways are triggered and associated to infection amplification. An ORF3a protein binds to TRAF3 and activates the NF- $\kappa$ B pathway, coding for the Ca<sup>+2</sup> ion channel. The ORF8b protein activates the inflammasome pathway via NLRP3. All of these pathways result in an increase in cytokine production, which causes respiratory problems. The JNK pathway, which is likewise activated by ORF3a,

ORF3b, and ORF7a, causes lung difficulties [37-40]. The viral infection can be diminished if the virions do not attach to the cell, as is conceivable when the virus is inactivated. Because it binds to the receptor ACE-2 more strongly than SARS-CoV, SARS-CoV-2 has a significantly greater rate of infection transmission and pathogenicity than SARS-CoV [41]. The spread of TMPRSS2 paired with ACE-2 causes the earliest phases of the infection, suggesting another possible therapeutic target for future pharmaceutical development [42].

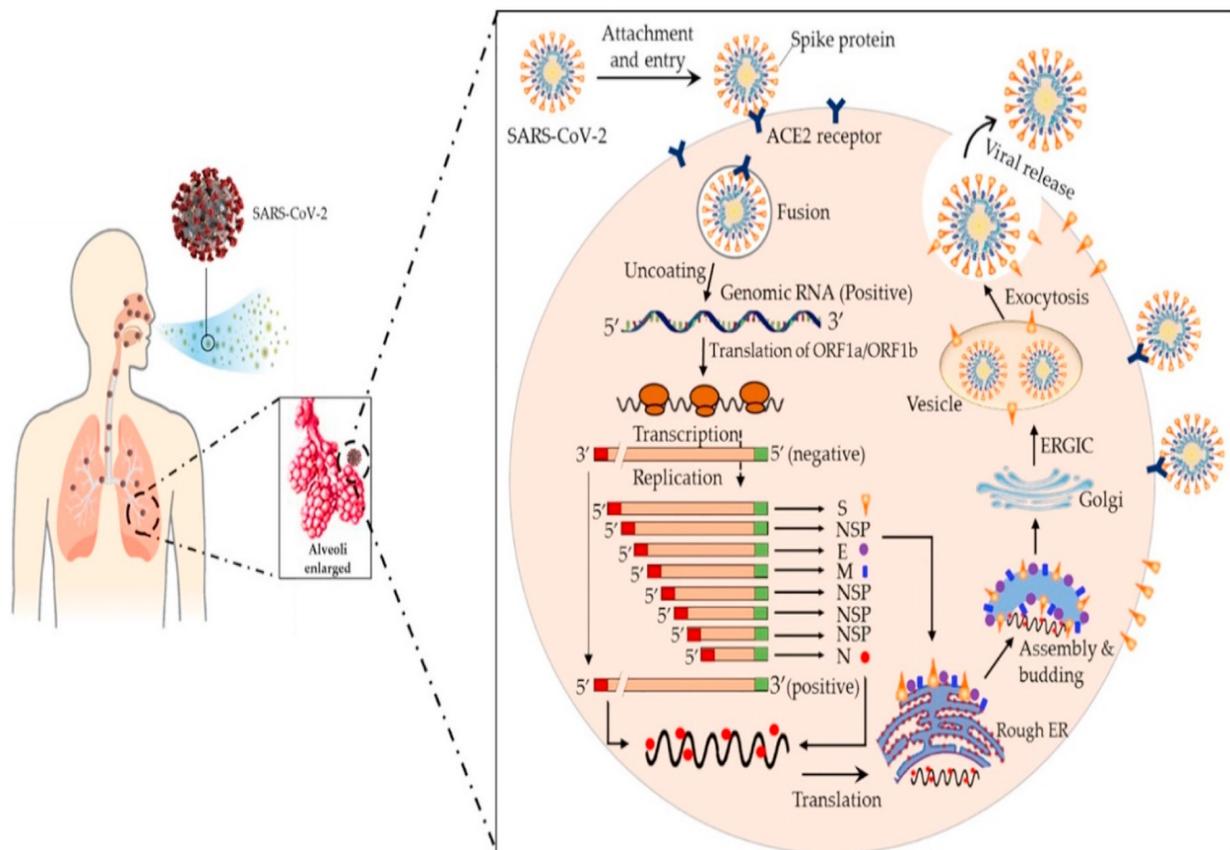


Figure 2: Schematic diagram of coronavirus infection [40]

#### 4. Therapeutic potential of phytoconstituents against coronaviruses

The globe is currently dealing with harmful circumstances that are preventing people from living normal lives. Currently, there has not any food and drug approved drugs present in the market.

and creating innovative therapeutic compounds and vaccines is still costly, time-consuming, and riddled with failure [41, 42]. With that in mind, it is essential to use other methods of conflict resolution. Due to their safer, more affordable, and lower toxicity profiles, medicinal plants have been the most widely used therapeutic alternatives against many viral infections since ancient times [43, 44]. Plant phytoconstituents has shown antiviral activity such as alkaloids, flavonoids, polysaccharides and others [45-48]. The **Table 1** summarizes some phytoconstituents with antiviral properties.

##### 4.1. Flavonoids

Plants include polyphenolic chemicals called flavonoids, which have a variety of biological effects [49]. Numerous flavonoids

are known to be beneficial against viral infections, particularly at the molecular level by preventing viral proliferation [50]. By inhibiting cellular receptors, flavonoids prevent viral multiplication and translation as well as virus entry into the cell [51-58].

##### 4.2. Alkaloids

Alkaloids have various pharmacological activity which is organic compound present in nature that containing basic nitrogen atoms [59]. Alkaloids were stated to inhibition of polymerase enzyme of DNA virus that prevent the viral replication [60]. These plants secondary metabolites may be good candidates for fighting viral infection and may help with the development of therapeutic molecules since they have DNA intercalating characteristics. It has been discovered that the antimalarial medicine resiquine, a synthetic quinine (alkaloid) derivative, is an effective treatment agent against COVID-19 [61-63]. Emetine extracted from ipecacuanha root has been shown to be effective against COVID-19 in the treatment of poisoning [64].

Table 1: Plants and their phytoconstituents having antiviral potential against coronaviruses [65-110]

Common name	Scientific name	Uses	Phytoconstituents
Ginger	<i>Zingiber officinale roscoe</i>	Respiratory manifestations agent	Chlorogenic Acid
Guduchi	<i>Tinospora cordifolia</i>	Antiviral agent	Berberine
Kutki	<i>Picrobiza kurrpa</i>	Immunomodulatory agent	Acetovanillone
Shatavari	<i>Asparagus racemocos</i>	Antiviral Agent	Asparoside-D
Green chiretta	<i>Andrographic paniculata</i>	Anti- Inflammatory Effects	Andrographolide
Turmeric	<i>Curcuma longa</i>	Antioxidant, Gastro Protective Effects, Anti-Inflammatory Effects	Diacylcurcumin
Neem	<i>Azadirachta indica</i>	Anti- Inflammatory Agent	Nimocinol
Black cumin	<i>Nigella sativa</i>	Antiviral Agent	Campesterol
Peppermint	<i>Mentha pipertia</i>	Antiviral Agent	Hesperidin
Onion	<i>Allium cepa</i>	Antihypertensive agent, Antimicrobial Agent	Methyl Ferulate
Garlic	<i>Allium sativum</i>	Antioxidants Agent	S-Allylcysteine Sulfoxide (Alliin)
Rhubarb	<i>Rheum emodi</i>	Antibacterial, Antioxidants Agent	Emodin
Wild thyme	<i>Thymus serpyllum</i>	Antiviral Agent	Apigenin
Lemon grass	<i>Cymbogon citrates</i>	Antiviral Agent	Neral
Nutmeg	<i>Myristica fragrans</i>	Antioxidant agent	Saponarin
Dalchini	<i>Cinnamomum verum</i>	Antiviral agent	Camphoratin D
Aloe-Vera	<i>Aloe barbadensis miller</i>	Antioxidant agent	Ferulolide
Fingered citron	<i>Citrus medica</i>	Antioxidant agent	Rhoifolin
Tongkat Ali	<i>Eurycoma longifolia</i>	Anti-inflammatory agent	Eurycomalactone
Harsingar	<i>Nyctanthes arbor-tristis</i>	Antiviral agent	Nictoflorin
Rydravanti	<i>Cressa cretica</i>	Antiviral plant	3,5-dicaffeoylquinic acid
Indian trumpet flower	<i>Oroxylum indicum</i>	Antiviral plant	Scutellarein
Lemon balm	<i>Melissa officinalis</i>	Antiviral agent	Melitic acid-A
Babchi	<i>Psoralea Corylifolia</i>	Anti-inflammatory agent	Homoharringtonine
Mustak	<i>Cyperus Rotundud</i>	Antiviral agent	Myrtenol
Liquorice	<i>Glycyrrhiza Globra</i>	Antiviral agent	Dehydroglyasperin C
Rasanjan	<i>Berberis asiatica</i>	Antiviral agent	Berbamine
Lemon	<i>Citrus Limon</i>	Antiviral agent	Luteolin
Ashwagandha	<i>Withania somnifera</i>	Antiviral agent	Withanoside V
Hurseradish tree	<i>Moringa oleifera</i>	Antiviral Agent	Niazinin
Mango	<i>Mangifera indica</i>	Antiviral, antioxidant agent	Amentoflavone
Leafy meadow rue	<i>Thalictrum foliolosum</i>	Antiviral Agent	Palmatine
Cashew Nut	<i>Anacardium occidentale</i>	Antiviral, antioxidant agent	Agathisflavone
Gokhru	<i>Pedaliu murex</i>	Antiviral Agent	Rubusc acid
Nisinda	<i>Vitex negundo</i>	Antiviral, antioxidant agent	Oleanolic acid
Black pepper	<i>Pipper nigam</i>	Anti-Inflammatory Agent	Sabinene
Tulsi	<i>Ocimum sanctum</i>	Antiviral agent	Ursolic acid
Bhumi Amla	<i>Phyllanthus niruri Linn</i>	Antiviral Agent	Pectolinarin
Amla	<i>Embllica officinalis</i>	Antiviral Agent	Quercetin
Indian Mulberry	<i>Morinda citrifolia</i>	Antiviral Agent	Nordamnacanthal
Glastum	<i>Isatis indigotica</i>	Antiviral Agent	Lopinavir
Bitter Bark	<i>Alstonia scholaris</i>	Antiviral Agent	Akuammicine N-Oxide
Papaya	<i>Carica papaya</i>	Antiviral, antioxidant agent	Anthraquinone
St. Christopher's Lily	<i>Crinum jagus</i>	Antiviral Agent	Oxopowelline
Guava	<i>Psidium guajava</i>	Antiviral, anti-inflammatory agent	Asiatic acid
Coconut palm	<i>Cocos nucifera</i>	Antiviral, Anti-inflammatory agent	Stigmasterol
Tasmanian blue gum	<i>Eucalyptus globulus</i>	Antiviral Agent	Cuniloside
Cinnamon	<i>Cinnamomum zeylanicum</i>	Antiviral, anti-inflammatory agent	Tenuifolin
Clove	<i>Syzygium aromaticum</i>	Antiviral, Anti-inflammatory agent	Bicornin
Ammoides	<i>Ammoides verticillata</i>	Antiviral, Anti-inflammatory agent	Isothymol



Figure 3: Medicinal plants with antiviral properties

#### 4.3. Phenolics

The phenols, which are polyphenolic chemicals found naturally in plants [111]. The presence of hydroxyl and methoxy group of phenolic compounds have showed antiviral activity [112, 113]. Phenols are interact with virus protein of envelope which help to inhibit virus fusion. Moreover, polyphenols may be efficient COVID-19 inhibitors [114-117].

#### 4.4. Essential oils

Essential oil present in many plants which is volatile in nature. It's shown a wide therapeutic effects such antiviral, anticancer, antioxidants and others [118, 119].

#### 4.5. Stilbenes

Plants containing stilbenes which are phenolic characteristic [120]. In numerous

literature, showed that stilbenes are interfere with ACE-2 complex and further, restrict entry of virus into host cell. Resveratrol and piceatannol are stilbenes with a strong affinity for this combination. In addition to the previously described antiviral qualities, certain additional stilbene compounds, such as trans-resveratrol, pinosylvin, and pterostilbene, also have low binding capacities [121-125].

#### 4.6. Glycosides

Glycosides containing simple sugar molecules as functional groups [126]. Plants have of variety of glycosides have pharmacological activity. For example, cardiac glycosides are operative against influenza virus, coronavirus, herpes simplex virus and cytomegalovirus [127]. Glycosides

are specifically target host cell protein so prominently effective against viral infections [128, 129].

#### 4.7. Saponins

Saponin are present in numerous plants which have non-ionic characteristic. Saponin have variety of therapeutic effect such as antiviral, antibacterial, antifungal and others.<sup>130</sup> Saponins are steroids medicines [131]. Saponin may interact with capsid protein leads to breakdown viral particulate. They can inhibiting viral particulate which have attached to host cells and prevents fusion. However, limited the spread of viral infections [132-134].

#### 4.8. Tannins

Tannins are plant obtaining constituents which have wide variety of biological and therapeutic effects. Moreover, viral infections have properties to increases formation of free radical and oxidative stress and tannins have the characteristic to show antioxidant property to minimized oxidative stress [135-139].

#### 4.9. Anthraquinones

Plants containing aromatic compounds known as anthraquinone which widely used for medical purposes. Anthraquinone have short toxicity and great activity. It is widely used for constipation, arthritis, cancer etc. [140-145]. As per literature, docking study

of anthraquinone demonstrate that effective against COVID-19. The docking study revealed that many anthraquinone and its derivatives such as emodin, aloin etc. effective against SARS-CoV-2 [146-148].

### CONCLUSIONS

In the present adverse COVID-19 situations across the world, it is critical to find medications or therapeutic solutions as soon as possible. Emerging new-fangled drugs and sorted new target has take a time and ensure their potency and toxicity is validated in clinicals trial of such drugs and target. Although medications and particular therapies for COVID-19 are now unavailable, researchers are looking for options to properly tackle the existing illness state. In this context, medicinal plants possessing particular phytoconstituents may offer a broad range of treatment options against COVID-19. Moreover, the uses of herble medication is benefitted to society due to their lowest toxicity and simple formulation. Based on computational screening methods like molecular docking, molecular modelling, ADMET Prediction and QSAR model generation makes the various phytoconstituents have effective against coronavirus and affinity against various therapeutic targets of coronavirus. Overall, the phytoconstituents as an

alternative drugs for potentially restrict coronavirus infection.

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### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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