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## Plants as a prospective source of natural anti-viral compounds and oral vaccines against COVID-19 coronavirus

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### Abstract

The proposal of novel drugs and approaches for effective treatment of the novel coronavirus is a necessity after the quick outbreak of the disease. Since the commencement of the coronavirus spread, enormous efforts have been made to protect, alleviate and cure the disease, though no specific treatment has been approved. While there have been convincing results in the use of chemical drugs and interferon therapy, such therapeutic approaches have various drawbacks and lack the required performance for the treatment of the new coronavirus. Medicinal plant species can provide a solution as a source of natural antiviral compounds by the accumulation of secondary metabolites and lectins as well as acting as a platform to express the viral immunogenic proteins. This study reviews the advantages and the results of previous research for the treatment of the novel coronavirus disease and previous generations of similar coronaviruses. Several plant-derived anti coronavirus compounds have been nominated that could be targeted for further research due to the similarity of the coronavirus disease in 2003 and the current coronavirus. This review regards plant species such as *Scutellaria baicalensis* (Baikal skullcap), and *Urtica dioica* (Stinging nettle) as suitable candidates for the new coronavirus antiviral research. Furthermore, the use of plants such as *Nicotiana tabacum* (Tobacco) for the expression of the coronavirus viral antigens can be a target for the future vaccinal research of the new coronavirus due to the efficiency of expression and intrinsic antiviral properties.

**Keywords:** 2019 Novel Coronavirus, Plants, Antiviral Compounds, Plant Recombinant Vaccines

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## Introduction

The Coronaviridae family is composed of enveloped single-stranded RNA viruses that were normally regarded as the origin of types of common cold, upper respiratory disorders and lower respiratory

infection in the case of the elderly and patients with a weak immune system. However, in 2003, the appearance of Severe Acute Respiratory Syndrome (SARS) caused by the coronavirus agent of SARS-Cov belonging to betacoronavirus subfamily, presented an urgent necessity of research about SARS related coronavirus. Nine years later another coronavirus appeared as Middle East Respiratory Syndrome (MERS) in Saudi Arabia with 2492 total laboratory-confirmed cases and 858 fatalities[1]. At present, The current outbreak caused by a new subtype of coronavirus named SARS-Cov2 has resulted in a pandemic with thousands of deaths and infected cases. This pandemic phenomenon is maintaining a sustained progression in the world, showing an emergency international alarm for finding an effective cure.

The SARS-Cov 2, SARS Cov and MERS Cov belong to the genera of the betacoronaviruses. At the first stage of the SARS-Cov coronavirus appearance, it was attempted to cure the disease by Ribavirin which revealed positive results in curing the patients. While drugs such as Aciclovir, Levofloxacin, Vancomycin, Caspofungin, and Meropenem were not able to show a significant relief in the patients [2]. The Lopinavir/Ritonavir with Ribavirin administration to the patients at the initial stages of the disease could reduce the mortality rate [3]. However, later it was confirmed that the Ribavirin treatment was associated with considerable toxicity and this approach was not successful to show compelling results in-vitro. Additionally, it was demonstrated by a recent study that the administration of Lopinavir/Ritonavir does not have a significant effect on the cases of COVID-19 [4]. The interferon therapy, the delivery of corticosteroid and immunoglobulins are the other methods that have been applied as the common treatment of the SARS-Cov. However, none of these approaches were successful in the treatment of SARS (2003). And new targeted anti-viral drugs were necessary. Therefore, it was sought to assess the structural properties of the SARS-related betacoronaviruses.

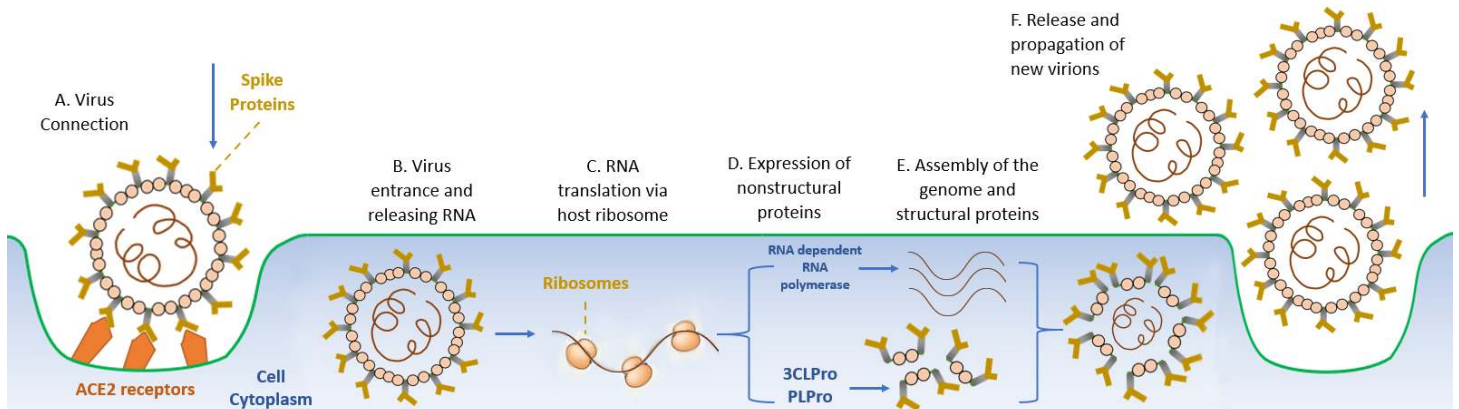


Figure 1. The schematic of the coronavirus viral cycle. The virus attaches to the ACE2 receptors of the human cells (A). It enters the cells and releases the RNA content (B). The translation of the RNA will be done using the host ribosomes of the cells (C) which results in the expression of the essential enzymes to produce the RNA replication and packaging proteins. 3CL<sup>Pro</sup> and PL<sup>Pro</sup> have an essential function to process the non-structural proteins required for the processing of the viral polyproteins (D). The packaging proteins and the RNA content are assembled to produce new virions (E). The virions exit the cells for starting another cycle of viral infection.

Anand et al (2003) determined a protein with three domains and 304 residues as the main protease of the SARS-Cov and following by this study various research targeted this protease for inhibition of the SARS-Cov activity [6-8]. Later, this protease has been named 3C Like Protease (3CL<sup>Pro</sup>). Papain-Like protease (PL<sup>Pro</sup>) was demonstrated as another target enzyme for the symptoms caused by SARS-Cov. While RNA-dependent RNA polymerase has a significant role in the coding of the genomic content of coronavirus upon infection, the 3CL<sup>Pro</sup> and PL<sup>Pro</sup> are regarded as key enzymes in the processing of the nonstructural proteins of the virus (nsps) which is thought to have a main role in the establishment of the viral replication (Figure1; [9, 10]. The surface of SARS-Cov is covered with the spike proteins that are able to attach to human Angiotensin-Converting Enzyme 2 receptors (ACE2). ACE2 receptors are normally expressed in the lungs, kidney, endothelium, heart, and intestine [11]. Targeting the SARS-Cov spike proteins as well as the blockage of human ACE2 proteins can be an alternative way to block the activity of the SARS-Cov.

## The current methods of new coronavirus treatment

A variety of the targets considering the inhibition of the RNA transcription, RNA modification, virus packaging enzymes, the capsid, and the surface proteins assist the virus to diffuse into the cells and can be regarded as strategies to deactivate or prohibit the propagation of RNA virus in cells and tissues [12]. The current methods of COVID-19 treatment are composed of the administration of drugs such as Remdesivir, Chloroquine, Arbidol, and Favipiravir and approaches such as interferon therapy [12, 13]. Currently, studies are focusing on further investigation of the biochemical materials that could inhibit the main proteases of the virus or the compounds that could inhibit the propagation rate of the virus in the cells. The plants provide an ultimate, natural source of enzyme and viral propagation inhibitors to be implicated as a treatment method of disorders caused by SARS-Cov and SARS-Cov2.

Fortunately, there is a considerable similarity between the SARS-Cov and SARS-Cov2 virus which is more than 80% identity and 96% similarity of the genome [15, 14]. It has been confirmed that the PL<sup>Pro</sup> and 3CL<sup>Pro</sup> of the SARS-Cov and SARS-Cov2 are conserved [16]. Additionally, it is observed that there is a 76.10% identity between the mentioned viruses [17]. Based on this similarity, it is expected that the results of the studies about the SARS-Cov could be implied for the research in the SARS-Cov2 to a high degree.

## Plants have considerable potential for the treatment of the coronavirus related SARS disease

Plants provide a wide source of viral protein inhibitors for the treatment of SARS. Generally, plants can express metabolites that can provide an inhibitory effect on the enzymes, proteins and the propagation of the virus. Although numerous studies have focused on the SARS 2003, there are a lower number of studies with the focus on the COVID-19 disease and mainly the articles are limited to in-silico studies of the plant compounds [16, 18]. Hopefully, based on the fact that most of the active proteins in the infection cycle of SARS-Cov2 are conserved, it can be expected that the result of a variety of researches about previous generations of coronaviruses especially SARS-Cov could be applicable to the new

coronavirus. Table 1 shows a selection of the approaches based on the plants, mentioning the representative agents based on our literature review that could have the value of further research for the COVID-19 disease. It is attempted to further discuss these strategies in the following sections.

Table 1. Potential antiviral strategies based on plants against new coronavirus.

Approach	Effective agent*	Plant	References
Using plant lectins for inhibition of the virus attachment	Utrica dioica Agglutinin (UDA)	<i>Utrica dioica</i> (Stinging nettle)	[19-21]
	Allium porrum Agglutinin (APA)	<i>Allium porrum</i> (Leek)	[19]
Natural plant secondary metabolites	Glycyrrhizin	<i>Glycyrrhiza glabra</i> (Licorice)	[22-24]
	Baicalin	<i>Scutellaria baicalensis</i> (Baikal skullcap)	[22, 25, 26]
	Quercetin	<i>Allium cepa</i> (Onion) <i>Allium sativum</i> (Garlic)	[27-29]
Plant bioreactors: Using plants to express vaccinal proteins (Plant Oral Vaccines)	Viral S1 Antigen	<i>Nicotiana tabacum</i> (Tobacco) Tomato	[30-32]
	Viral N Antigen	<i>Nicotiana tabacum</i> (Tobacco)	[33-35]

\* The representative agents have been mentioned by various studies to have positive results in previous research.

## Plant lectins

The plant immunity is an elaborate system that can efficiently detect and deactivate the invading pathogens with a variety of tools considering cell surface and intracellular receptor proteins. Plant lectins are carbohydrate-binding proteins that can act as immunologic receptors and defense proteins

and are found in a variety of species such as tobacco, soy, and leek. Plant lectins can be regarded as one of the plant-based compounds that could be targeted as a treatment for COVID-19. There are a variety of plant compounds that has been found by several studies to inhibit the proliferation trend of the SARS-Cov.

#### Urtica dioica agglutinin lectin

Stinging nettle (*Urtica dioica*) has been used in various countries as traditional medicine for years. This plant has been reported to have therapeutic effects on cardiovascular, immunity, neuronal and digestive systems [36]. The agglutinin lectin is extracted from the rhizomes of the common stinging nettle. Previously it was indicated that from the lectins that have been extracted from the selective plant species, the Allium porrum Agglutinin (APA) of Leek, Urtica dioica Agglutinin (UDA) of stinging nettle and NICTABA lectin of Tobacco (*Nicotiana tabacum*) was able to show the highest inhibition tendency to prohibit the proliferation rate of the virus to 50% (EC50) at less than 1.3 µg/ml pure extract with low toxicity in-vitro [19]. Similarly, further studies confirmed that the UDA has an impact on the inhibition of the SARS-Cov virus in-vitro [20]. Experiments have proposed that the lectins will interrupt the viral attachment and the effect of lectins has the highest performance when they are delivered at the early stages of the infection cycle [19]. Later the antiviral effect of the UDA has been assessed in-vivo in Bulb C mouse models and it was found that the UDA significantly decreased the mortality caused by SARS and reduced the weight loss [21]. This study also proposed that the UDA prevents the virus attachment by inhibition of the SARS-CoV spike (S) glycoprotein [21]. The evidence from the previous research shows that UDA can be a suitable compound for further research in the COVID-19 arena.

#### The secondary metabolites of the plants

Secondary metabolites are considered as non-necessary compounds for plant cells living. Such metabolites are expressed in response to biotic and abiotic stresses. The expression of the secondary metabolites is increased upon stress appearance. Plant active compounds such as Trashinones, Flavonoids, Carotenoids, and Diaryheptanoids can be regarded as examples. There is a variety of plant secondary metabolites that have been studied for the inhibition of SARS-Cov that are found to have a



strong antiviral and anti-SARS-Cov activity. Some of the important examples of such compounds have been discussed in the following.

### Glycyrrhizin

Glycyrrhizin is the major component in the licorice (*Glycyrrhiza glabra*) root. This compound has been used traditionally for the treatment of gastritis, bronchitis, and jaundice and is reported to have antioxidant and anti-inflammatory activity that can stimulate the formation of interferons in the body [37]. It has been proposed that Glycyrrhizin can decrease the attachment of the SARS-Cov agents to the cells especially during the initial phase of the viral infection cycle [39]. Glycyrrhizin is composed of Flavonoids, Glycyrrhetic acid,  $\beta$ -sitosterol and hydroxyl coumarins [37] and has been observed to have a significant anti-SARS-Cov activity by Cinatl et al (2003). Later Pilcher (2003) regarded the licorice plant and Glycyrrhizin as a prospective method of making a commercial drug against SARS-Cov, adding the fact that there is a long way until making a commercial drug for the SARS-Cov. The anti-SARS-Cov activity of Glycyrrhizin was further confirmed by other studies [22-24] and numerous review articles have been published as a result of positive antiviral activity of Glycyrrhizin [40-42]. The in-silico study for prediction of Glycyrrhizin behavior for COVID-19 disease has noted the Glycyrrhizin as a potential inhibitor of SARS-Cov2 [18, 43]. However, no studies have been found in the SARS-Cov, for approval of the in-vivo effectiveness of the Glycyrrhizin. Yet, based on the promising results of the mentioned studies this compound might be a potential for the development of an anti-COVID-19 disease drug.

### Baicalin

Baicalin is one of the major constituents of the plants in the *Scutellaria* genus and is the main origin of the *Scutellaria baicalensis* pharmaceutical properties. This Flavone glucuronide is previously found to have anti-apoptotic and antioxidant properties and has been previously used for the treatment of pulmonary arterial hypertension. The anti-SARS-Cov activity of this compound was first shown by Chen et al. (2004) with a stronger inhibitory effect compared to Glycyrrhizin, Interferon-alpha, and Interferon-beta 1a and considerably low toxicity concentration for the cell lines in-vitro. The anti-viral activity of this compound was found so important that later a grant for the patent of anti-SARS drug

production with this biochemical compound was approved [26]. The in-vitro assessment of the extracted flavonoids from the *Scutellaria baicalensis* also showed significant anti-viral activity on the Lipopolysaccharide activated cells while the oral administration of the compound significantly increased the survival rate of influenza A virus-infected mice [25]. Furthermore, the in-vivo result confirmed the anti-viral activity of the Baicalin in-vivo environment. However, no in-vivo study was noticed for the effect of Baicalin on SARS-Cov infected model animals. The in-silico study of the Baicalin for simulation of the compound effect in the case of COVID-19 disease demonstrated a favorable tendency of Baicalin to inhibit Angiotensin-converting enzyme 2 (ACE2). The extract of the *Scutellaria baicalensis* was able to inhibit the 3CL<sup>Pro</sup> activity of the new SARS-Cov2 virus in-vitro in a recent investigation which further approves the potential of this compound for additional studies in COVID-19 disease [44].

### Quercetin

Organosulfur compounds are amply found in the plants of the *Allium* genus such as onions (e.g. *Allium cepa*), garlic (e.g. *Allium sativum*) and leek (*Allium porrum*). Generally, organosulfur compounds are the organic macromolecules that contain sulfur in their biochemical structure. In a recent in-silico study for SARS-Cov2, it was revealed that the organosulfur materials from the *A.porrum* can have significant potential in inhibition of the Human ACE2 enzymes and therefore can it can have the potential to inhibit the connection of the SARS-Cov2 to the cells [45].

Quercetin is a flavonoid that is abundantly discovered in the onion and garlic species and can be found as sulfonic substituents (although less occurring) [27]. Quercetin-3- $\beta$ -galactoside was shown by Chen et al. (2006) to have inhibition activity of 3CL<sup>Pro</sup> of SARS-Cov. Further studies confirmed the inhibition of 3CL<sup>Pro</sup> of the SARS-Cov by both Quercetin and Quercetin-3- $\beta$ -galactoside in-vitro [28, 29]. It was also noticed that quercetin 3- $\beta$ -D-glucoside has the potential to inhibit the 3CL<sup>Pro</sup> of the MERS-Cov [47]. This compound is found to have low toxicity to the cells in-vitro, and it is one of the major natural components that is targeted for the treatment of the COVID-19 disease.

## Other plant metabolites and products

Scutellarein is another ample natural flavone in the *Scutellaria* genus. This compound is observed to have the anti-viral, anti-inflammatory and antioxidant ability. As this metabolite is also discovered in the *Scutellaria baicalensis* it might be possible that various anti-viral features in the reports about the anti-SARS properties of the *S. baicalensis* extract were the outcome of Scutellarein presence alongside the Baicalin [48]. Later, this compound was found to have an inhibitory effect on nsP13 coronavirus helicase activity. Additionally, in a recent study, the antiviral activity of this compound was assessed in-vitro and a strong replication inhibition was shown for the case of novel COVID-19 disease. Such results indicate the strong potential of plant species such as *S. baicalensis* to be used against SARS-Cov agent.

Li et al. (2005) assessed a variety of the herbal extracts in organic solvents such as ethanol and chloroform and they were able to show the extract of *Lycoris radiata* as the plant that encounters the highest anti-SARS-Cov activity with a significantly lower dose of effectiveness (about 2.1 to 2.4 ug/ml). This study proposes that the antiviral activity of the extracts is due to the presence of Lycorine in the *L. radiata* plant [49]. Hesperetin is another flavonoid that is observed to have an inhibitory effect on the SARS-Cov 3CL<sup>Pro</sup> [50]. Hesperetin is normally found in the species of citrus (Lemons) genus in-vitro. Chen et al (2006) revealed that the selective terpenoids and Lignoids extracted from plants such as *Juniperus formosana*, *Cryptomeria japonica* and *Chamaecyparis obtuse* showed a significant inhibitory effect for 3CL protease of SARS-Cov [51].

Apart from the examples that were represented in the plants that might show compelling antiviral activity against COVID-19 disease, many other studies have assessed the antiviral activity of different plants and biochemical metabolites against the previous generation of SARS related coronavirus, considerably SARS-Cov and MERS-Cov that each might provide a solution against the new COVID-19 disease. Table 2 presents the overview of the studies that have been done against SARS-related coronavirus especially SARS-Cov.

Table2. Plants with the potential of the anti-SARS-Cov activity.

Family	Name	Inhibition approach	Effective Compound	Inhibition potential (IC50/EC50) *	Reference
Amaryllidaceae	<i>Allium sativum</i> (Garlic)	ACE2 receptor inhibitor	Allyl disulfide	-	[45]
			Allyl trisulfide	-	
Anacardiaceae	<i>Galla chinensis</i> (Nutmeg tree)	Viral spike protein and human ACE2 receptors inhibitor	Tetra- <i>O</i> -galloyl- $\beta$ -d-glucose	4.5-240 $\mu$ M	[52]
Apiaceae	<i>Angelica keiskei</i> (Ashitaba)	3CL <sup>pro</sup> Inhibitor	Chalcones	11.4-129.8 $\mu$ M	[53]
Betulaceae	<i>Betula pubescens</i> (Downy birch)	3CL <sup>pro</sup> Inhibitor	Betulinic acid	8.2 $\pm$ 0.7 $\mu$ M	[51]
Betulaceae	<i>Alnus japonica</i> (East Asian alder)	PL <sup>pro</sup> inhibitor	Plant extract	4.1 $\mu$ M	[54]

Brassicaceae	<i>Isatis indigotica</i>	3CL <sup>pro</sup> Inhibitor	Hesperetin	8.3 $\mu$ M	[50]
			Sinigrin	217 $\mu$ M	
Celastraceae	<i>Tritergium regelii</i> (Regel's threewingnut)	3CL <sup>pro</sup> Inhibitor	Celastrol	10.3 $\mu$ M	[55]
			Pristimerin	5.5 $\mu$ M	
			Tingenone	9.9 $\mu$ M	
			Iguesterin	9.9 $\mu$ M	
Cephalotaxaceae	<i>T. nucifera</i> (Japanese nutmeg-yew)	3CL <sup>pro</sup> Inhibitor	Plant extract	100 $\mu$ g/mL	[56]
Crassulaceae	<i>Rhodiola kirilowii</i>	Viral growth inhibitor	Luteolin	4.5-240 $\mu$ M	[52]
Cupressaceae	<i>Chamaecyparis obtusavar formosana</i>	3CL <sup>pro</sup> Inhibitor	Savinin	25 $\mu$ M	[51]
			Hinokinin	>100 $\mu$ M	
			Betulonic acid	20 $\mu$ M	

	(Formosan Hinoki Cypress)				
Cupressaceae	<i>Cryptomeria japonica</i> (Japanese cedar)	Viral growth inhibitor	<i>Hydroxy-deoxy-cryptojaponol</i>	>10 $\mu$ M	[51]
Cupressaceae	<i>Thuja orientalis</i>	Viral growth Inhibitor	Plant extract	130 $\pm$ 1.2 ug/ml	[57]
Cupressaceae	<i>Juniperus oxycedrus</i> (Cade)	Viral growth Inhibitor	Plant extract	130 $\pm$ 1.2 ug/ml	[57]
Dioscoreaceae	<i>Dioscoreae Rhizoma</i> (Cinnamon-vine)	Viral growth inhibitor	Plant extract	200 $\mu$ g/ml	[58]
Fabaceae	<i>Glycyrrhiza glabra</i> (Liquorice)	Viral growth inhibitor	Glycyrrhizin	30 ug/ml	[24, 38]

Fabaceae	<i>Pterocarpus santalinus</i> (Red sanders)	3CL <sup>pro</sup> Inhibitor	Savinin	9.1 ± 2.4 μM	[51]
Fabaceae	<i>Cassiae Semen</i> (Sickle Senna)	Viral growth inhibitor	Plant extract	200 μg/ml	[58]
<i>Fabaceae</i>	<i>Psoralea corylifolia</i>	PL <sup>pro</sup> inhibitor	Plant extract	15 μg/ml	[59]
Gentianaceae	<i>Gentiana Radix</i> (Gentian)	Viral growth inhibitor	Plant extract	200 μg/ml	[58]
Lamiaceae	<i>Salvia miltiorrhiza</i> (Red sage)	PL <sup>pro</sup> inhibitor	Tanshinones	0.8 -30.0 μM	[60]
Lamiaceae	<i>Scutellaria baicalensis</i> (Georgi Baikal skullcap)	Viral growth inhibitor	Plant extract	-	[61] [62]

Lamiaceae	<i>Scutellaria lateriflora</i> (blue skullcap)	Helicase inhibitor	Scutellarein	-	[63]
Lauraceae	<i>Laurus nobilis</i> (Laurel)	Viral Growth inhibitor	Plant Extract	120 µg/ml	[57]
Lauraceae	<i>Cinnamomum cassia</i> (Cortex Chinese cassia)	3CL <sup>pro</sup> Inhibitor	Plant extract	30.3 ± 2.6 µg/ml	[64]
Lauraceae	<i>Cinnamomum cassia</i> (Cortex Chinese cassia)	3CL <sup>pro</sup> Inhibitor	Plant extract	30.3 ± 2.6 µg/ml	[64]
Linaceae	<i>Linum usitatissimum</i> (Flax)	3CL <sup>pro</sup> Inhibitor	Herbacetin	-	[65]
Loranthaceae	<i>Loranthi Ramus</i> (Mulberry)	Viral growth inhibitor	Plant extract	200 µg/ml	[58]
Meliaceae	<i>Toona sinensis</i> Roem (Chinese cedar)	Inhibit the cellular entry of	Quercetin	-	[58]



		SARS-CoV			
Menispermaceae	<i>Stephania cepharantha</i> <i>Hayata</i>	Viral Growth inhibitor	Biscoclaurine	-	[66]
Myricaceae	<i>Myrica faya</i> (Bayberry)	Helicase inhibitor	Myricetin	-	[63]
Paulowniaceae	<i>Paulownia tomentosa</i> (Princess tree)	PL <sup>pro</sup> inhibitor	Flavonoids	5.0 $\mu$ M	[67]
Plantaginaceae	<i>Veronica linariifolia</i>	Viral growth inhibitor	Luteolin	4.5-240 $\mu$ M	[52]
Polygonaceae	<i>Rheum palmatum</i> (Ornamental rhubarb)		Plant extract	13.76 $\pm$ 0.03 $\mu$ g/ml	[68]
Polygonaceae	<i>Rheum officinale</i>	Viral spike protein and	Emodin	1-10 $\mu$ g/ml	[69]

	<i>(Rhubarb)</i>	human ACE2 receptors inhibitor			
Polygonaceae	<i>Reynoutria</i> <i>(Multiflora</i> <i>Tuber)</i>	Viral spike protein and human ACE2 receptors inhibitor	Emodin	1-10 µg/ml	[69]
Santalales	<i>Rhizoma</i> <i>Cibotii</i> (Showy mistletoes)	3CL <sup>pro</sup> Inhibitor	Plant extract	200 µg/ml	[58]
Sapindaceae	<i>Litchi chinensis</i> (Lichi)	3CL <sup>pro</sup> Inhibitor	Flavonoids extract	-	[65]
<i>Saururaceae</i>	<i>Houttuynia</i> <i>cordata</i> (Fish leaf)	3CL <sup>pro</sup> Inhibitor and RNA- dependent RNA polymerase (RdRp) Inhibitor	Plant extract	>200 µg/ml	[70, 71]

Saururaceae	<i>Houttuynia cordata</i> (Fish mint)	3CL <sup>pro</sup> Inhibitor	Plant extract	50 µg/ml	[70]
Solanaceae	<i>Nicotiana benthamiana</i> (Benth)	Viral growth inhibitor	NICTABA Lectin	-	[33, 72]
Theaceae	<i>Camellia sinensis</i> (Black tea)	3CL <sup>pro</sup> Inhibitor	Tannic acid	3 µM	[73]
			3- isotheaflavin-3-gallate	7 µM	
<i>Urticaceae</i>	<i>Urtica dioica</i> (Stinging nettle)	Viral spike protein inhibitor	<i>Urtica dioica</i> agglutinin	1.1 ± 0.4 µg/ml	[20, 21]
Zingiberaceae	<i>Curcuma longa</i> <i>Isatis</i>	3CL <sup>pro</sup> Inhibitor	Curcumin	40 µM	[51]

\*IC50 is an indication of the concentration (µM or ug/ml) where the activity of the viral protein is reduced up to 50%. EC50 is the indication of the concentration (µM or µg/ml) where the activity of the viral growth is reduced up to 50%.

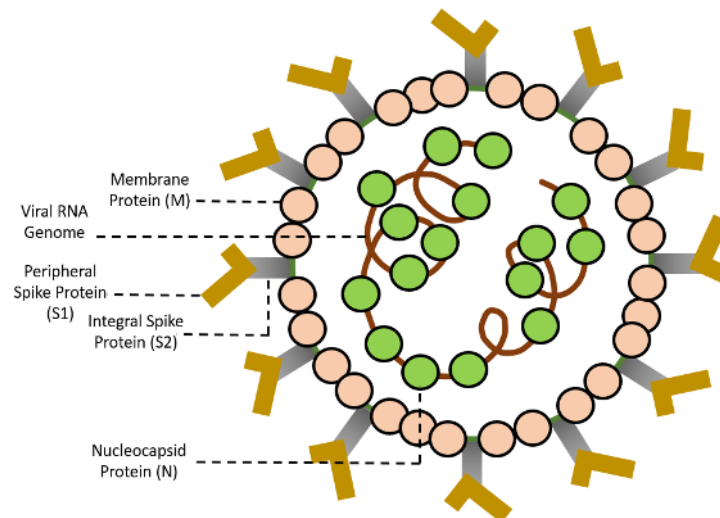


Figure 2. The structure of coronavirus proteins. The spike proteins (S) of the virus are composed of an integral S2 and peripheral S1 protein that is involved in the connection of the virion to the cells. Antibodies against S1 protein will inhibit the propagation of the virus. The nucleocapsid proteins are packaging the viral RNA genome and have an essential role in the viral self-assembly.

## Using the plants as oral vaccines

Application of plants as the vaccines especially with the focus in the oral delivery has numerous advantages such as the lack of viral and bacterial infection in the final product, ease of scaling and benefiting from the bioencapsulation (Storing the expressed protein within the natural environment of the cells) provided by the tissues, cells, and organelles of the cells which bring other advantages such as ease of transport and lowering the logistics fees [74]. Production of vaccines under plant platform against the new coronavirus can be a good solution to the definite massive demand of the world as the scaling of production is easy for plant-based vaccines. Plant cells have this ability to show eukaryotic post-translational modifications which gives them another advantage over usage of bacterial platforms such as *E. coli* to express and store the proteins. Plants can be employed as a bioreactor for overexpression of a compound that might have anti-viral activity. Consequently, it is a suitable approach to find agents that can be expressed under plant systems to induce the immunological system against the virus in order to have mucosal or long-term immunity.

Previous studies have focused on the production of a vaccine based on overexpression of the SARS-Cov surface proteins in the plant species by transformation techniques such as bacterial infection and gene gun transformation to express the viral proteins in the plants. Such viral proteins can stimulate the immunity of the host by introducing the antigens to the human body after consumption. The main proteins that are considered by experiments are composed of the S1 subunit of the SARS-Cov spike protein, membrane protein (M) and the nucleocapsid of the virus called N protein (Figure 2). Although there have been studies about the immunological activity of the M protein as a target for plant viral vaccines [72], studies have mainly focused on S and N proteins. The genome of S1 or N protein can be mounted to a vector and be delivered to the host organism for transcription, expression, and accumulation of the viral antigen [74]. The introduction of the new piece of codon to the plant will finally produce a transgenic plant that is able to express and accumulate the viral N or S proteins in the inner segments and organelles of the plant cells of plant tissue. The general overview of the required considerations and challenges for the production of plant vaccines (mainly in seed oral vaccines) has been discussed previously by our group [74]. There are mainly two types of SARS-Cov virus viral antigen proteins that have been aimed to be expressed in the recombinant plant platform, S1 and N proteins.

### The expression of N protein

N protein is the nucleocapsid protein of the SARS-Cov (Figure 2). It is demonstrated that the antibodies against the N and S protein were clearly detected in the patients of the early stages of SARS-Cov disease [34]. It is also discovered that the SARS-Cov N protein was able to induce both temporal and long-term memory T-cell response [33]. For this reason, the N protein is regarded as one of the effective inductors of the humoral and cellular responses in the SARS-Cov contamination process [33]. Studies for expression of N protein are mainly done on the tobacco platform. After showing the feasibility of the N protein expression in Tabaco platform by several pieces of research, it was found that the oral delivery and the injection of the N protein to the BALB-C mice was able to increase respectively the amount of IgA and IgG in the experimental mice sera, indicating the Anti-SARS Cov activity of the vaccines [33]. The previous investigation also reveals that the expression of N protein in the plants can

be used as a rapid and facile diagnostic tool for SARS-Cov infection. The transgenic expressed oral delivery of the N proteins have been assessed in the patients with SARS. The N proteins that were expressed in the tobacco platform using potato virus X infection were only successfully appeared in the immunoblotting sera of the patients that had SARS-Cov and not any other irrelevant respiratory syndromes [35]. Consequently, the acquired data from the several pieces of research indicates that the expression of the N protein in the plants can be an introduction to further research for the new coronavirus disease.

### The expression of S1 protein

The expression of the spike glycoprotein of the SARS-Cov is followed by the creation of a large polypeptide that is finally cleaved by proteases that are encoded by the host or virus to S1 and S2 subunits. S1 is the peripheral part of the virus that is believed to contain the main receptor-binding domain (RBD) on the N-terminal part. It is noticed that the antibodies against S1 protein are strongly efficient in the RBD interaction. Therefore, it is aimed to target the S1 genes to the part of the cells and organelles within the plants such as tobacco, tomato and lettuce platforms.

The previous research for expression of the S1 protein in the plants proved compelling evidence of the plant's potential to be used as a bioreactor for expression of SARS-Cov viral antigen proteins. The S1 proteins were expressed in the cytosol [30] or chloroplast [31] with an accumulation rate of up to a maximum of 10.2% of Total Soluble Protein (TSP). The oral delivery of the S1 proteins in the platform of tomato resulted in a significant IgA increase while the injection of the S1 protein from the dried root of tobacco resulted in a significant detection of the IgG in western blot and ELISA results [32].

On the whole, the transgenic plants have this potential to provide an approach for the production of plant vaccines against COVID-19 disease. However, the usage of plant cells as a bioreactor is subjective to several ethical and environmental considerations. As this process will result in the generation of a new transgenic plant, it is probable that the propagation of the plant species as the result of the uncontrolled breeding might affect the species within the ecosystems, create an imbalanced niche or

even cause poisoning to the species that might consume the plant randomly. Consequently, the transgenic plant culture should be done under restricted control [74].

## Controlling the plants' anti-viral compounds expression via environmental conditions

Based on the fact that the expression of the lectins and secondary metabolites of the plants are highly dependent on the environmental conditions. Alternatively, it is possible to increase the expression of an anti-viral compound within the plant by changing the environmental circumstances to induce a more stressful condition for the plant. As mentioned earlier in the article some plant species such as tobacco can express anti-SARS lectins that tend to inhibit viral propagation [19]. It is also found that the expression of the lectins in the species such as tobacco can be increased by the presence of pathogens, pest insects and other biochemical materials that could induce the immunogenic response in the plant species. In this case, it is possible to increase the effective lectin content for a higher yield in case of the attitude for non-oral delivery or to increase the effective dose in case of oral delivery [74]. For this reason, the type of pest or invader species [75], the variations in the stress environment [76] and the biochemical (such as Jasmonates) compounds [77] can alter the expression of the lectins in the plants especially in the expression of Nictaba of tobacco. It is worth mentioning that the application of the plant biotechnology technics can also provide the ability of the overexpression of the lectin genes such as UDA and Nictaba agglutinin to provide a higher yield and dosage of the anti-viral compound in the plants.

## The effectivity of the anti-viral plants' oral delivery

In this review, we have recommended various plants that can have the anti-SARS Cov2 potential. However, the oral delivery of such compounds might be further advantageous as oral delivery is facile and non-invasive. In the case of the usage of plants as the vaccines for expression of the anti-SARS Cov agents, it was observed that the oral delivery of vaccines to animal model was able to induce the mucosal immune responses [32, 33]. Meanwhile, the oral delivery of the plant baicalin was shown to successfully

reduce the mortality in the influenza-infected mice [25]. However, the question is whether the direct oral delivery of the compounds will be also effective in terms of having antiviral activities. It was confirmed by several studies that most of the plant anti-SARS agents can inhibit the connection of the viral agents to the cells [39]. Therefore it can be postulated that most plant anti-viral agents might apply a protective behavior against the entrance and propagation of the viral agents in the host body. In this case, adding the edible plant species that produce anti-SARS-Cov compounds such as leek, onion, garlic and stinging nettle root (the common nettle) in the food diet might be a good strategy against infection of the new COVID-19 disease.

## Conclusion

Based on the high similarity of the genome and the receptors of SARS-Cov and SARS-Cov2 this review attempted to suggest possible plant species that might be implicated as anti-SARS-Cov2 agents. Plant species can provide a natural, cost effective and with less side effects approaches of drug discovery against COVID-19 disease. Our study suggested the plant species such as *U. dioica* and *S. baicalensis* might encounter the protection, relief or treatment potential against COVID-19 disease. Among such plant compounds, lectins such as *Utrica dioica* agglutinin and plant secondary metabolites such as Glycyrrhizin and Baicalin have shown promising results in SARS-Cov as well as a favorable in-silico results in the COVID19 disease. Such compounds might be a good choice for further research toward finding a novel natural treatment approach. Meanwhile, several studies have tried to use the plants as a bioreactor to express the SARS vaccinal agents or to overexpress the vaccinal agents. Perhaps the use of tobacco plant might be a suitable option as numerous studies have demonstrated positive results in production and immunization in-vivo by deployment of the tobacco platform for transformation. Furthermore, tobacco contains NICTABA lectin which is a strong antiviral agent. Overall, more studies are needed in order to further assess the anti-viral ability of plant species.

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