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Phytochemicals as therapeutics against COVID-19: An in-silico study

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Abstract

Since December 2019, the worldwide spread of COVID-19 has brought the majority of the world to a standstill, affecting daily lives as well as economy. Under these conditions, it is imperative to develop a cure as soon as possible. On account of some of the adverse side effects of the existing conventional drugs, researchers all around the world are screening natural antiviral phytochemicals as potential therapeutic agents against COVID-19. This paper aims to review interactions of some specific phytochemicals with the receptor binding domain (RBD) of the Spike glycoprotein of SARS-CoV-2 and suggest their possible therapeutic applications. Literature search was done based on the wide array of in-silico studies conducted using broad spectrum phytochemicals against SARS-CoV-2 and other viruses. We shortlisted 26 such phytochemicals specifically targeting the S protein and its interactions with host receptors. To validate the previously published results, we also conducted molecular docking using the AutoDockVina application and identified 6 high potential phytochemicals for therapeutic use based on their binding energies. Besides this, availability of these compounds, their mode of action, toxicity data and cost-effectiveness were also taken into consideration. Our review specifically identifies 6 phytochemicals that can be used as potential treatments for COVID-19 based on their availability, toxicology results and low costs of production. However, all these compounds need to be further validated by wet lab experiments and should be approved for clinical use only after appropriate trials.

Keywords: Phytochemicals, SARS-CoV-2, S-Protein, Molecular docking, ACE 2.

1. Introduction

Coronaviruses are a diverse group of enveloped positive strand viruses infecting many different animals, and they can cause mild to severe respiratory infections in humans (Ye et al. 2020,Mackenzie and Smith 2020,Gralinski and Minachery 2020). Among them 3 epidemics caused by coronavirus family [Severe acute respiratory syndrome (SARS-CoV) (Ye et al. 2020), Middle East respiratory syndrome (MERS-CoV) (Raj et al. 2014), and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Mackenzie and Smith 2020,Gralinski and Minachery 2020,Zhu et al. 2019)] affected large number of people throughout the world. These 3 types of corona viruses are zoonotic in nature and cause respiratory tract infections which can sometimes be fatal (Ye et al. 2020). But SARS-CoV-2 surprisingly with its high transmissibility and reduced virulence thrusted into the spotlight situating a world-wide pandemic (Ye et al. 2020,Mackenzie and Smith 2020).

Towards the end of December, 2019, a new disease of unknown aetiology appeared in Wuhan, China (Mackenzie and Smith 2020, Gralinski and Minachery 2020, Zhu et al. 2020, Sanyaolu et al. 2020, Guo et al. 2020, Chen et al. 2020, Mizumoto and Chowell 2020, Siordia 2020, Jiag et al. 2020). Cluster of patients exhibited symptoms of viral pneumonia including fever, difficulty in breathing, and bilateral lung infiltration with unknown cause, which interestingly had similarity with patients with SARS and MERS (Gralinski and Menachery 2020, Su et al. 2015, Su et al. 2016, Raj 2014, Lai and Cavanagh 1997, Mizomoto and Chowell 2020,-Siordia 2020, Jiang et al. 2020). They were connected with Huanan sea food market of Wuhan, which sells not only sea food but also live animals, including poultry and wildlife (Mackenzie and Smith 2020, Gralinski and Minachery 2020, Zhu et al. 2020). Bronchoalveolar-lavage fluids were collected from patients (Gralinski and Minachery 2020, Zhu et al. 2020). From this fluid nucleic acids were extracted and polymerase chain reaction (PCR) performed with nucleic acid of an uninfected person as a negative control (Gralinski and Minachery 2020, Zhu et al. 2020, Yip et al. 2020, Chan et al. 2020, To et al. 2020). Followed by RT PCR, gene sequencing scientist concluded emergence of a novel coronavirus (2019-nCoV, also known as SARS-CoV-2) (Gralinski and Minachery 2020, Zhu et al. 2020, Yip et al. 2020, Chan et al. 2020). On January 30, 2020 the World Health Organization (WHO) declared the outbreak as a "Public health emergency of international concern" and subsequently on March 11, a global pandemic was declared by the name of COVID-19 (Coronavirus Infectious Disease 2019) (Guo et al. 2020,17). From the day SARS-CoV-2 was first encountered to late November 2020 the infection has been spreading in a humongous manner. More than 60,000,000 cases and more than 1,4000,000 deaths have been recorded worldwide till now *(Figure 1)*.

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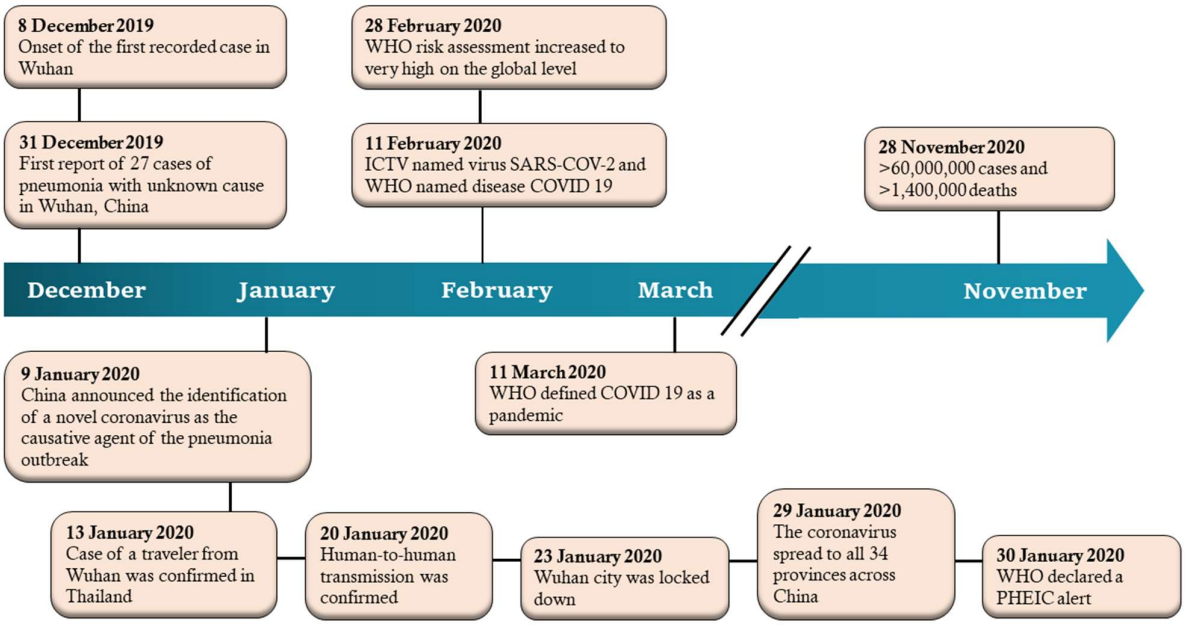

Figure 1: Natural history and epidemiological timeline of COVID-19 pandemic from 8 December,2019 to 28 November,2020. [This image was created using microsoft powerpoint application]

Another dangerous aspect of this virus is rapid and severe progression of clinical manifestations of individuals with underlying health conditions or comorbidities often leads to multiorgan failure, and even death (Mackenzie and, Zhu et al. 2020, Sanyaolu et al. 2020, Guo et al. 2020, Chen et al. 2020, Mizumoto and Chowell 2020, Siordia 2020, Jiag et al. 2020).

2. General mechanism of SARS-CoV-2 infection

The pleomorphic SARS-CoV-2 is roughly spherical in shape, with crown-like projections on the surface which are referred to as S glycoproteins (Boopathi et al. 2020). It has a positive single stranded RNA genome, roughly 30 kb in length, and shares about 88% similarity with SARS-CoV and about 67% similarity with MERS-CoV genomes (Andersen et al. 2020). It is, however, most closely related to Bat coronavirus RaTG13 (sequence similarity almost 96%), suggesting the virus first originated in bats and then passed on to humans after mutating in an intermediate host, moist likely pangolins (Andersen et al. 2020, Xiaolu et al. 2020, Wei et al. 2020, Lam et al. 2020). The SARS-CoV-2 reference genome (NC_045512.2) consists of two polyproteins ORF1a, ORF1ab (the largest open reading frame in the genome), 4 structural proteins Spike (S), Envelope (E), Membrane (M) and Nucleocapsid (N). It also contains 6 accessory proteins, ORF3a, ORF6, ORF7a, ORF7b, ORF8 and ORF10. The Spike protein (S) is a trimeric glycoprotein required for viral attachment to host cells and entry, E and M proteins are necessary for viral assembly, organization and host-viral interactions, whereas N protein is usually associated with the RNA genome of SARS-CoV-2 (Wu et al. 2020, Yoshimoto 2020, Boopathi et al. 2020).

The life cycle of SARS-CoV-2 starts from its entry into the human respiratory tract, usually through nose and mouth, sometimes eyes. On reaching the lower respiratory tract, the virus attaches to the Angiotensinogen Converting Enzyme 2 (ACE2) receptors expressed on the surfaces of epithelial cells lining the respiratory tract via the Receptor Binding Domain (RBD) of the S protein. This binding is also facilitated by cellular Transmembrane serine protease 2 (TMPRSS2) coreceptor (Bhuiyan et al. 2020). In addition, Furin, a host cell protease cleaves the conserved furin cleavage site between the S1 and S2 domains of the S protein after it's initial attachment to ACE2 receptors, a process critical for membrane fusion and viral entry (Boopathi et al. 2020). After entering the cell via receptor mediated endocytosis, the virus releases its genetic material into the cytoplasm and hijacks the host protein synthesis machinery to translate ORF1a and ORF1ab. This process generates two polyproteins pp1a and pp1ab polyproteins, which are cleaved by 3CL proteases to form 16 non-structural proteins (NSPs) which play important roles in replication and assembly (Bhuiyan et al. 2020). One of these, NSP12 is the RNA dependent RNA Polymerase (RdRP), which transcribes – strands of RNA genome and again uses this – strand as template to synthesize hundreds of + stranded RNA genomes and sub-genomic mRNAs (*Figure 2*) (Yoshimoto 2020, Lai and Cavanagh 1997). The latter are used for synthesizing various structural and accessory proteins which are transported from the cytoplasm to the

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Endoplasmic reticulum Golgi Intermediate Compartment (ERGIC) (Lai and Cavanagh 1997). Simultaneously, the newly synthesized + stranded RNA genomes are targeted to ERGIC and there the virion assembly takes place. After assembly, the newly synthesized virions are transported to the cell membrane by vesicles and leave the cell by exocytosis to infect nearby host cells (Lai and Cavanagh 1997). The increased pressure of viral load in the ER ultimately kills the host cells, causes the immune system of the body to release inflammatory cytokines, accumulation of mucus in the respiratory tract and ultimately death in severe cases (Lai and Cavanagh 1997, Liang et al. 2020, Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneumonia of the Chinese Preventive Medicine Association 2020, Ye et al. 2020, Jean-Louis and Fabio 2020, Onder et al. 2020).

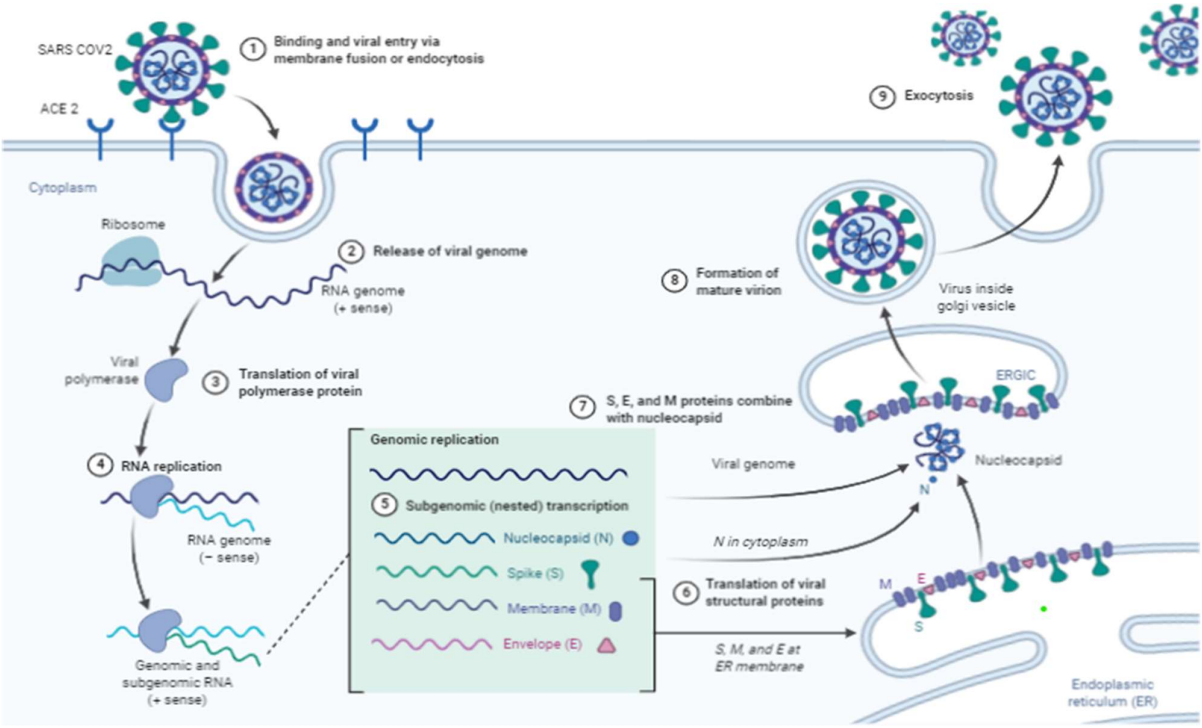

Figure 2: General mechanism of entry into host cell and life cycle of SARS COV 2. Virus particles, after entry into the respiratory tract, enters the lung alveolar cells via receptor mediated endocytosis, transcribes and translates its genomic and sub-genomic RNA to form viral proteins. The new sets of viral genomes and proteins are assembled inside the Endoplasmic Reticulum Golgi Intermediate Compartment (ERGIC) and the virions are released by exocytosis to infect neighbouring cells. [This image image was created using Biorender online illustration tool]

3. Receptor binding comparison between SARS-CoV and SARS-CoV-2

SARS-CoV and SARS-CoV-2 both belong to the genus of beta coronavirus (Bai and Warshel 2020). The first report of SARS-CoV came in 2002 in Guangdong, China. It had a fatality rate of 10% (Tai et al. 2020). SARS-CoV-2 as named by Coronaviridae Study Group was reported from Wuhan, China around December 2019 (Tai et al. 2020). The name corona was suggested because its spike proteins resemble a crown. SARS-CoV and SARS-CoV-2 have a whole genome sequence similarity of 88% while Receptor Binding Domain (RBD) has a similarity of 73%-78% (Bai and Warshel 2020, Rossi et al. 2020).

The most prominent difference between SARS-CoV and SARS-CoV-2 is their differential affinity of RBD towards ACE2. It has been studied that 14 residues of SARS-CoV S-protein RBD interact with human ACE 2 which are Tyr436, Tyr440, Tyr442, Leu443, Leu472, Asn473, Tyr475, Asn479, Gly482, Tyr484, Thr486, Thr487, Gly488 and Tyr491. However, in SARS-CoV-2 only 8 of which are found to be conserved (Tyr449, Tyr453, Asn487, Tyr489, Gly496, Thr500, Gly502, and Tyr505) and substitution has occurred in Leu455, Phe456, Phe486, Gln493, Gln498 and Asn501 (Ali and Vijayan 2020). SARS-CoV-2 has a higher affinity than SARS-CoV for ACE2 receptor (Rossi et al. 2020, Ali and Vijayan 2020). On the contrary it is very astonishing to find that binding affinity of entire S protein of SARS-CoV-2 with ACE2 receptor is comparable or lower than entire S protein and ACE2 interaction in SARS-CoV (Rossi et al. 2020). This anomaly is mainly due to the fact that RBD alternates between "standing up" and "lying down" position (Rossi et al. 2020). Various experiments such as flow cytometry and Cryo EM have proved that spikes alternate between standing up and lying down position respectively (Rossi et al. 2020).

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Entry of both SARS-CoV and SARS-CoV-2 into the host cell involves two proteases Transmembrane protease Serine 2 (TMPRSS2) and Cathepsins (Rossi et al. 2020). However, in addition to both of these CoV-2 contains an additional furin like cleavage site which proves to be very important for their entry into the lung cells (Rossi et al. 2020). Serine protease cleavage site is very much responsible for thrombotic complications as one of the serine proteases is activated by thrombin (Rossi et al. 2020). This may lead to various complications which ultimately results into plasma leakage and alveolar obstruction (Rossi et al. 2020).
The electrostatic interactions between SARS-CoV-2 and ACE2 is 3 kcal/mol higher than that between SARS-CoV and ACE2 (Amin et al. 2020). Maximum Van Der Waals interaction observed of 1.6kcal/ mol between SARS-CoV Y457 and ACE2 T27 whereas 2.1 kcal/mol was observed in between SARS-CoV-2 D491 and ACE2 K353 (Amin et al. 2020).
Researchers proposed that a mutation V404 □ K417 resulted in higher binding interactions which created a salt bridge between K417 and D30 (Amin et al. 2020). Whereas weakening of interaction with E329 is due to R426 □ N439 mutation (Amin et al. 2020). However, literature survey study has come into the conclusion that former mutation has caused strong electrostatic interactions which have suppressed the mutation of the second (Amin et al. 2020).

4. Use of phytochemicals against SARS-CoV-2 and their advantages against conventional drugs

ACE2 is the membrane bound receptor which facilitates the entry site of SARS-CoV-2 in the human host. ACE2 shows the catalytic activity in many tissues such as heart, kidney, intestine apart from lungs (*Figure 3*). The presence of ACE2 in such tissue confirms the risk of heart attack, kidney damage of the person suffering from COVID-19 (Davidson et al. 2020).

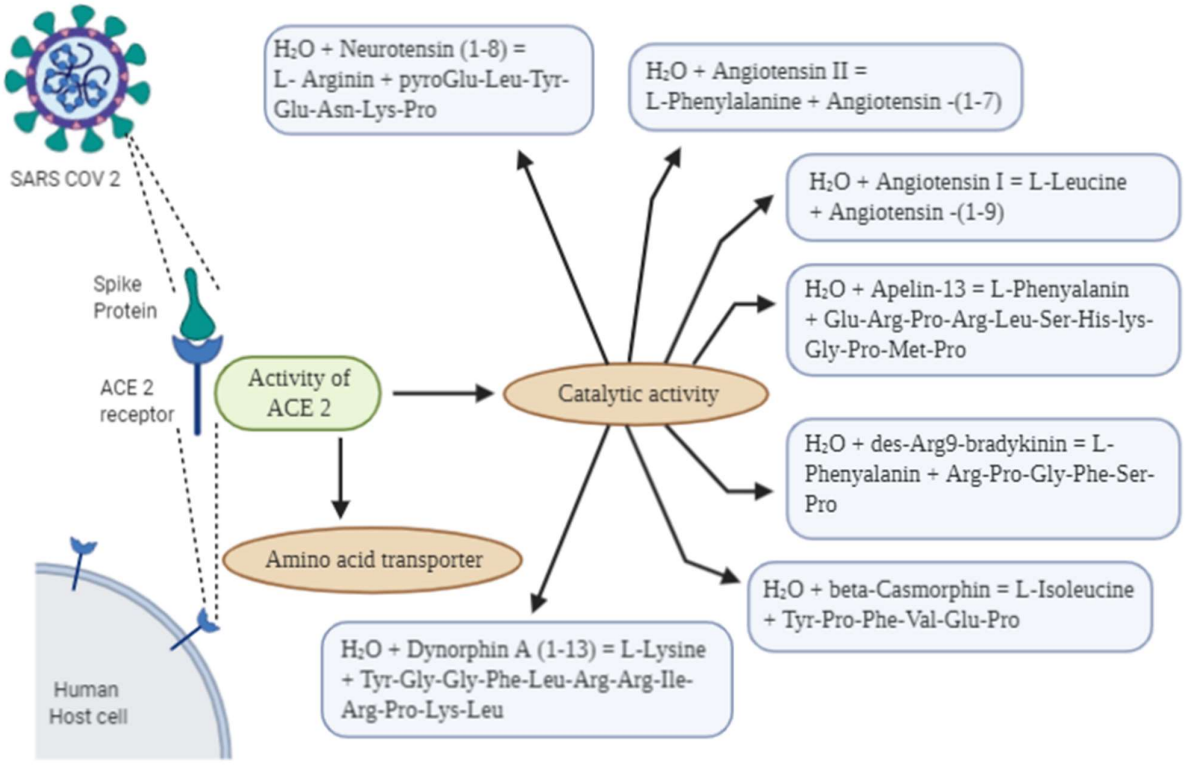

Figure 3: Schematic representation of the activities performed by human ACE2 receptor. ACE2 Receptors play a very important role in human metabolism, both as amino acid transporters and because of their catalytic functions. [This image was created using Biorender online illustration tool]

In SARS-CoV-2 infection, the S-protein receptor binding domain binds with the ACE2 receptor with the help of TMPRSS2 (Transmembrane protease serine 2). This protease is used as priming the S-protein-ACE2 complex formation. The S-protein is composed of few peptide subunits which mediates viral entry via ectodomain, which

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consists of 3 S1 subunit heads responsible for receptor binding and a trimeric S2 subunit facilitates the membrane fusion (Davidson et al. 2020, Ho et al. 2006).

Recently, in the wake of the pandemic, several previously used broad spectrum drugs have been repurposed for treating complications associated with COVID-19 (Cynthia et al. 2020). However, their efficacy remains in question due to their non-specific mode of action against SARS-like coronaviruses, unintended adverse side effects and increased resistance of microbial pathogens against allopathic drugs (Ganjhu et al. 2015). Thus, efforts are being made to revert back to natural products, particularly Plant Secondary Metabolites (PSMs) which used to be extensively used for treating several kinds of human diseases before the advent of modern medicine. PSMs are chemical compounds produced by plants as a natural defense mechanism against herbivores and microbes. They are a source of natural antiviral compounds that could be a viable alternative to conventional drugs, as they are mostly safer and more cost effective (Ganjhu et al. 2015). Other than that, they are available from natural crude extracts of plants and have been shown to specifically target proteins of SARS like coronaviruses resulting in inhibition of entry into host cells, interfering with intermediate metabolic pathways or inhibition of DNA/RNA synthesis (Ganjhu et al. 2015). For example, several phytochemicals interfere with the cell entry mechanisms of SARS-CoV-2 by binding with the receptor binding motifs of S-protein.In this paper we have screened 26 phytochemicals to determine the feasibility as potential inhibitors against the viral protein. Among them some phytochemicals bind with the S-protein and few interact with the ACE2 receptor (*Table 1*)

Table 1: List of 26 plant secondary metabolites showing binding affinities to SARS COV 2 S-protein or human ACE2 receptors. The classes of Plant secondary metabolites, their availability in the market, costs and target sites of action have been listed. Tick marks indicate whether they interact with S-protein or ACE2 or both. Costs have mostly been standardized to US$ per 25 milligrams except that of Nimbin and Withaferin A (Arvindekar et al. 2015, Nivetha et al. 2020, Basu et al. 2020, Varshney et al. 2020, Salman et al. 2020, Gangarapu et al. 2020, Pandit and Latha 2020, Lin et al.2013, Enmozhi et al. 2020, Khalifa et al. 2020, Warowicka et al. 2020)

Type of Metabolite	Name	Availability	Cost Efficiency	Interaction with	
				S-Protein	ACE2
Flavonoid	Hesperidin	Widely available	approx 70$/25mg	Present	Present
	Chrysin	Widely available	approx. 47$/25mg	Present	Present
	Cirsimaritin	Available	approx. 12000$/25 mg	Present	Absent
	Chrysoeriol	_____	_____	Present	Absent
	Quercetin	Widely available	approx. 160$/25 mg	Present	Absent
	Luteolin	Widely available	approx. 274$/25 mg	Present	Absent
	Apigenin	Moderate	152$/25 mg	Present	Absent
	Silybin	Poor availability Synthetic supplement designed, Silipide	approx. 230$/25 mg	Present	Absent
	Catechin		approx. 1080$/25 mg	No report of S-protein binding	Absent

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		_____			
Alkaloid	Magnoflorine	Moderate	420.6$/25 mg	Present	Absent
	Vasicinone	_____	approx. 1600$/25 mg	Present	Absent
	Piperine	Moderate	approx. 142$/25 mg	Present	Present
	Thebaine	_____	_____	Present	Absent
	Berberine	Widely available	approx. 130$/25 mg	Present	Absent
Polyphenols	Emodin	Moderate	approx. 72.5$/25mg	Present	Present
	Curcumin	Widely available	80$/25 mg	Present	Present
Terpenoids	Rosmanol	Moderate	approx. 1500$/25 mg	Inhibits SARS-CoV-2 peptidase	Absent
	Nimbin	Widely available	2mg – 200 USD	Present	Absent
	Andrographolide	Widely available	18$/25 mg	Present	Absent
Stilbenoid	Resveratrol	Widely available	approx. 116$/25mg	Inhibits SARS-CoV-2 peptidase	Absent
Catechin	Epigallocatechin gallate (EGCG)	Widely available	approx. 196$/25 mg	Present	Absent
_____	Chrysophanol	Widely available	approx. 90$/25 mg	Present	Absent
	Seselin	Widely available	_____	Present	Absent
	Tinosponone	_____	_____	Present	Absent
	Withaferin A	Widely available	approx. 580$/25 mg	Present	Absent
	Cordioside	Moderately	1000CH – Rs 106	No report of S-protein Binding	Absent

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5. Molecular docking of phytochemicals against S-Protein and Ace2 receptor

Numerous in- silico studies have already been conducted to predict the binding affinity of various phytochemicals to different SARS-CoV-2 proteins like S-protein, Main Protease, RNA dependent RNA Polymerase (RdRP) and human ACE2 receptor (TY et al. 2006, Benfenati et al. 2010, de Sousa et al. 2015). For this study, primarily the phytochemicals showing interactions with S protein were selected.

Literature search was performed on PUBMED CENTRAL (PMC) and Google Scholar to screen for phytochemicals showing the highest binding affinities to S- protein or S-protein-ACE2 RBD (Ho TY et al. 2006, Benfenati et al. 2010, Chiow et al. 2015, de Sousa et al. 2015, Utomo et al. 2020, Wen et al. 2007, Gangarapu et al. 2020, Subbaiyan et al. 2020, Nivetha et al. 2020, Krishnasamy et al. 2020, Pandit and Latha 2020). Keywords like "SARS COV 2", "PSM", "Phytochemicals" etc were used for the searches and the search set was till November 2020. Additional details such as the sources, availability, costs and modes of action were noted along with their respective binding energies wherever possible. In order to validate and standardize those results, molecular docking was done again using the 26 shortlisted phytochemicals (*Table 2*) and out of them, based on Binding energies, 6 phytochemicals, Hesperidin, Epigallocatechin gallate (EGCG), Rosmanol, Luteolin, Resveratrol and Quercetin were identified as having the highest potentials for use in therapeutics against SARS CoV 2 (*Table 3*).

Table 2: List of all the 26 PSMs selected for this study. The table shows binding energies of the selected PSMs with the viral S-protein as well as human ACE2 receptor, whenever applicable. Docking was performed using AutoDockVina and then visualized and annotated using PyMol version 3.7

Plant Secondary Metabolites (PSMs)	Binding Energy (B.E) with S-protein	Binding Energy (B.E) with ACE 2
Hesperidin	-8.5 kcal/mol	-------
Chrysophanol	-7.5 kcal/mol	-------
Seslin	-7.4 kcal/mol	-------
Emodin	-7.5 kcal/mol	-------
Chrysin	-7.2kcal/mol	-6.9 kcal/mol
Rosmanol	-8.4 kcal/mol	-------
Magnoflorine	-7.1 kcal/mol	-6.6 kcal/mol
Tinosponone	-7.3 kcal/mol	-------
Cirsimaritin	-7.2 kcal/mol	-6.7 kcal/mol
Chrysoerial	-6.9 kcal/mol	-6.9 kcal/mol
Vasicinone	-6.3 kcal/mol	-5.5 kcal/mol
Quercetin	-7.8 kcal/mol	-------
Luteolin	-8.0 kcal/mol	-------
EGCG	-8.5 kcal/mol	-------
Curcumin	-6.8 kcal/mol	-------
Apigenin	-7.4 kcal/mol	-------
Nimbin	-7.7 kcal/mol	-------
Piperine	-6.7 kcal/mol	-------
Thebaine	-7.2 kcal/mol	-6.5 kcal/mol
Berberine	-6.7 kcal/mol	-6.6 kcal/mol
Andrographolide	-6.2 kcal/mol	-------

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Silybin	-8.3 kcal/mol	-------
Withaferin A	-7.6 kcal/mol	-7.2 kcal/mol
Cordioside	-7.6 kcal/mol	-6.9 kcal/mol
Catechin	-7.5 kcal/mol	-------
Reseveratrol	-7.8 kcal/mol	-6.9 kcal/mol

Table 3: PSMs showing highest potential as therapeutics. Hesperidin and EGCG showed highest Binding energies followed by Rosmanol, Luteolin, Resveratrol and Quercetin. Also, the specific amino acids involved in the interactions between PSMs and S-protein/ACE2 receptors have been added in the table. Among them, Luteolin and Quercetin bind to the same pockets within the S-protein-ACE2 binding interface as Hesperidin and EGCG, respectively.

High Potential PSMs	Interaction with the Spike glycoprotein	Amino acids involved in the interaction with the RBD
Hesperidin	Binding Energy = -8.5 kcal/mol	Chain A (S-protein) = His-34, Lys-353 Chain E (ACE2 receptor) = Arg-403, Arg-408 It binds inside the pocket of the S-protein and ACE 2 binding interface. (Fig. – 2.1)
Epigallocatechin gallate (EGCG)	Binding Energy = -8.5 kcal/mol	Chain A (S-protein) = Arg-393, Asn-394, Asp-350. It binds to a pocket inside the RBD interface of the viral S-protein. (Fig. – 2.2)
Rosmanol	Binding Energy = -8.4 kcal/mol	Chain A (S-protein) = Ser-47, Asn-51 Binds to the pocket of the Spike protein and may alter the conformation the protein. (Fig. – 2.3)
Luteolin	Binding energy = -8.0 kcal/mol	Chain A (S-protein) = His-34, Lys-353, Arg-403 Binds to the same pocket as the hesperidin ligand. (Fig. – 2.4)
Resveratrol	Binding Energy = -7.8 kcal/mol	Chain A (S-protein) = Tyr-196, Asn-210, Glu-208 It binds to a pocket inside the RBD interface of the viral S-protein. (Fig. – 2.5)
Quercetin	Binding energy = -7.8 kcal/mol	Chain A (S-protein) = Arg-393, Asn-394 Binds to the same pocket as the EGCG ligand. (Fig. 2.6)

5.1 Protein-ligand Docking

The potential plant secondary metabolites were undergone through the protein-ligand docking process in order to find their affinity towards the receptor binding domain (RBD) of the S-protein interacting with the ACE 2 receptor, present in the host cell.

To perform the protein-ligand docking process, the Crystal structure of SARS-CoV-2 spike receptor-binding domain bound with ACE2 (PDB ID - 6M0J) (Lan et al. 2020) was used as the receptor molecule and the potential plant secondary metabolites (PSMs) were the ligand molecules. The protein preparation and ligand preparation was done using the AutoDockTools (version 1.5.6). The protein molecule contains Chain A of the Spike Glycoprotein domain and Chain E of the ACE 2 receptor domain. At first all the water molecules and heteroatoms were deleted and

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Kollman charges were added evenly throughout the residues of the protein molecule and then the ligand was prepared by adding the Gasteiger charges, further the torsion roots were detected and the number of torsions were checked.
In the next step the grid parameters were set, for performing blind docking process. The grid was set to cover the whole protein in order to get the best binding site for the ligands. Then finally the docking process was done using the AutoDockVina (Trott and Olson 2010) which uses the united-atom scoring function method to find the best fit for the ligand. For the docking process the energy range was taken to be 4 and the exhaustiveness, which is to be the time spent on the search depending upon the number of the atoms, was set to 8 in order to get the best results.
The output files were analyzed using the PyMOL 3.7 application and the results of the docking process are represented (*Table 2*). The most potential PSMs are shown along with their interaction points with the protein interfaces (*Table 3*) [*Figure 4(a,b,c,d,e,f)*]

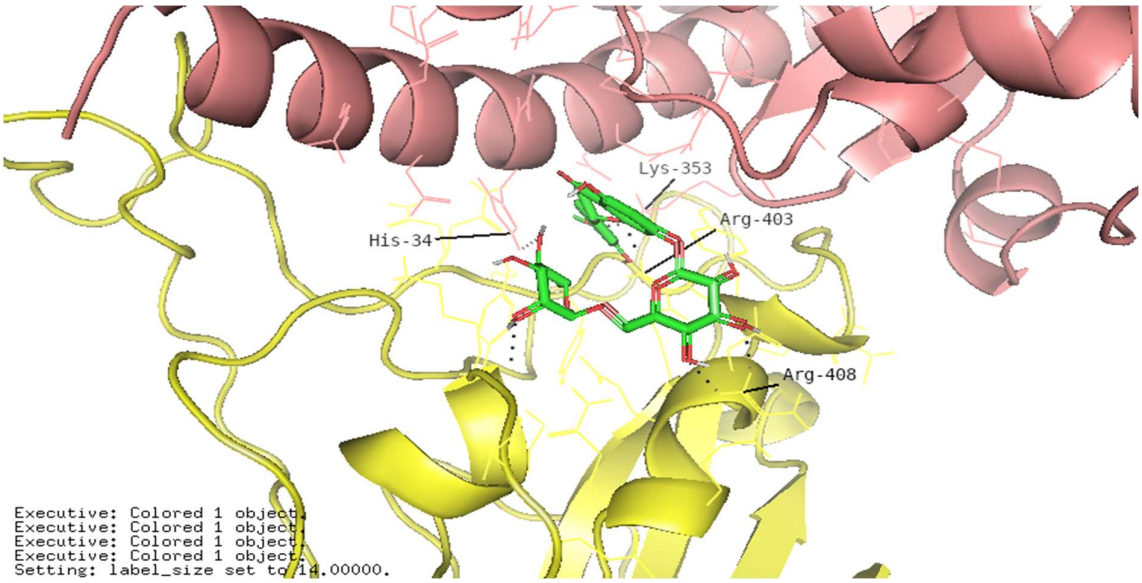

Figure 4(a) Hesperidin binding into the pocket formed between the RBD of S-protein and ACE 2, interacting with His-34, Lys-353 of S-protein and Arg-403, Arg-408 of ACE 2. Thus, proving it to be the most potential phytochemical. [This image was created using PyMOL 3.7 structure rendering tool]

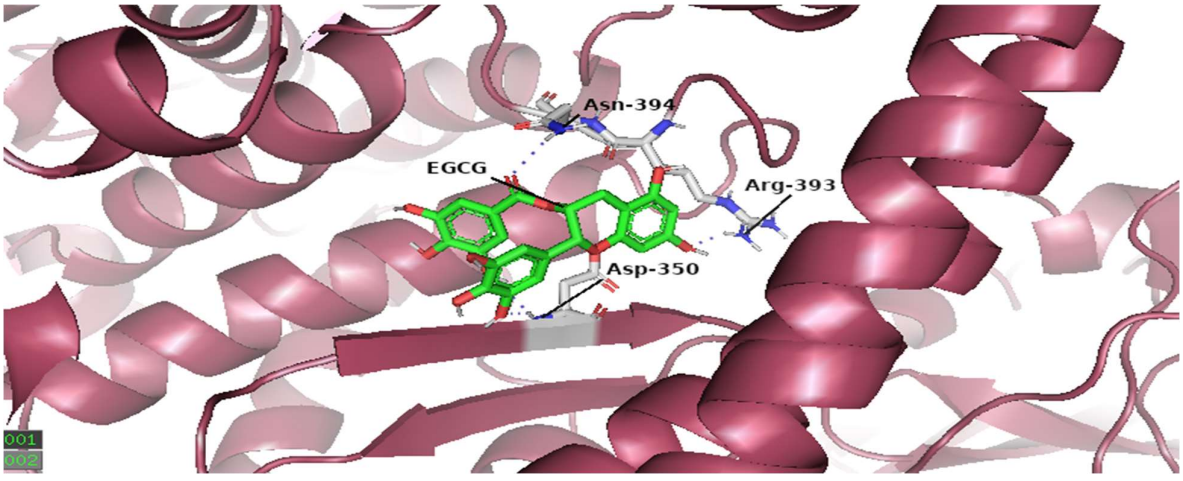

Figure 4(b) EGCG, having the second highest binding energy sits inside a pocket of the RBD interface of the S-protein and interacting with the 3 residues viz. Arg-393, Asn-394, Asp-350. [This image was created using PyMOL 3.7 structure rendering tool]

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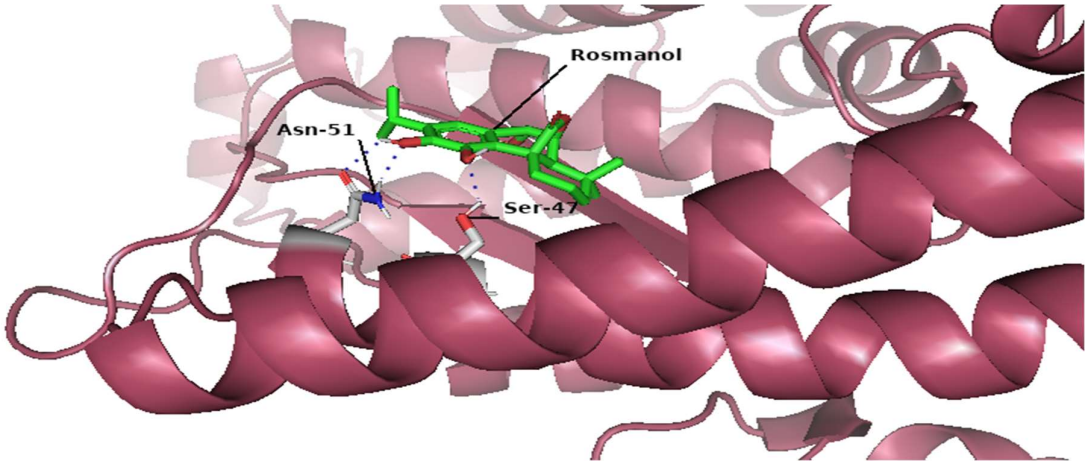

Figure 4(c) Rosmanol binds to a different pocket inside the S-protein and interacts with 2 residues viz. Ser-47, Asn-51. [This image was created using PyMOL 3.7 structure rendering tool]

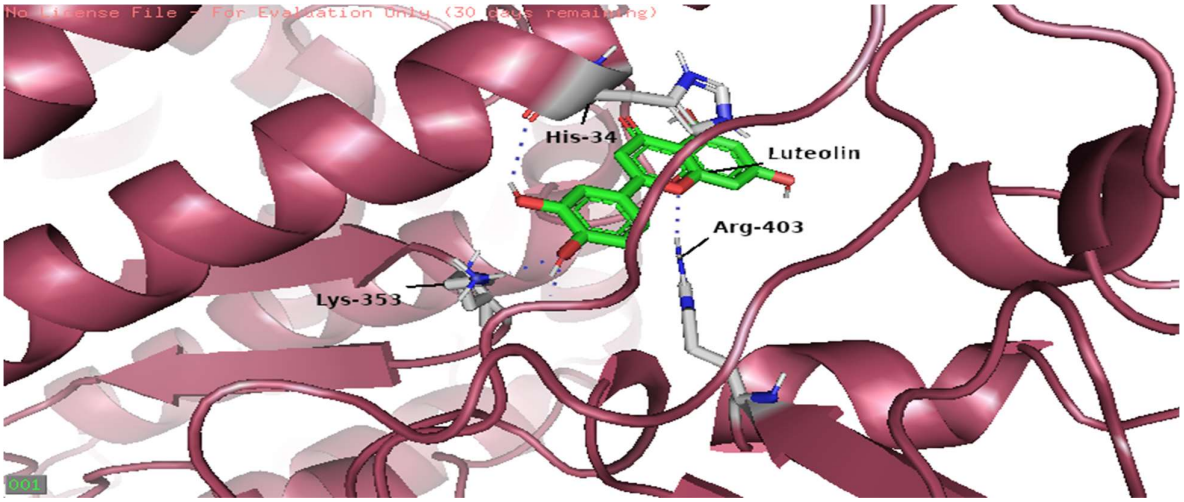

Figure 4(d) Lutelin binds to the same pocket formed between the S-protein and ACE 2 interface and interacts with the same residues as the hesperidin. [This image was created using PyMOL 3.7 structure rendering tool]

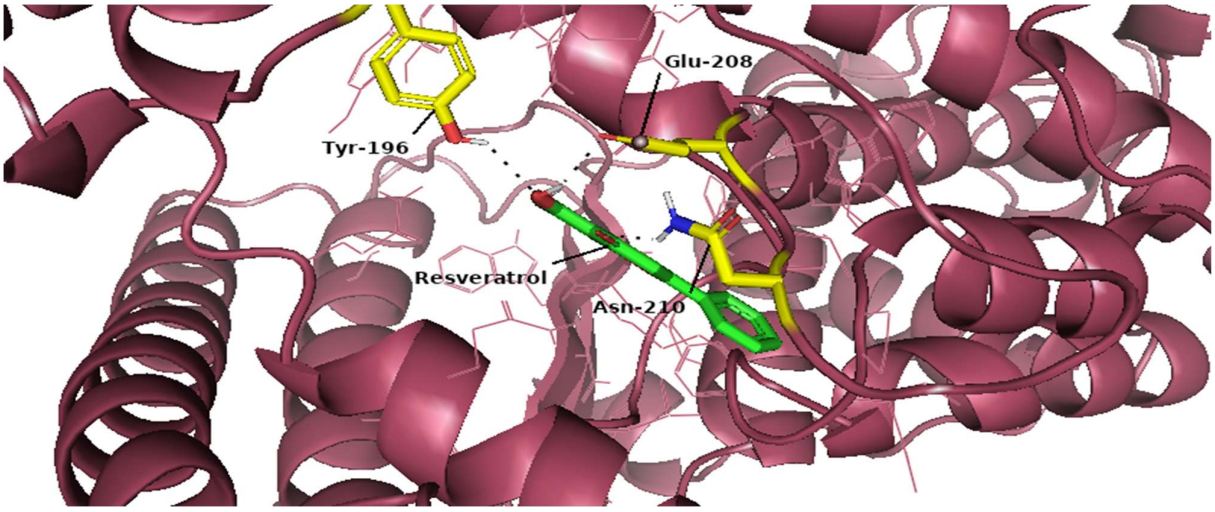

Figure 4(e) Resveratrol binds to a pocket inside the chain A of the S-protein and interacts with Tyr-196, Asn-210, Glu-208. [This image was created using PyMOL 3.7 structure rendering tool]

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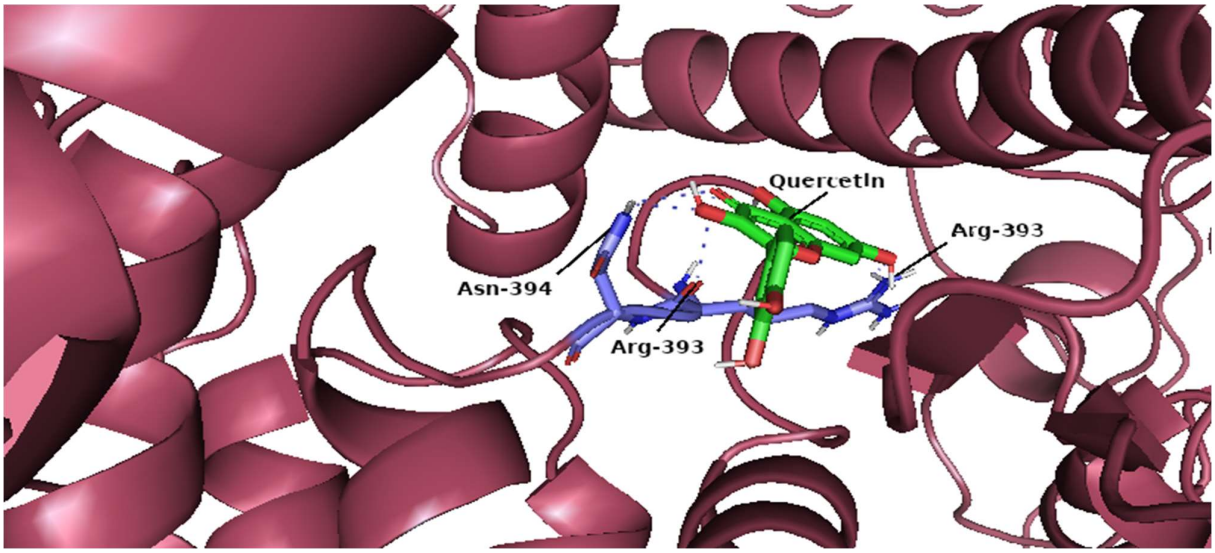

Figure 4(f) Quercetin binds to the same pocket on which the EGCG binds comparatively lower binding energy. [This image was created using PyMOL 3.7 structure rendering tool]

6. Conclusion

As the World Health Organization (WHO) announced the pandemic of COVID 19, efforts are being made to find the cure. With conventional medications either failing or taken in higher concentrations could produce side effects our focus has shifted to develop a phytochemical based treatment which could be used in prevention of infection.
In this study a total of 26 phytochemicals were reviewed and docked among which 6 were taken into consideration namely Hesperidin, Epigallocatechin Gallate (EGCG), Rosmanol, Luteolin, Resveratrol and Quercetin based on their binding interactions with the Receptor Binding Domain of Spike Glycoprotein and their availability and cost effectiveness.
The results of the docking performed via AutoDockVina, stated that Hesperidin, EGCG has the highest binding interactions followed by Rosmanol. Hesperidin binds in such a way that it interacts with Chain A of the S protein and Chain E of ACE 2 and binds inside the pocket of S protein and ACE binding interface. Similar kinds of interactions have been found in Luteolin however some alterations have been found which decreased its binding energy by 0.5kcal/mol.
EGCG and Quercetin both bind into the pocket inside the RBD interface of the viral S protein however an additional Asp350 interaction makes the binding of the former a more suitable one.
Rosmanol binds to a pocket of S protein cause alteration in its structure and Resveratrol binds inside the RBD interface of viral S protein showing binding energy of -7.8 kcal/mol. Literature study showed no evidence of binding of Catechin and Cordioside with viral S protein, however our reports suggest that it binds with the viral S protein.
This paper is an in-silico based study. Further confirmations are required through wet lab and clinical trials to test their efficacy in animal cells and validate these results. Apart from this concern arises on delivery methods, hence our proposal would be to use this as a form of spray which would allow quicker, more effective and faster actions. We hope that our review would contribute to the already existing plethora of information on SARS CoV-2 and use these phytochemicals as a remedy against this dreadful virus which has taken the life of millions.

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