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Research Article

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Computational Identification of Potential Ligands for SARS-CoV-2 Spike Protein: A Docking Study with Natural Compounds and Antiviral Drugs

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Abstract

The ongoing global challenge posed by SARS-CoV-2 highlights the urgent need for novel antiviral strategies, particularly targeting the viral Spike protein crucial for host cell entry. This computational study aimed to identify potential ligands for the SARS-CoV-2 Spike protein using molecular docking simulations. Both conventional and covalent docking approaches were employed to screen a diverse set of compounds, including natural products from various plant matrices (cocoa, Hypericum perforatum, Hedera helix, wormwood, sage) and approved or experimental antiviral drugs, with a specific focus on nitrile-containing compounds for covalent interactions with Cysteine 136. For conventional docking, several natural compounds demonstrated high binding affinities. Notably, epicatechin gallate and procyanidin A2 from cocoa, and compounds from Hypericum perforatum (e.g., hypericin, amentoflavone, biapigenin) showed promising scores and favorable ADME profiles. Ivy compounds like hederacoside and alpha-hederin exhibited high scores and were observed to occupy key amino acids within the Spike protein's ACE2 binding interface. Among the antiviral drugs, Ritonavir yielded some of the best docking scores, particularly with the receptor-bound Spike conformation, while Oolonghomobisflavan-A and -B also displayed excellent scores and are known to inhibit COVID proteases.

In covalent docking targeting Cysteine 136, Bauhinin and Bursatellin emerged as top-scoring natural compounds. Among drugs, the beta-blocker Epanolol and the antidepressant Vilazodone showed significant binding to this exposed cysteine residue. This finding for Vilazodone is particularly notable given existing clinical studies suggesting an association between antidepressant use, including Vilazodone, and reduced risk of severe COVID-19 outcomes. In conclusion, this study identifies several promising natural compounds and existing drugs as potential Spike protein ligands through both conventional and covalent binding mechanisms. These findings warrant further experimental validation, potentially exploring the synergistic effects of natural compound mixtures, and investigating the clinical implications of identified drug-protein interactions.

Legend for Compound Abbreviations

C : Catechin
EC : Epicatechin
ECG : Epicatechin gallate
EGC : Epigallocatechin
GC : Gallocatechin
EGCG : Epigallocatechin gallate
OOBF : Oolonghomobisflavan

Keywords: SARS-CoV-2, Spike Protein, Molecular Docking, Natural Compounds (Phytocompounds), Covalent Docking

1. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the SARS-CoV-2 virus, has been and continues to be an unprecedented global health challenge. Despite the significant contribution of currently available vaccines in mitigating disease severity and spread, a small percentage of the population exhibits a reduced or even absent immune response. Furthermore, the continuous emergence of new viral variants with mutations in the Spike protein constantly underscores the need to develop alternative or complementary therapeutic approaches capable of acting directly on the virus.

The Spike (S) protein of SARS-CoV-2 is a crucial molecular target. It mediates the binding of the virus to host cell receptors (primarily ACE2) and the subsequent fusion of viral and cellular membranes, representing the initial and fundamental step for viral entry. The Spike glycoprotein is a Class I fusion protein that comprises two main regions, known as S1 and S2, which are responsible for these two distinct functions. The S1 region contains the receptor-binding domain (RBD), which is directly responsible for binding to cellular surface receptors. Its essential role makes it a strategic vulnerability for therapeutic intervention, encompassing both vaccine development and targeted antiviral drug design.

In this context, computational studies, particularly virtual screening techniques such as molecular docking, offer an efficient and cost-effective approach for novel drug discovery. These methods enable the rapid exploration of virtual libraries containing thousands of compounds, identifying those with the highest binding potential to a specific protein target. This significantly reduces the time and resources required compared to traditional experimental approaches. The present study aims to identify novel potential ligands for the SARS-CoV-2 Spike protein, focusing on both natural compounds derived from plant matrices like roasted cocoa, Hypericum perforatum (Hypericum), Hedera helix (ivy), and Salvia officinalis (sage), as well as approved or experimental antiviral drugs. To achieve this, an exhaustive computational screening was conducted using molecular docking (both conventional and covalent approaches) on the trimeric structure of the Spike protein (e.g., PDB ID: 6VSB, in its prefusion conformation). The objective was to identify molecules capable of effectively interacting with the binding site or with key residues, such as cysteine 136. This approach seeks to provide promising candidates for future experimental investigations, thereby contributing to the ongoing search for new effective therapeutic strategies against COVID-19.

2. Materials and Methods

This computational study was conducted using the Flare software suite (Cresset, Cambridge, UK), an advanced platform for molecular modeling and virtual screening. Specifically, the Docking module, supporting both conventional and covalent approaches, was employed for molecular anchoring.

2.1. Receptor and Ligand Preparation

The three-dimensional structures of the SARS-CoV-2 Spike protein trimer were obtained from the Protein Data Bank (PDB) and used as models. Two distinct conformations were utilized:

- **PDB ID:** 6VSB (Prefusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up), representing the pre-fusion conformation of the full trimeric Spike protein.
- **PDB ID:** 6LZG (Structure of novel coronavirus spike receptor-binding domain complexed with its receptor ACE2), representing the receptor-binding domain (RBD) of the Spike protein bound to its host receptor, Angiotensin-converting enzyme 2 (ACE2).

Before their use in docking simulations, the structures of both proteins were prepared. This involved removing non-essential water molecules, optimizing the positions of hydrogen atoms, and assigning correct protonation states to amino acid residues, considering physiological pH. For the 6LZG complex, the binding interface between the Spike RBD and ACE2 was considered as the docking site. These two distinct conformations of the Spike protein (or its RBD) expose different residues at their binding interfaces, thus potentially accommodating ligands with varying affinities and interaction profiles.

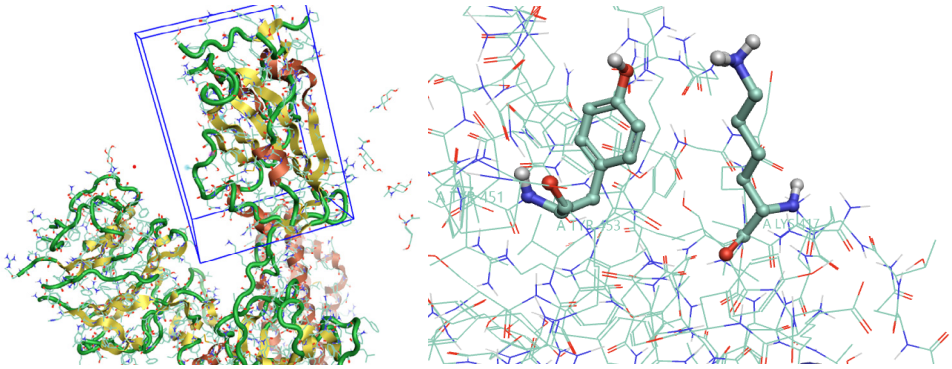

Figure 1: Coronavirus Spike Protein with the S1 Domain, Including Key Residues K417 and Y453 within the Receptor Binding Domain (RBD), Highlighted. [1]

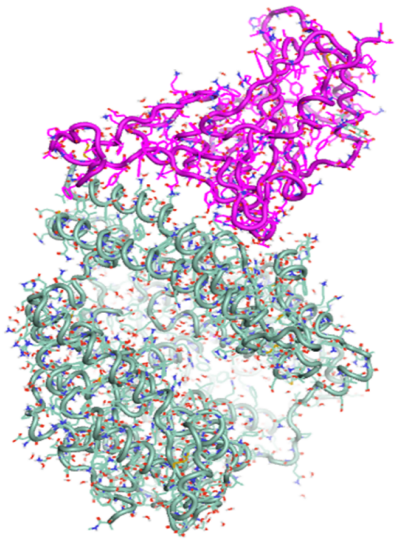

Figure 2: ACE2 Receptor in Green and Spike Protein in Pink.

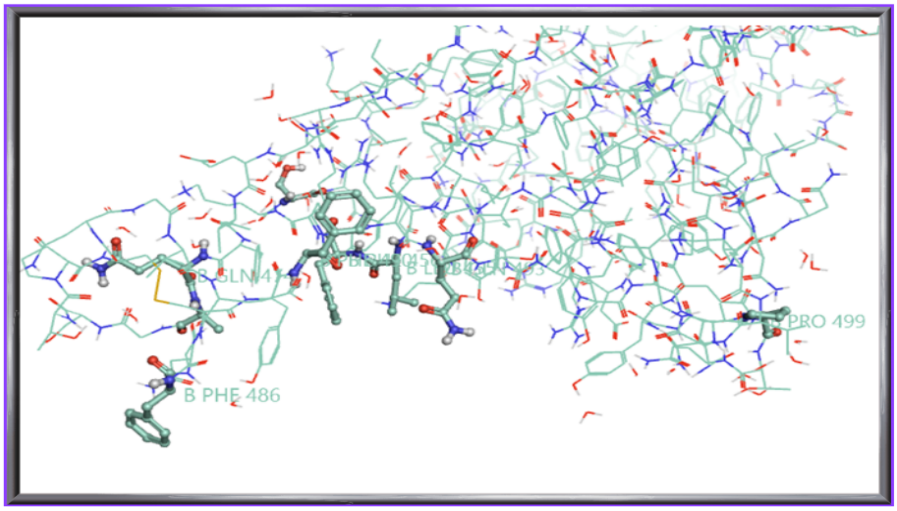

Figure 3: Detailed View of the Spike Protein and Amino Acid Residues Involved in Binding with Angiotensin-Converting Enzyme 2 (ACE2).

Ligands were selected from two main categories:

- **Natural Compounds:** A library of natural compounds was constructed, comprising extracts and active principles identified from plant matrices of interest, specifically roasted cocoa (Theobroma cacao) [Table 1], Hypericum (Hypericum perforatum) [Table 3], ivy (Hedera helix) [Table 2], and sage (Salvia officinalis). Cacao was chosen due to its diverse chemical composition, including catechins, alkaloids, flavonoids, and tannins. Hypericum and ivy were included for their documented antiviral properties, with ivy specifically approved in supplements for respiratory tract affections [2,3]. Compound libraries for each species were generated by downloading compounds in SDF format from PubChem, referencing compounds identified in specific studies [4-6]. Compounds from hops (Humulus lupulus) and wormwood (Artemisia absinthium) were also screened, but they did not yield significant binding scores.

(-)-Epicatechin	Epicatechin gallate	Tyramine_
(-)-Epigallocatechin gallate	Epigallocatechin	Vanillic acid
+catechin	Gallocatechin	
1-Phenylethylamine_	histamine_	
amandamideStructure2D	luteolin	
apigenina	Naringenin_	
Caffeic acid	Oxalic acid	
caffeina	safrolo	
-Catechin gallate_	teofilline	
chinina	tetraidrobetacarbolina	
Chlorogenic acid	Theobromine	
clovamide	tryptamine	

Table 1: Cocoa Compounds (Theobroma Cacao)

2d ederacodide C	hederagenin	Structure2D_helixoside
2D Structure alpha ederin	hidroxycinnamic acid	vitamin c
beta carotene	kaempferol	vitamin E
beta sitosterol	oleanolic acid	
caffeic acid	oleic acid	
campesterol	palmitoleic acid	
chlorogenic acid	panaxydol	
cholesterol	petroselinic acid	
cis vaccenic acid	quercetin	
emetin	rosmarinic acid	
falcarinol	scopolin	
falcarinone	stigmasterol	

Table 2: Ivy Compounds

Adhyperforin	menthol
amentoflavone	miquelianin
Biapigenin	pirrolizzidina
Hyperforin	Procyanidin B2
hyperoside	pseudoipericine
ipericina	quercitrin
isoquercitrin	

Table 3: St. John's Wort Compounds

- **Antiviral and Reference Drugs:** A selection of widely studied, discussed, or utilized antiviral drugs (even those with variable clinical outcomes for COVID-19) was included in the screening. These drugs were curated from various public sources and databases to represent a heterogeneous set of molecules with known antiviral activity or relevance to SARS-CoV-2 research. Examples include viral protease inhibitors (e.g., lopinavir, ritonavir), RNA polymerase inhibitors (e.g., remdesivir, favipiravir, ribavirin), and drugs with presumed antiviral or immunomodulatory activity (e.g., chloroquine, hydroxychloroquine). [Include your table of drugs here or refer to it, e.g., "See Table 4 for the complete list of selected drugs."]. The inclusion of these drugs served to establish a benchmark for binding scores and to compare the affinity of natural compounds with molecules whose biological activity and safety profiles are already partially characterized. Although

the primary mechanism of action for many of these drugs is not directly targeted at the Spike protein, their computational screening against this target allowed for the exploration of potential unexpected interactions and the evaluation of their affinity relative to the natural compounds.

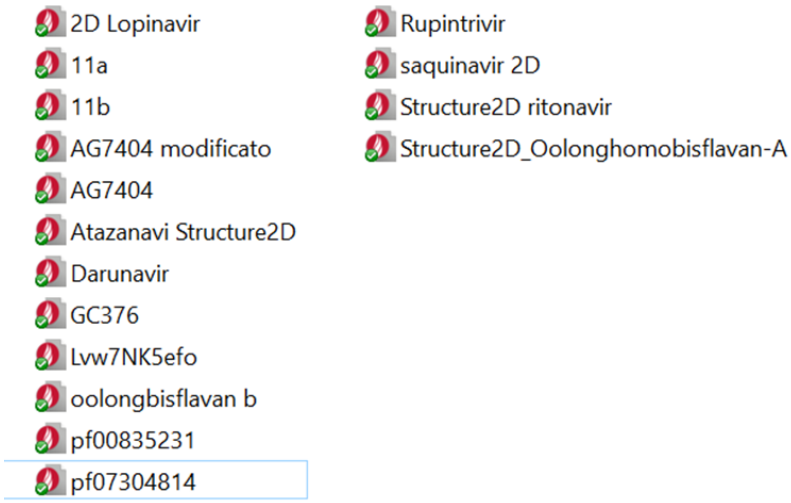

Table 4: Antiviral Drug

2.2. Molecular Docking Methodology

Virtual screening was conducted using two complementary molecular docking approaches:

- **Conventional (Non-Covalent) Docking (Structure-Based Screening):** This methodology was employed to evaluate the non-covalent binding affinity between ligands and the Spike protein. The active site was defined around the binding region of the S1 subunit and its interface with the ACE2 receptor (refer to Figure 1). The docking parameters were set to allow ligand flexibility and limited flexibility for some key residues within the binding site. The docking score was utilized as the primary metric to assess binding affinity, with more negative scores indicating stronger binding. The types of interactions (e.g., hydrogen bonds, hydrophobic interactions, electrostatic interactions) between the ligand and the protein were also analyzed.

Classification score: Optimized to accurately predict the 3D positions of docked ligands.
dG: Optimized to accurately estimate the protein-ligand binding energy, assuming the correct orientation of the ligand.
VS: Optimized for maximum efficiency in virtual screening experiments, discriminating between active and inactive compounds.

- **Covalent Docking:** This approach was employed to identify compounds capable of forming a stable and irreversible (or quasi-irreversible) covalent bond with a specific residue on the Spike protein, a mechanism of action often associated with potent inhibitors. For this study, cysteine 136 was selected as the target for covalent bond formation.

2.2.1. Rationale for Cysteine 136 Selection

The selection of cysteine 136 (Cys136) was based on several considerations:

- **Accessibility and Exposure:** Cys136 is an exposed residue on the surface of the Spike protein, making it accessible for interaction with external ligands, unlike other cysteines that may be involved in internal disulfide bonds within the protein structure and thus less reactive or available. [Content Suggestion]: The general explanation about cysteine's role in protein folding and enzyme catalysis, while true, is quite broad for a Methods section. Keep this section focused specifically on why Cys136 was chosen for your study. You can remove sentences like "I residui cisteinici sono residui chiave nella funzionalità delle proteine in genere..." to maintain conciseness and focus on the experimental design.

- **Thiol Reactivity:** The thiol group (-SH) of cysteines is known for its high nucleophilicity and reactivity, particularly towards electrophiles such as nitrile groups present in some natural and synthetic compounds.

- **Sulfide-Nitrile Reaction:** The conjugation reaction between a thiol group (such as that of cysteine) and a nitrile group is particularly relevant. This reaction proceeds via the initial formation of a thioimidate adduct which, in the presence of an adjacent amine (such as from the protein backbone or a nearby residue), can cyclize into a stable, and in some cases irreversible, thiazoline ring (e.g., through a Michael-type reaction or cycloaddition). This reaction is well-documented in the literature for its selectivity, efficiency, and often its ability to proceed at ambient temperature [7]. This reactivity has also been utilized in analytical recognition assays for the formation of stable covalent bonds.

Scheme 1: Reaction between Nitrile-Containing Compounds and Cysteine Via Cycloaddition. Adapted from Berteotti et al., 2014 [7].

Potential Inactivation Mechanism: Covalent binding to a crucial residue of the Spike protein could lead to its stable functional inactivation, thereby preventing virus-host interaction.

The covalent docking process simulated the formation of the bond between reactive ligands (e.g., those containing nitrile groups or other electrophilic moieties) and the thiol group of Cys136, evaluating the binding energy and stereochemical plausibility.

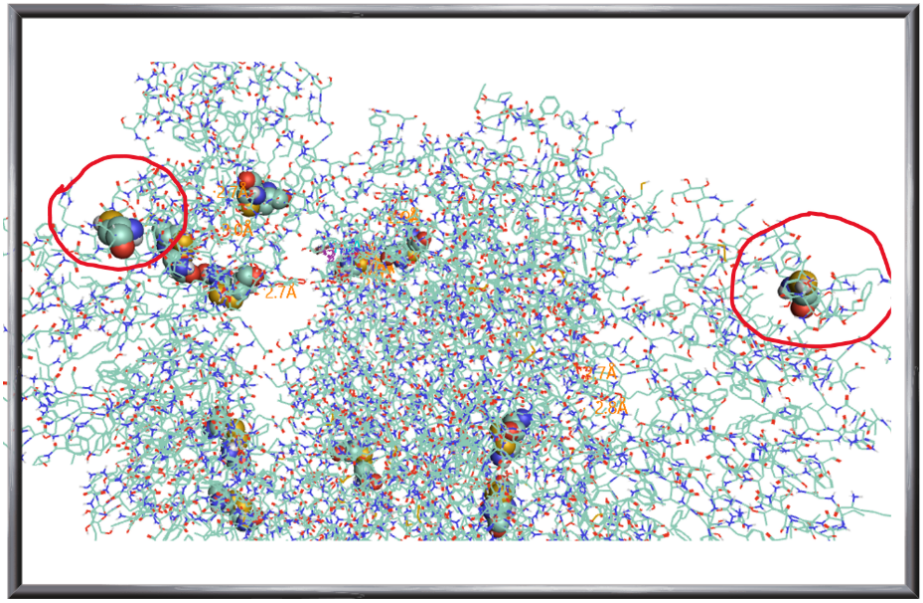

Figure 4: Cysteine Residues of the Spike Protein: Unbound (Circled in Red) and those Involved in Disulfide Bonds (Represented as Spheres)

2.3. Results Analysis and Selection Criteria

Compounds were classified based on their docking scores (where more negative scores indicate a higher binding affinity) and the quality of the interactions established with key protein residues. During the molecular docking process, for each ligand tested, multiple possible conformations within the receptor binding pocket were generated and evaluated. The software calculates an affinity score for each generated pose (binding pose). Only the conformation presenting the most favorable binding score (i.e., the lowest, or most negative, depending on the metric used by the software to indicate stronger affinity) was considered the 'optimal' or 'best' pose and used for subsequent results analysis. Visual analyses of the binding poses were performed to confirm the plausibility of the interactions and to identify potential interactions with residues critical for the Spike protein's function. Only compounds with the best scores and significant interactions with the protein were selected for in-depth analysis and discussion. The sum of scores (rank score, delta G, virtual screening score) was considered to evaluate which molecules best fit the protein.

3. Results

3.1. Docking of Natural Compounds on the Spike Protein

Docking simulations were performed for compounds identified in cocoa (Table 1), ivy (Table 2), and Hypericum (Table 3). The results are illustrated in Figure 5. Epicatechin gallate and procyanidin A2 achieved the highest scores based on the sum of three partial scores (rank score, delta G, and VS score). Compounds from wormwood (Artemisia absinthium) and hops (Humulus lupulus) were also screened but did not yield significant binding scores.

As observed in Figure 7, two compounds from ivy, hederin and hederacoside, being voluminous compounds, appear to cover the entire involved surface, indicating favorable pharmacodynamics. However, due to their large molecular weights (472 Da and 1205 Da, respectively), they are predicted to have unfavorable pharmacokinetics (absorption, distribution, metabolism, excretion,

i.e., ADME profile), despite some antiviral drugs also being large molecules (e.g., ritonavir, 720 Da).

Some compounds from Hypericum (Figure 8) exhibited good docking scores and showed a favorable ADME profile (data not shown). Sagecoumarin from sage also presented a promising score. Docking simulations performed on the pre-fusion Spike protein and the ACE2-bound Spike protein yielded substantially similar binding score values.

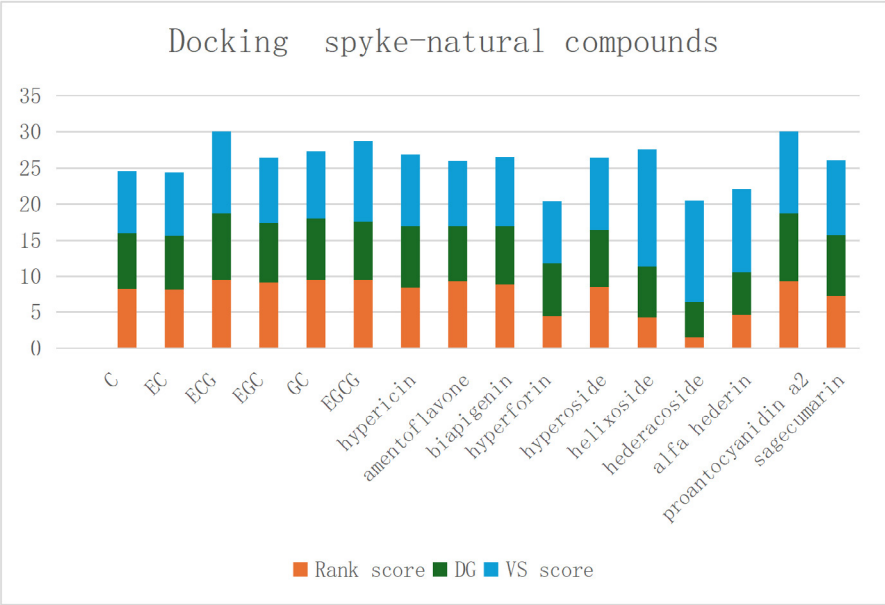

Figure 5: Top Conventional Docking Scores for Natural Compounds from Cocoa, Hypericum, Ivy, and Sage on the Spike Protein. For Abbreviations of Catechin Compounds, Please Refer to the Legend.

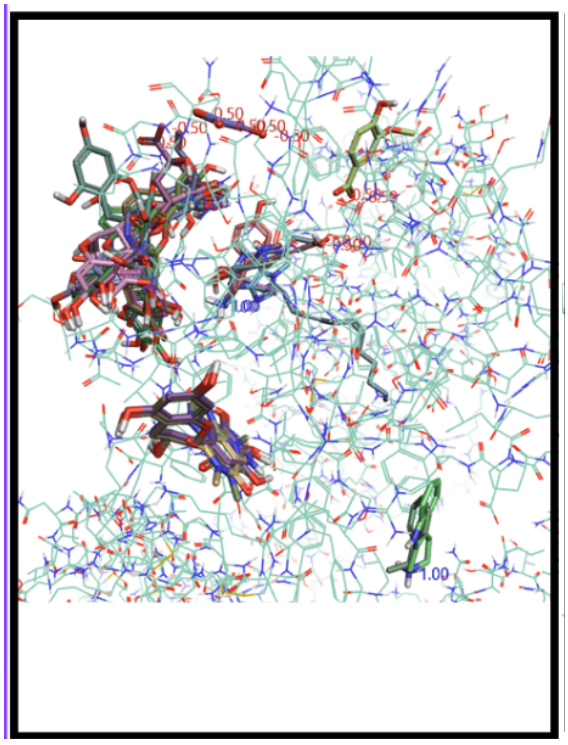

Figure 6: Cocoa Compounds Bound Simultaneously to the C-Terminal Domain (CTD) of the Spike Protein

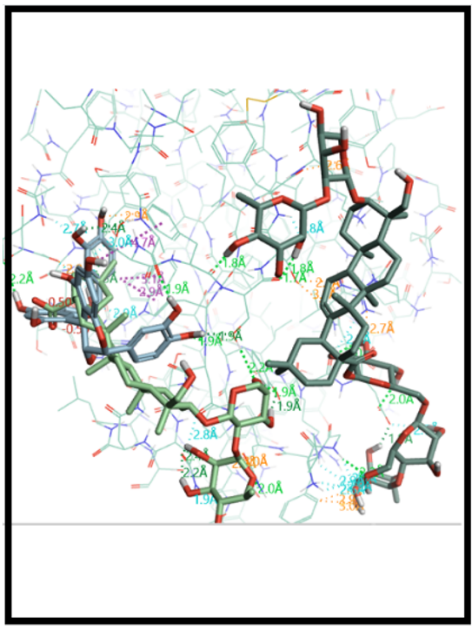

Figure 7: Alpha Ederin (Light Green) and Hederacoside (Dark Green) Simultaneously Bound to the CTD of the Spyke Protein

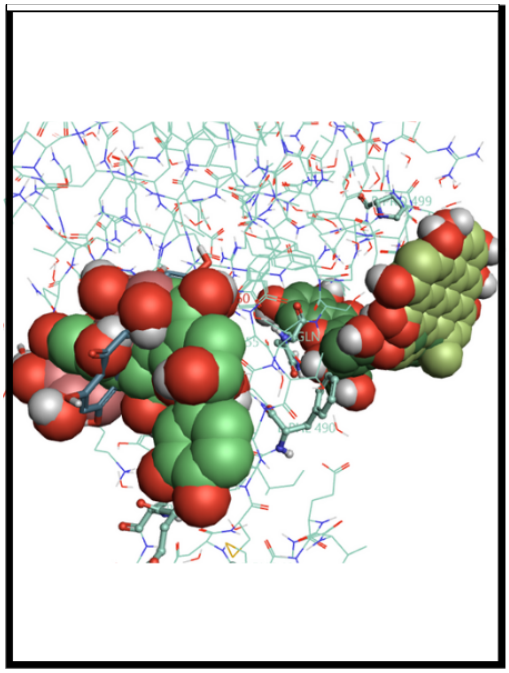

Figure 8: Top-Scoring St. John's Wort Compounds (Hypericin, Amentoflavone and Biapigenin) Depicted as Spheres

3.2. Docking of Antiviral Compounds on Spike Protein

Antiviral compounds from various sources and with diverse mechanisms were tested, given that the Spike protein does not have small-molecule drugs specifically known to target it.

Oolonghomobisflavan (a dimer of epigallocatechin), which exhibits antiviral activity, achieved the best docking scores among these compounds [8]. It is a highly polar molecule with a Topological Polar Surface Area (TPSA) of 395 Å². For orally bioavailable drugs, a common reference value for TPSA is around 60 Å², suggesting that Oolonghomobisflavan is unlikely to readily cross biological membranes and therefore has an unfavorable pharmacokinetic profile for systemic absorption. Ritonavir was the antiviral drug that yielded the best docking scores. While Ritonavir's primary role in COVID-19 treatment (e.g., in combination with Nirmatrelvir) is as a pharmacokinetic booster that reduces hospitalizations and prevents long-term COVID-19, its high docking score in this study suggests a potential interaction with the Spike protein [9].

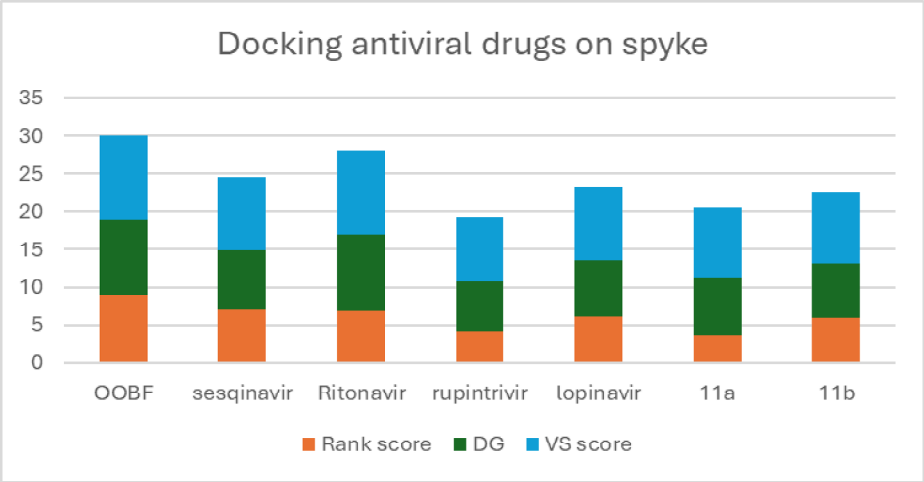

Figure 9: Docking Scores of Antiviral Drugs on Spike Protein

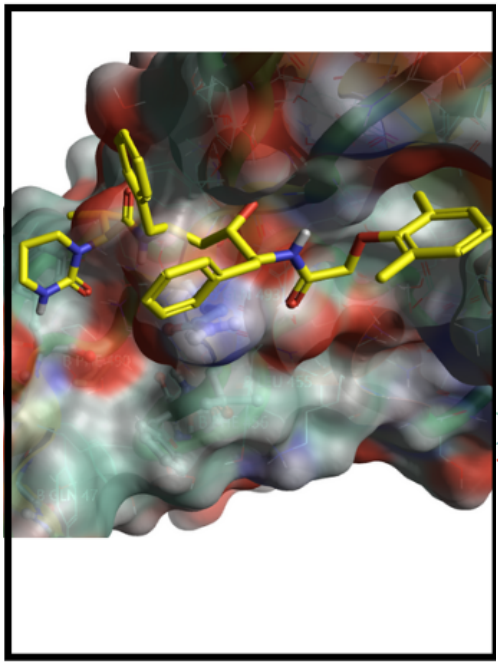

Figure 10: Lopinavir Bound to the Spike Protein Depicted as a Surface (Red Areas with Positive Polarity, Blue Areas with Negative Polarity, Grey Apolar).

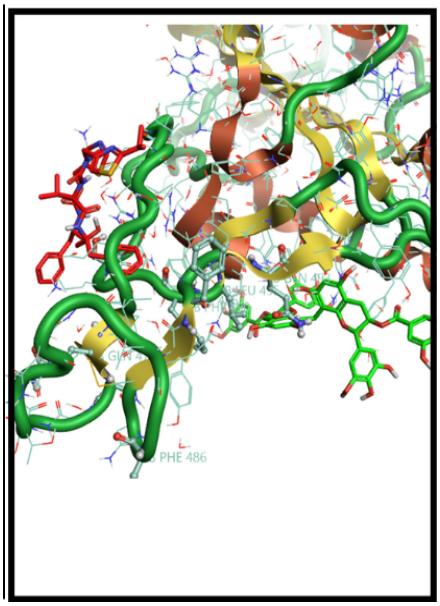

Figure 11: Ritonavir (in Red) and Oolonghomobisflavan (in Light Green) Bound to the Protein Spyke Depicted with Ribbons

3.3. Covalent Docking on Spike Protein

Covalent docking simulations were performed on the Spike protein, targeting not the entire molecule, but specifically cysteine 136, as it is the only cysteine residue not involved in a disulfide bond and thus most suitable for this type of interaction. Natural compounds containing nitrile groups (Table 5) and approved or experimental drugs containing nitrile (Table 6) were tested [10,11]. The best results were obtained for Epanolol, a beta-blocker, and Vilazodone, an antidepressant, which achieved the highest scores among the drug set (Figure 14). For the natural compounds (Figure 13), Bauhinin and Bursatellin yielded the best scores. Bauhinin is a natural phytochemical found in the Bauhinia genus, characterized by a flavonoid glycoside structure. The bursatellin-oxazinine family is a series of nitrile-containing marine natural products derived from tyrosine, originating from gastropod and bivalve mollusks.

5-methy tio esano solfossido nenitrile	dnacin a1	Mycalisine
5-methylthiopentanenitrile	epitionitrile	Pre-kinamycin
acacipetalin	epurpurins	prunasin
Ambiguinine	halimedin	rhodiocyanoside
Bauhinin	heterodendrin	ricinidine
b-cyanoglutamic acid	Indoleacetonitrile	Saframycin
borrelidin	lithospermoside	sarmentosin
BURSATELLIN	lotaustralin	simmonsin
calyculin Structure2D	malloapeltine	Sutherlandin
cianuro idrossibutene	mandellonitrile	toyocamycin
Coclauril	menisdaurin	valesamine n ooxide
Cyanopuupehenol	multifidin	

Table 5: Natural Nitrile Compounds (Reference 10)

alogliptin	gallopamil	ravuconazole
anastrazole	IDX899 fosdevirine	rilpivirine
Bicalutamide	isavuconazole	RS-8359
BMS-191095	KR-31378	RU-58841
BMS-214662	kw-5092	saxagliptin
bosutinib	L-778123	Strontium ranelate
CC-5079	lanoconazole	tanaproget
CHS-828	lersivirine	terbogrel
cilomilast	letrozole	trilostane
cimetidine	levocabastine	TYB-2285 Acreozast

cromacalim	levosimendan	verapamil
cromakalim	lodoxamide ethyl	vidagliptin
cyamemazine	lodoxamide	vilazodone
cyanoguanidine	luliconazole	Vildagliptin
dapivirine	milrinone	zaleplon
diphenozylate	MIV-150	
donitriptan	neratinib	
EKB-569	nivaldipine	
entacapone	NO-1886 Ibrolipim	
epanolol	NVP-DPP-728	
escitalopram	olprinone	
etravirine	pericyazine	
fadrozole	PF-0998425	
Febuxostat	pinacidil	
finrozole	piritramide	
FYX-051 Topiroxostat	progesterone	

Table 6: Drugs Containing Nitrile Groups Approved and Under Investigation

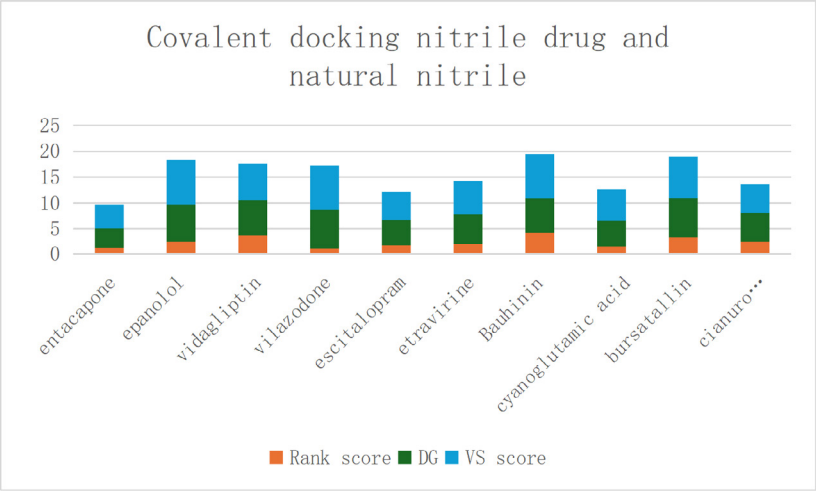

Figure 12: Best Scores of Covalent Docking of Drugs Containing Nitrile Groups and Natural Nitrile Compounds

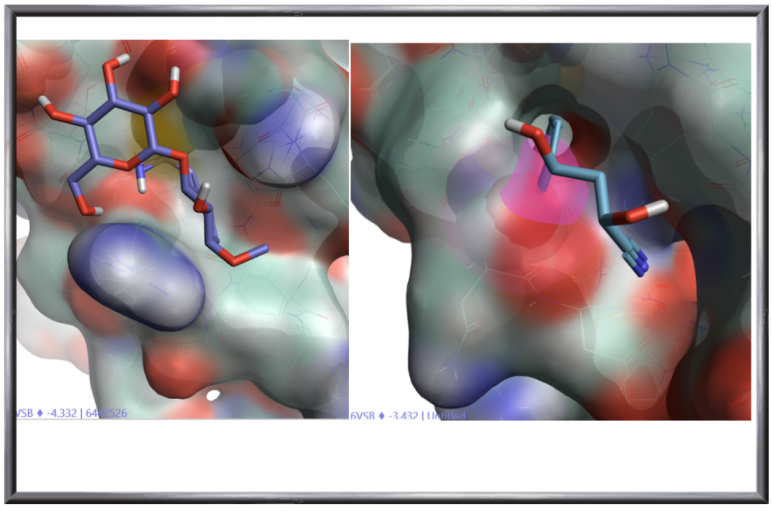

Figure 13: Bahin and Bursatelin Covalently Bound to the Spike Protein

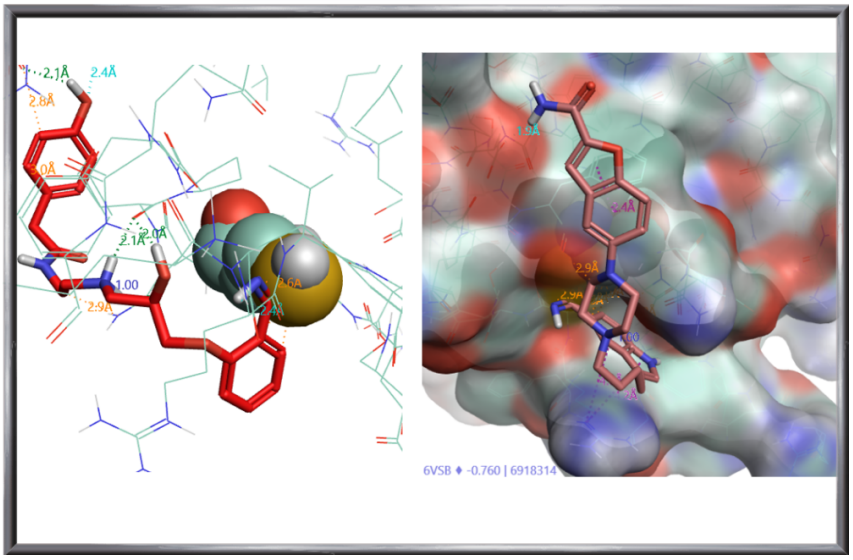

Figure 14: Epanolol and Vilazodone, Covalently Linked to the Spyke Protein (Cysteine 136 in the Left Image is Depicted with Spheres)

4. Discussion

In classical pharmacology, the activity of a single compound on a protein (receptor or otherwise) is typically evaluated. However, when considering the intake of a natural species such as cocoa, ivy, or Hypericum, multiple compounds are simultaneously present. These compounds can bind to different positions on the target protein, depending on their individual affinities. In the context of antiviral compounds, whether natural or synthetic, the goal is to bind to the viral target and, in this case, inhibit the Spike protein. It would be particularly interesting to experimentally test whether mixtures of natural compounds, such as hypericin, amentoflavone, and biapigenin—which demonstrated the best scores for Hypericum perforatum—could inhibit the virus.

Upon observation of Figures 7 and 8, it is evident that amino acids within the Spike protein that are crucial for binding with the Angiotensin-converting enzyme 2 (ACE2) receptor are occupied by interactions with the natural compounds. This suggests a potential mechanism for interfering with viral entry. Furthermore, existing studies on the use of antiviral drug mixtures have shown more satisfactory results compared to the use of a single molecule, supporting the potential of multi-component approaches [12]. A relevant study on antidepressant use in COVID-19 indicated significant associations between citalopram, escitalopram, venlafaxine, desvenlafaxine, mirtazapine, doxepin, and vilazodone, and a reduced risk of worse COVID-19 outcomes [13]. This clinical observation aligns with our computational findings regarding the docking potential of Vilazodone on the Spike protein.

5. Conclusions

This study performed molecular docking simulations of key compounds found in several plant matrices (roasted cocoa beans, Hypericum, ivy, wormwood, sage), alongside currently used and experimental antiviral drugs. Additionally, a specific analysis was conducted on drugs and natural products containing nitrile groups, which are capable of forming covalent bonds with cysteine residues on proteins.

The results from conventional docking revealed good affinity for the Spike protein with compounds such as:

- Catechins (catechin, epicatechin, epigallocatechin gallate, epicatechin gallate, epigallocatechin, gallocatechin) present in cocoa (Theobroma cacao).
- Procyanidin A2, amentoflavone, biapigenin, hyperoside, and hypericin from St. John's Wort (Hypericum perforatum).
- Ivy (Hedera helix) compounds including hederacoside, alpha-hederin, hederagenin, elixoside, and procyanidin A1. These compounds yielded high scores and demonstrated binding over a large surface area, interacting with multiple amino acids involved in the Spike protein's binding to the ACE2 receptor.

For antiviral drugs, both currently in use and experimental, higher activity was observed when docked to the receptor-bound conformation of the Spike protein, with Ritonavir notably showing strong scores. Oolonghomobisflavan-A and -B also exhibited excellent scores and are reported to inhibit COVID proteases [14]. Regarding covalent docking with nitrile-containing compounds forming bonds with cysteine groups, while these compounds successfully bound covalently to Cysteine 136 (the only exposed cysteine not involved in a disulfide bond within the three homotrimers of the Spike protein), the overall scores were not exceptionally high compared to the best conventional binders. Specifically, Bauhinin and Bursatellin were the top-scoring natural compounds, and Epanolol and Vilazodone were the top-scoring drugs in this covalent approach. Based on these findings, it would be interesting to investigate clinically whether patients undergoing treatment with Vilazodone (an antidepressant drug) exhibited a lower incidence of COVID-19 compared to the general population [15-19].

Protein Visualizations

Protein representations with bound compounds were created using Flare.

Acknowledgements

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Statement on the Use of Artificial Intelligence

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Conflict of Interest Statement

The authors declare no conflict of interest.

Graphs

Graphs were generated using Microsoft Excel (academic license).

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