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REVIEW ARTICLE

Spike protein of SARS-COV-2 as a potential target for phytochemical constituents: A literature review

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A B S T R A C T

SARS-CoV-2 belongs to well-known SARS Coronaviridae family. One of the main structural proteins of SARS-CoV-2 is the spike protein that is present around the surface of a viral cell and plays an essential role in viral attachment, fusion and invasion in host cell. Once a virus invades a cell, it replicates and infects other cells. The fundamental role of spike protein in the progression of viral infection has led to an increased interest in exploring agents that target the viral spike protein for effective control of CoVID-19. The related data from published articles reviewed and numerous phytochemicals that reportedly target the spike proteins of coronaviruses by computational studies briefly discussed. These active constituents possess the potential to develop as therapeutic and antiviral agents against SARS-CoV-2.

Keywords: *Phytochemical Spike protein, potential target, SARS-COV-2*

Introduction

The coronaviruses have been known since the 20th Century, viruses of this family have previously been identified to cause various forms of mild and severe disease conditions, both in man and animal.[1] The SARS-CoV-2 virus originated in 2019 at Wuhan, China from where it spread far and wide resulting in a global pandemic.[2] The virus has phenomenal impact internationally affecting the lives of millions and responsible for the mortality of millions of people. As of 31 October, 2021, according to global updates by the World Health Organization (WHO), nearly 246 million people have been infected with the virus, and 5 million have lost their lives due to CoVID-19 [3] as shown in Figure 01. Initially, information concerning the new virus, SARS-CoV-2 belonging to the coronaviridae family, was considerably scarce, particularly regarding effective treatment of the disease caused by the virus, named as CoVID-19 by WHO. However, as public's health interests created a high demand for information extensive research of SARS-CoV-2 conducted. The virus possesses great similarity with two previously well-known coronaviruses, that are responsible for causing SARS (Severe Acute Respiratory Syndrome) in the year 2002 and MERS (Middle East Respiratory Syndrome) in the year 2012.[4] Thus, the virus was named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) due to significant resemblances with the SARS-CoV (the virus responsible for SARS).[5]

Spike protein as potential therapetic target

The SARS-CoV-2 virus is an enveloped single-stranded RNA virus, comprising of various non-structural proteins and four main structural proteins: the spike protein (S), envelope protein (E), membrane protein (M) and the nucleocapsid (N).[6] The spike protein (S) is the key protein involved in invasion of virus inside host cells. Envelope protein (E) and the membrane protein (M) play important roles in the viral assembly, while the nucleocapsid protein (N) encloses the genetic material (RNA).[7]

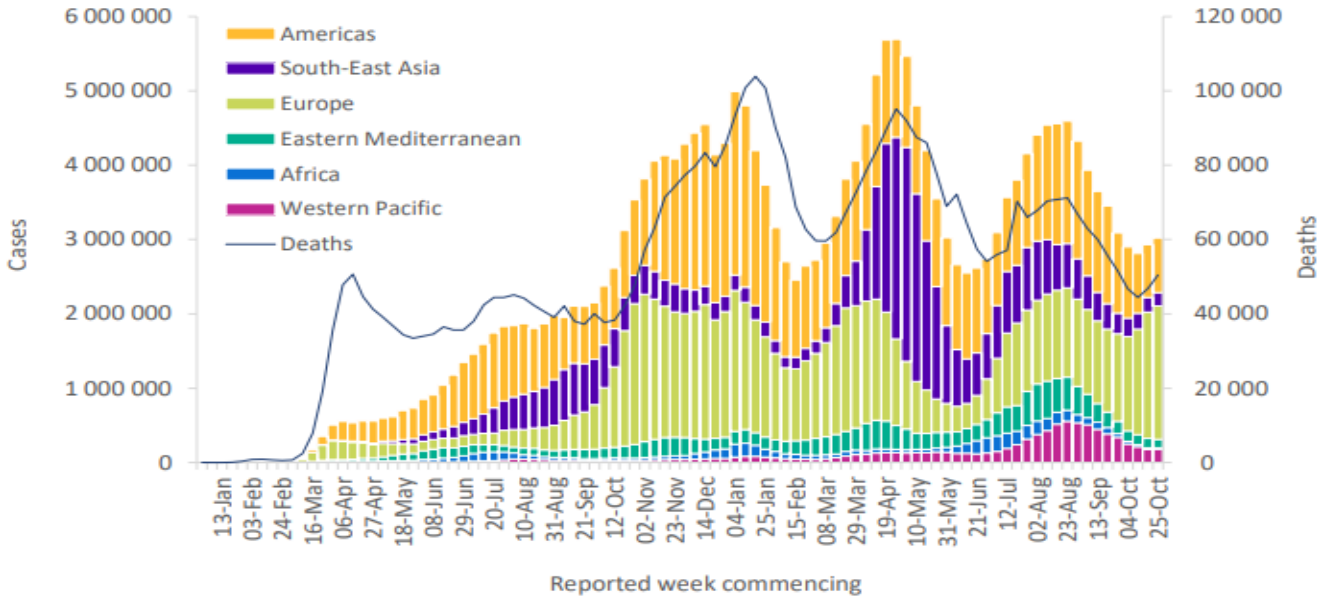

Figure 1: The weekly CoVID-19 reported cases and deaths around the globe October, 2021

The name *corona* (Latin for crown) and the crown-like appearance of coronaviruses occurs due to the presence of the spike proteins which protrude from the viral envelope, all out around the surface of the cell.[8] The spike protein is a surface glycoprotein that attaches to the host cell receptors and promotes viral entry into host cells and triggers the infection process.[9] as shown in Figure 2. Viral entry takes place through two mechanisms via fusion with the host cell membrane or via undergoing endocytosis, in case of which the membranes fuse from within the endosome.[10] Once inside the cell the virus replicates its genetic material, it forms and assemble new virions, which are then released from the cells and infect further cells and proliferate in a similar manner.[11] The spike protein consists of two main functional domains, the S1 domain being responsible for binding with receptors of the cells and the S2 domain that is involved in the fusion of the viral membrane with the host cell membrane.[12] The mode of infection of SARS-CoV-2 occurs along the same mechanism as SARS-CoV, via interaction with ACE2 (Angiotensin converting enzyme 2). ACE2 is a membrane bound peptidase, abundantly present in epithelial cells of the blood vessels, lung, kidney and the intestines, the enzyme is involved in processes of the immune system and the cardiovascular system.[13] Analysis by cryogenic electron microscopy, revealed that though the SARS-CoV and SARS-CoV-2 viruses are similar and both target the ACE2, however the new virus SARS-CoV-2 was found to possess nearly 10-20 times higher affinity for ACE2 than SARS-CoV.[14]

Studies have revealed that viral entry into human cell, and subsequent spread of infection occurs only after the spike protein interacts with ACE2.[15] The essential roles of the spike protein in viral attachment, fusion, entry and infection, have led to it being considered an important and effective potential target in the development of therapeutic agents and vaccines for managing CoVID-19.[16] Infact, the CoVID vaccines currently available, also depend on the viral spike protein for their effectivness.[17] Yet, while various vaccines have been developed, distributed and administered all over the world, the corona pandemic is ongoing, as is the search for new therapeutic agents against the virus. Many previously approved and safe drugs have been investigated, reinvestigated and in some cases being utilized for their activity against the disease, similarly, natural products being a rich source of phytochemicals are also being thoroughly explored in the search of a cure.[18]

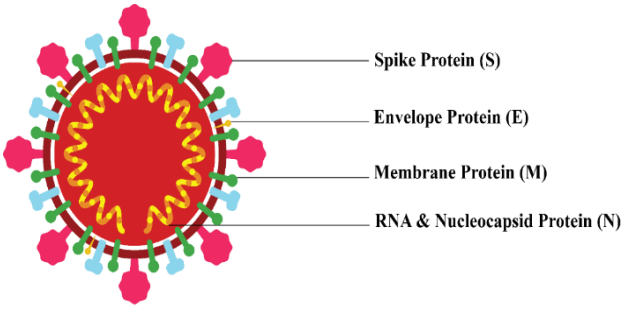

Figure 2: Spike protein as a potential therapeutic target, depicting the main viral structural protein

Methodology

A review of the existing literature was conducted through means of databases including Google scholar, PubMed and ScienceDirect using related keywords such as "SARS-CoV Spike protein", "coronaviruses", "spike protiens", "phytochemicals", "medicinal plants" and "natural products" were used, individually and collectively. Over 76 of the resultant articles were then extensively explored and the relevant information concerned was extracted. Only the data regarding natural plant-derived phytochemicals which could target the Spike protein of SARS-CoV-2 was included. The information about natural products that can target the proteases and those that interfere in replication was excluded. The collected data are discussed and presented in tabloid form to aid in comprehension and understanding.

Discussion

Phytochemicals as candidates to target spike protein

Described in this review, are some phytochemicals that have investigated for their protective roles in the fight against SARS-CoV-2 due to their interactions with the spike protein of the coronavirus. In the initial months of the pandemic, one of the first virtual screening study conducted, analyzed over 40,000 candidates, including FDA approved drugs and natural products obtained from the ZINC database and literature. This study showed that drugs used for the treatment of Hepatitis C (also an enveloped, single stranded RNA virus) could be potentially used for CoVID-19 due to their ability to bind and interfere with the spike protein. The natural compounds that found to be effective were amyrin, loniflavone, procyanidin, phillyrin, proanthocyandin, sericoside, punicalagin, strictinin, rutin and tirucallina.[19]

Traditional Chinese Medicines (TCM) also possess many natural products capable of treating various types of diseases and conditions. The phytochemicals that have shown activity against the spike protein of the human coronaviruses include anthraquinones like emodin and rhein, a synthetic anthraquinone derivative, and a tannin tetra-o-galloyl-d-glucose.[19] Emodin from the genus Rheum and Polygonum exerted its activity by the inhibition of the interaction between the SARS-CoV spike protein and the human ACE2. Tetra-O-galloyl- d-glucose from Galla chinensis and luteolin from Veronicalina riifolia exerted anti-viral by binding with the spike protein of SARS.[20,21] Similarly, a study conducted on thirteen compounds of plants in the TCM system pharmacology (TCMSP) database, discovered a compound Dihydrotanshinone I to possess high binding affinity with the viral spike protein.[22]

Plants belonging to the Glycyrrhiza spp. exert various pharmacological actions and are extensively utilized in the TCM system.[23] Phytochemicals of Glycyrrhiza glabra, particularly the flavonoids (Glycyrrhizin, Glabridin, Liquirtigenin) and constituents including Glycyrrhizic acid and Glycyrrhetinic acid are known to have activity against the SARS-CoV. These agents act through multiple mechanisms, which include influencing the viral attachment between the host cells and spike proteins and by hindering viral replication via effects on the nucleocapsid and functional proteins. The phytochemicals have found to have binding affinity with SARS-CoV-2 through molecular docking studies include glycyrrhetic acid, shinflavanone, glycyrrhizin, glabridin, hispaglabridin a, and glabrin b.[11] An *In-silico* molecular docking study of phytochemicals belonging to Glycyrrhiza glabra comparatively performed against proposed standards (Lopinavir, Rotinavir) for activity against the spike protein, concluded that plant phytochemicals glycyrrhizic acid, liquiritin, glyasperin a and isoliquiritin apioside displayed similar or higher binding activity than the standards. The glycyrrhizic acid showed the highest affinity and is thought to be the most effective spike inhibitors from the constituents of Glycyrrhiza glabra.[24]

Another molecular docking study on 10 naturally occurring compounds against the spike protein of the SARS-CoV-2 revealed three phytochemicals that

presented with the ability to bind and inhibit the interaction between the viral spike protein and the ACE2 receptors. Namely fisetin, quercetin and kaempferol, possess the potential to be explored for *in-vitro* and *in-vivo* studies against the new coronavirus.[25] Curcumin, bisdemethoxycurcumin and demethoxycurcumin, from the curcuma sp., tangeretin, hesperetin, hesperidin, nobiletin, naringenin from the citrus sp., brazilein and brazilin from caesalpinia sappan (sappan wood), galangin and acetoxychavicol acetate from Alpina galangal (Galangal), were found to possess good binding affinity with a binding domain of the spike protein of the SARS-CoV-2 when investigated via molecular docking by researchers in Indonesia. According to this study, the medicinal plants and its phytochemicals could be beneficial in the treatment and prevention of the viral infection, and compounds with high binding affinities could be potential therapeutic agents in the management of CoVID-19.[26]

Hesperidin from valeriana jatamansi, anthraquinones and rhein from Cassia angustifolia, anthraquinones and chyrsin from oroxylum indicum and emodin from rheum emodi have reported as the spike inhibitors for SARS-CoV. Through docking studies, focused on targeting the bound structure of the spike glycoprotein of SARS-CoV-2 and human ACE2, three of the above-mentioned compounds identified as more likely to be beneficial in the treatment of the viral infection. Namely i) hesperidin, a flavonoid present abundantly in lemons and oranges, ii) chyrsin, a flavonoid naturally occurring in honey and propolis, and iii) a polyphenol emodin, present in many plants like aloe vera, senna, rhubarb etc.[27] Acetogenins from Annona muricate, particularly cis-annonacin displayed significant docking properties with high binding affinity and low binding energy and is suggested to be investigated with further studies.[26]

Essential oils are well known for their pharmacological activities, essential oils from different plants aid in the treatment of various acute conditions, chronic diseases and against bacterial and viral infections. A study investigated the anti-viral potential of the constituents of essential oils obtained from plants belonging to the Lamiaceae, Lauraceae, Myrtaceae, Apiaceae, Fabaceae and Geraniaceae families by *in-silico* screening against the spike protein of SARS-CoV-2. This study reported that anethole, cinnamaldehyde, carvacol, geraniol, cinnamyl acetate, thymol, pulegone, L-4-terpineol have the potential to inhibit the spike protein of SARS-CoV-2 and could potentially be effective agents in the treatment of CoVID-19.[27]

In a virtual screening study of 52 plants belonging to the Ayurvedic system medicine, the researchers identified several phytochemicals that displayed promising activities against CoVID-19, which not only had high binding affinity with just the Spike protein (S) of SARS-CoV-2, but also the Papain-like protease (PL-Pro) and the Main protease (M-Pro), that are non-structural proteins necessary for viral replication and lifecycle. The phytochemicals are kuwanon X from Morus alba, punicafolin, emblicanin A, punigluconin, phyllanemblinin A from Phyllanthus emblica, rutin from Azadirachta indica, lithospermic acid from Salvia miltiorrhzia, amarogentin and amaroswerin from Swertia chirata. In this study, the authors suggested that Morus alba and Phyllanthus emblica could prove effective in the treatment of infection with SARS-CoV-2.[25]

In addition, phytochemicals of Mangifera indica, Mukia maderaspatana, Justicia adhota tested for affinity against the SARS-CoV-2 spike protein. Diphyllin and tuberculatin, especially those form the Malabar nut (Justicia adhota) showed significant selective binding affinity with the spike protein, these phytochemicals showed better affinity than even some anti-viral medications and standards.[22]

Kabasura Kudineer is a Siddha formulation (Indian herbal medicine) that is composed of fifteen natural products and has used for the treatment of influenza and fevers accompanied with flu-like- symptoms. JACOM is an Indian herbal formulation that is a combination of five plants, which has shown to be effective against influenza. This medicine when screened *in-silico* against SARS-CoV-2 spike protein in a study, displayed nine phytochemicals that had high affinity with the spike protein. These included magnoflorine from sida acuta, 5-hydroxy-7,8-dimethoxyflavanone from andrographis paniculata, tinosponone from tinospora cardiofolia, cirsimaritin, chrysoeriol and 6-methoxygenkwanin from plectranthus amboinicus, quercetin and vasicinone from justicia adhatoda, and lastly luteolin from Costus speciosus. In the fore mentioned study, the authors concluded with an intent to utilize these six plants, containing phytochemicals with anti-viral activity and develop an effective novel herbal formulation (SNACK-V) against SARS-CoV-2.8 Table 1).

Table 1: Potential phytochemicals with their plant sources reported to target the spike protein.

Sr.	Phytochemical	Class	Plant source	Reference
1.	5-Hydroxy-7,8-dimethoxyflavanone	Flavonoid	*Andrographis paniculata*	8
2.	Amarogentin	Glycoside	*Swertia chirata*	17
3.	Amaroswerin	Glycoside	*Swertia chirata*	17
4.	Anethole	Volatile oils	Apiaceae, Fabaceae, Geraniaceae Lamiaceae Lauraceae Myrtaceae	9
5.	Carvacol			
6.	Cinnamaldehyde			
7.	Cinnamyl acetate			
8.	Geraniol			
9.	Thymol			
10.	Pulegone			
11.	L-4-terpineol			
12.	Brazilein	Aromatic hydrocarbon	*Caesalpinia sappan*	23
13.	Brazilin	Heterocyclic compound	*Caesalpinia sappan*	23
14.	Chyrsin	Flavonoid	*Oroxylum indicum*	1
15.	Cirsimaritin	Flavonoid	*Plectranthus amboinicus*	8
16.	Chrysoeriol	Flavonoid	*Plectranthus amboinicus*	8
17.	6-Methoxygenkwanin	Flavonoid	*Plectranthus amboinicus*	8
18.	*cis*-Annonacin	Acetogenins	*Annona muricate*	16
19.	Curcumin	Curcuminoids	*Curcuma sp.*	23
20.	Demethoxycurcumin	Curcuminoids	*Curcuma sp.*	23
21.	Bisdemethoxycurcumin	Curcuminoids	*Curcuma sp.*	23
22.	Diphyllin	Lignan	*Justicia adhota*	17
23.	Tuberculatin	Diphyllin glycoside	*Justicia adhota*	17
24.	Emodin	Anthraquinones	*Rheum emodi* *Rheum* and *Polygonum* (Genus)	1, 26
25.	Fisetin	Flavonoid	Fabaceae	15
26.	Galangin	Flavonoid	*Alpina galangal*	23
27.	Acetoxychavicol acetate	Phenol ester	*Alpina galangal*	23
28.	Glabridin	Flavonoid	*Glycyrrhiza sp.*	11, 21
29.	Glyasperin A	Flavonoid		
30.	Glycyrrhetic acid	Triterpenoid		
31.	Glycyrrhizin	Triterpenoid		
32.	Glabrin B	Flavonoid		
33.	Liquiritin	Flavonoid		
34.	Hispaglabridin A	Flavonoid		
35.	Isoliquiritin apioside	Flavonoid		
36.	Shinflavanone	Flavonoid		
37.	Hesperetin	Flavonoid	*Citrus sp.*	23
38.	Nobiletin			
39.	Naringenin			
40.	Tangeretin			
41.	Hesperidin	Flavonoid	*Citrus sp Citrus aurantium* *Valeriana jatamansi*	1, 23
42.	Kamferol	Flavonoid	Angiospermae	15
43.	Kuwanon X	Flavonoid	*Morus alba*	17
44.	Lithospermic acid	Flavonoid	*Salvia miltiorrhzia*	17
45.	Luteolin	Flavonoid	*Costus speciosus* *Veronicalina riifolia*	8, 26
46.	Magnoflorine	Alkaloid	*Sida acuta*	8
47.	Punicafolin	Tannin	*Phyllanthus emblica*	17
48.	Emblicanin A	Flavonoid glycoside	*Phyllanthus emblica*	17
49.	Punigluconin	Tannin	*Phyllanthus emblica*	17
50.	Phyllanemblinin A			
51.	Phillyrin	Lignan	*Forsythia suspensa*	7
52.	Proanthocyandin	Flavonoid	*Vitis vinifera*	7
53.	Punicalagin	Tannin	*Terminalia catappa*	7

54.	Quercetin	Flavonoid	*Justicia adhatoda*	8, 15
55.	Vasicinone	Alkaloid	*Justicia adhatoda*	15
56.	Rhein	Anthraquinones	*Cassia angustifolia*	1
57.	Rutin	Flavonoid	*Azadirachta indica*	17
58.	Sericoside	Triterpenoid	*Terminalia sericea*	7
59.	Strictinin	Tannin	*Camellia sinensis*	7
60.	Tetra-O-galloyl-d-glucose	Anthraquinones	*Galla chinensis*	26
61.	Tinosponone	Active constituent	*Tinospora cardiofolia*	8
62.	Tirucallin A	Tannin	*Euphorbia tirucalli*	7
63.	Dihydrotanshinone	Quinone	*Salvia miltiorrhiza*	22

Conclusion

This new coronavirus continue to threaten, infect and take the lives of people all over the world. The interaction between human/host cell ACE2 receptors and the viral spike protein has led to an increased interest in agents that can inhibit the actions of the spike protein and subsequently viral infection and entry into the cells. In this review, phytochemicals that have found to possess anti-viral activities due to their binding affinities and binding energy values via *in-silico* molecular docking studies against the coronavirus spike protein have compiled. Data of more than 60 phytochemicals belonging to various classes, including alkaloids, anthraquinones, flavonoids, glycosides, lignans, quinones, saponins, tannins, triterpenoids and volatie oils were summarized in this review. These plant-derived phytochemicals can be explored (*in-vitro*, *in-vivo*) and developed further as therapeutic agents against the SARS-CoV-2 virus.

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