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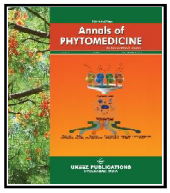

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Molecular docking analysis of ten plant products for the inhibition of spike glycoprotein and prospective use as anti-COVID compounds

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Abstract

The threat of the COVID-19 pandemic has persisted unabated over the past two years. The current response to maintaining public health has been guided by the vaccination of the population. The success of this policy has been mixed COVID coming back in each region in waves driven by new variants. Given that boosted immune response to COVID-19 owing to the vaccine also having an expiration time, it is important to look at alternative options to protect against COVID-19. In this regard, bioactive substances commonly found in food or food additives present a viable option to shield against consequential COVID-19 infection. We investigate 10 bioactive plant products for possible antiviral use against the SARS-CoV-2 virus, which causes COVID-19 infection. We test these compounds by *in silico* docking to the Spike glycoprotein, one of the major determinants of COVID-19 infection. The AutoDock Vina software was used to scan and score the docking sites on a Spike protein ectodomain model. The top twenty hits were saved for each of the ten compounds and then the common and unique docking sites were delineated noting the putative binding affinity in each case. The results show that all ten plant products are high-affinity binders to the Spike protein, the S2 domain being the primary binding site. Very few binding interactions are found on the receptor binding domain, which means that topically used of these molecules such as in nasal spray would not be effective. In the ingestible form, the compounds can bind to the Spike molecule and disable it from driving virus-host fusion, its main function. It can thereby limit the cell-to-cell spread of the virus thus enforcing localization and clearance by the host immune system.

1. Introduction

Ever since COVID-19 cases started to increase steeply in the early year 2020, we have had seven waves of infection worldwide (https://www.worldometers.info/coronavirus/). Each of these waves has been driven by the emergence of a new variant of the SAR-CoV-2 virus (Lippi *et al*., 2022). As such, this is not surprising because RNA viruses are known to have error-prone polymerases (Acevedo *et al*., 2014).These give rise to new mutant viruses at frequent intervals. Some of the mutations may be neutral, while others could be advantageous allowing them to efficiently infect and spread across the host further. The estimates for rates of substitution and evolutionary rate ratio of the SARS-CoV-2 virus have been computed from available genomic data in public repositories (Yi *et al*., 2021). Though, these estimates are not very accurate due to the short evolutionary span of data available, they are approximately 1.5×10^{-3} mutations per nucleotide, per genomic replication for the single-stranded genome (Duffy *et al*., 2008).Therefore, with more virus replication the pool of mutant viruses continues to grow making the threat of the COVID-19 pandemic persist unabated in times to come unless humans develop a natural immunity to it.

The primary public health response for protecting against COVID infection has been through vaccination.There are currently more than 150 vaccines under clinical development or available under different platforms (Abdou *et al*., 2021) as found from the World Health Organization Vaccine Tracker (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines). These are RNA, DNA, protein, inactivated/attenuated virus, and viral vector (or viral vector + antigen-presenting cell) based. Despite wide spread vaccination, some persons are still contracting COVID-19, and such variants that escape to other hosts from a vaccinated individual could evolve with increased transmissibility as seen with B.1.1.7 [the alpha variant] (Graham *et al*., 2021). The enhanced fitness of the virus has indeed led to increased breakthrough infection rates of SARS-CoV-2 variants in vaccinated individuals (Kustin *et al*., 2021), recorded also in real-world studies (McEwen *et al*., 2021). Therefore, the vaccination policy has been mixed in success with recurrent COVID coming back in each region in waves driven by new variants and subsequently spreading worldwide due to airtravel. In practice, the vaccinated individuals present a boosted immune response against COVID-19 for a limited time (Ward *et al*., 2022), it is therefore important to look at alternative options to protect against COVID-19.

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Recently, two antiviral pills have been launched in the market that targets virus replication. These are Paxlovid - nirmatrelvir co-packaged with ritonavir, and another is molnupiravir manufactured by Pfizer and Merck, respectively. These medicines are for emergency use on are to be administered to persons with COVID, who are yet to be admitted to the hospital but are at high risk to be hospitalized. The Pfizer pills are to be prescribed to children above 12 years of age with at least 40 kg body weight, while the pill from Merck is to be administered to persons above 18 with no alternative therapy available. The pills come with side effects, such as dizziness, nausea, and diarrhea, while the Pfizer pill may additionally induce muscle pain, high blood pressure, and lack of taste. Therefore, improved antivirals that are effective in preventing viral infection, replication, and spread are still needed urgently. Previous attempts to repurpose antivirals like favipiravir, remdesivir, and kaletra for COVID-19 treatment have not been fully effective (Qomara *et al*., 2021). The use of drugs like 2-deoxy-D-glucose for adjunct therapy has also not shown encouraging results in randomized trials (Tu *et al*., 2020). Therefore, no drug is still available as a silver bullet in fighting COVID-19.Treatments that use antiviral and also improve human immunity power, therefore, offer the best recourse to defend against coronavirus infection.

The role of traditional medicine in the protection against COVID-19 has received much attention. This can be gauged from the fact that the World Health Organization (WHO) has encouraged the use of traditional medicines wherever it is scientifically evidenced.The current tracker of the clinical trial on herbal or traditional medicine shows 47 instances at the Clinical Tracker site (https://www.clinicaltrials.gov/ct2/results?cond=COVID-19+AND +%22 COVID-19%22) which is about 0.5% of the total number of clinical trials recorded for COVID-19. Understandably, more effort is needed in investigating bioactive compounds to harvest their benefit for human health. Currently, traditional medicine is being widely used as adjuvant therapy to not only boost immunity before infection but also alleviate health complications post-COVID infection. In specific instances, the herbal extract has also been shown as an effective anti-viral agent against COVID (Sarkar *et al*., 2022).

In this paper, we will study ten natural plant active constituents by molecular docking analyses that are known to have anti-inflammatory, antioxidant, immunomodulatory, and antiviral properties. These plants are *Coffea arabica*, *Curcuma longa*, *Glycyrrhiza glabra*, *Zizyphus vulgaris*, *Sisymbrium irio*, *Borago officinalis*, *Althaea officinalis*, *Malva sylvestris*,*Cordia Latifolia*, and *Adhatoda vasica*, and their corresponding active ingredients are Caffeine (Compound Identifier (CID) 2519), Curcumin (CID 969516), Glycyrrhizin (CID 14982), Jujuboside B (CID 24721031), Glucolepidiin (CID 656547), Linoleic acid (CID 5280450), Kaempferol (CID 5280863), Malvone A (CID 135542082), Allantoin (CID 204), Vasicine (CID 72610), respectively. Caffeine is known to have a strong antioxidant property (Hall *et al*., 2015), while curcumin inhibits different molecules contributing to inflammation (Chainani *et al*., 2003). Glycyrrhizin is a pharmacolo-gically active triterpene saponin with antiviral properties demonstrated against SARS-CoV 1 *in vitro* (Luo *et al*., 2020). Jujuboside B is also a saponin with anti-coagulation, and anti-restenosis activity (Seo *et al*., 2013), and has also shown antiasthmatic potential (Ninave *et al*., 2018) and reduces vascular tension [18]. Glucolepidiin, also known as ethyl glucosinolate gets enzymatically hydrolyzed in the body to create an isothiocyanate product that has antimicrobial properties (Romeo *et al*., 2018). Linoleic acid is an essential fatty acid, a precursor to other molecules in the body that is known to promote health, especially heart health although the permissible ingestion level is not clear (Jandacek *et al*., 2017). Kaempferol has pharmacological effects on oxidation, inflammation, and tumor and virus regulation (Devi *et al*., 2015). Not much is known about Malvone A, but *Malva sylvestris* extract having this compound has shown antioxidant, anti-inflammatory,and anti-microbial activity (Mousavi *et al*., 2021).Allantoin is an immunomodulatory compound and has been found to promote wound healing (Araujo *et al*., 2010). Vasicine is known for its antioxidant, anti-inflammatory, and bronchodilatory properties (Gulati *et al*., 2016). We intend to check if the principal compounds in the extracts can also bind to the Spike protein of the SARS-CoV-2 virus. The Spike protein is the major determinant of COVID-19 infection as it is responsible for attachment to the host receptor and penetrating the cell (Pal *et al*., 2021). It is also responsible for the cell-to-cell spread of the virus once it has replicated inside the host. Therefore, inhibiting the Spike protein can block the spread of the virus post-infection. The choice of the molecules is guided by the consideration that it should boost the host response against the virus and also inhibit the virus to elicit an effective therapy.

2. Materials and Methods

2.1 Creating the ligand dataset

The choice of the ligands was driven by our recent review of publications on plant extracts (Farag *et al*., 2021). Herein, we were able to identify ten plant extracts that have anti-inflammatory, antioxidant, immunomodulatory, and antiviral properties. From these plants, we selected one important bioactive molecule for study. The rationale was that these compounds may have a dual action of boosting the host defense response and also inhibiting the virus. The plant extracts and the compounds along with their compound IDs have already been mentioned in the introduction. Among them, the three-dimensional (3D) structures of Caffeine (CID 2519), Curcumin (CID 969516), Glucolepidiin (CID 656547), Linoleic acid (CID 5280450), Kaempferol (CID 5280863), Malvone A (CID 135542082), Allantoin (CID 204), Vasicine (CID 72610) were retrieved from the NCBI PubChem (http://pubchem.ncbi.nlm.nih.gov) compound database in SDF format and optimized in Discovery Studio (Version 4.1). Glycyrrhizin (CID 14982), and Jujuboside B (CID 24721031) had only two-dimensional structures, these were also imported into Discovery Studio software and a conformer was generated using the default parameters.

2.2 Absorption, distribution, metabolism, and excretion studies

The bioavailability of the compounds by absorption post oral ingestion, their metabolism, their potential to cause carcinogenesis, cross the blood-brain barrier, and amenability for clearance are important properties that determine their suitability as a drug. Properties of active compounds were calculated using the toxicity prediction by komputer assisted technology (TOPKAT) module within the Discovery Studio software. It is an established software whose models have been published as reports for the European Commission Joint Research Center (JRC) in QSAR Model Report Format (QMRF).Wespecifically estimated the compounds' properties as per the National Toxicity Program, USA, and as per Federal Drug Administration, USA guidelines. In addition, we estimated the compounds for properties, such as degradability, carcinogenicity, skin, and ocular toxicity.

2.3 The receptor molecule: Spike protein

The 3D crystal structure coordinates of Spike glycoprotein of SARS-CoV-2 were retrieved from the file with protein data bank (PDB) identifier (ID):6VXX. It was downloaded from the Research Collaboratory for Structural Bioinformatics (RCSB) website (https://www.rcsb.org) (Walls *et al*., 2020). The structure was determined by cryoelectron microscopy at 2.80 Å resolution using a single particle reconstruction method. The coordinates cover only the ectodomain (1281 residues) of the protein and are in the closed state. This state corresponds to the conformation of the Spike protein before the virus fusion event.The protein exists in a trimeric state with C_3 symmetry. The coordinates for the following segments are missing from the protein 1-26, 144-164, 828-853. These segments are more than 20 residues and therefore very likely to exist as irregular structures and hence not modeled. Other missing segments were modeled as a loop by the Discovery Studio software. All water molecules were removed from the structure and polar hydrogen atoms were added by Discovery Studio. The Autodock Tools (Xia *et al*., 2020) were used to save the files in the pdbqt format.

2.4 The binding site determination

The ligand binding site was determined using Autodock Vina (Trott *et al*., 2010) in the receptor where the ligand was docked. For this, a three-dimensional map of the grid box was defined (in the conf.txt file) that enclosed the receptor molecule. The three-dimensional map was made as wide as the size of the receptor (Spike glycoprotein) itself so that the ligand was likely to be docked to all parts of the receptor (blind docking).The ligands and receptor molecules saved in the pdbqt format were copied into a folder and the Vina program was run through the command prompt. They were run using three exhaustiveness values of 100, 200, and 300. The top 20 hits with the lowest energy score (-ve ΔG) were saved for each ligandin each run. A ligand was said to bind to a common site if it shared common residues. The residues in the binding site were determined by screening all residues with atoms within a 4.0 Å distance.

3. Results

Table 1: Molecular details of the ligands studied

Ligand	Mol. formula	Mol. Wt. (g/mol)	Log P	Hydrogen bond donor	Hydrogen bond acceptor	Rotatable bonds
Caffeine	$C_8H_{10}N_4O_2$	194.19	-0.07	0	3	0
Curcumin	$C_{21}H_{20}O_6$	368.4	3.29	2	6	8
Glycyrrhizin	$C_{42}H_{62}O_{16}$	822.9	2.8	8	16	7
Jujuboside B	$C_{52}H_{84}O_{21}$	1045.2	0.5	11	21	10
Glucolepidiin	$C_9H_{17}NO_9S_2$	347.4	-1.3	5	11	6
Linoleic acid	$C_{18}H_{32}O_2$	280.4	7.05	1	2	14
Kaempferol	$C_{15}H_{10}O_6$	286.24	2.0	4	6	1
Malvone A	$C_{12}H_{10}O_5$	234.2	1.8	2	5	1
Allantoin	$C_4H_6N_4O_3$	158.12	-3.1	4	3	1
Vasicine	$C_{11}H_{12}N_2O$	188.23	0.4	1	2	0

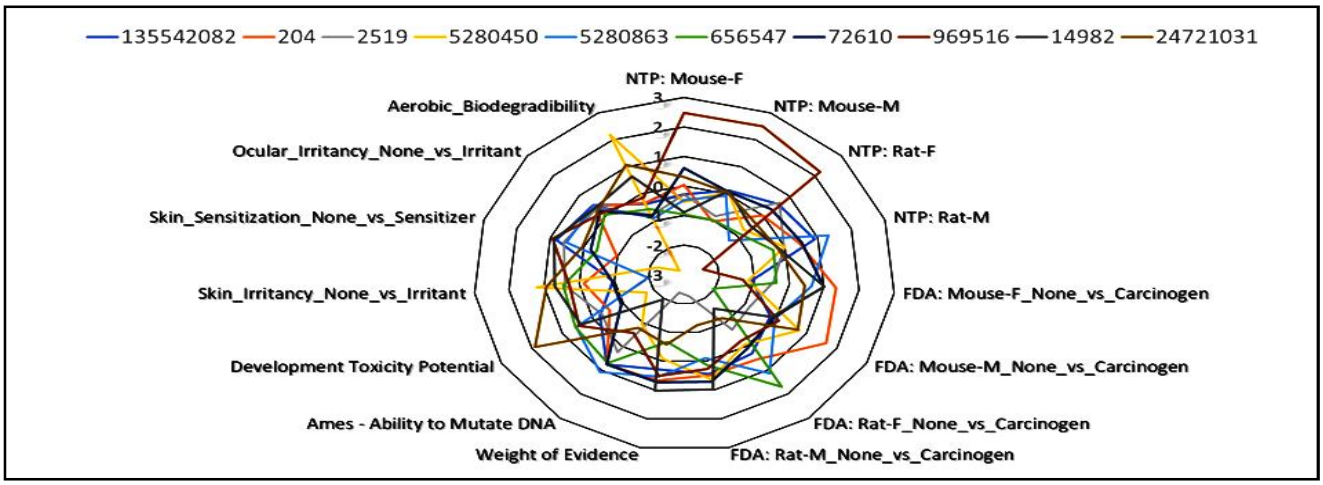

Figure 1: The various toxicity scores of ten compounds assessed by 16 parameters. The scores have been normalized by converting them into a Z-score ((observed-mean)/(standard deviation)) to plot on a single scale. Values > ± 2 are significantly away from the mean score of the compounds. The labels M and F refer to male and female, respectively. NTP refers to the National toxicology program, USA, and FDA is the Federal Drug Administration, USA. Most labels are self-explanatory; the weight of evidence gives a numerical strength of evidence for adverse effects. The ten compound identifiers (CID) are given as numerical values on the top and are mapped as follows: 135542082: Malvone A;204: Allantoin; 2519: Caffeine; 5280450: Linoleic acid; 5280863: Kaempferol; 656547: Glucolepidiin; 72610: Vasicine; 969516: Curcumin;14982: Glycyrrhizin; 24721031: Jujuboside B.

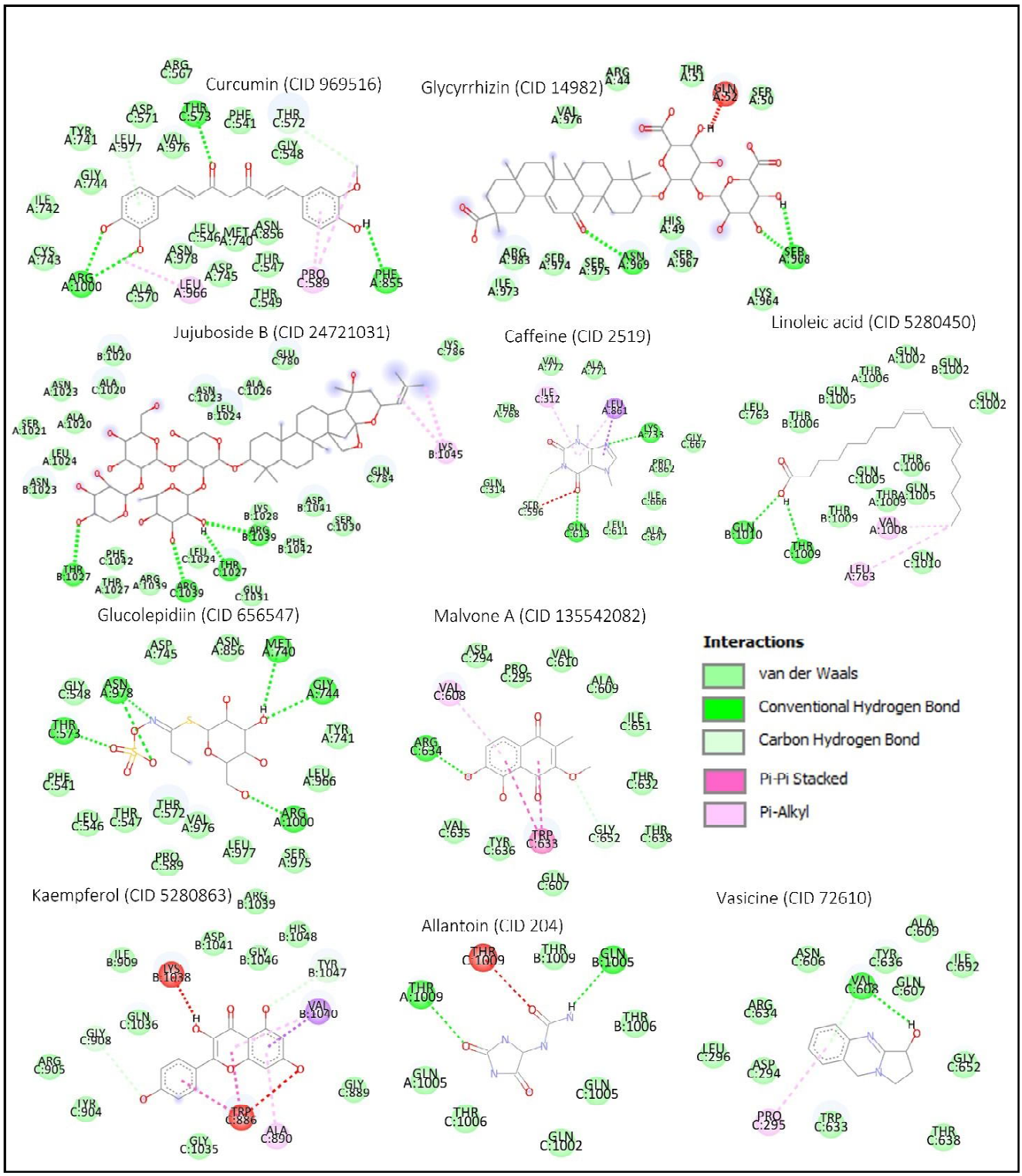

Figure 2: Schematic diagrams showing the non-bonded interactions of the highest affinity docked compounds with the greatest number of poses from replicate experiments. The interactions are shown by dashed lines and the type of interaction is indicated by the color legend. Dashed lines in red colors also indicate hydrogen bonds, where the hydrogens are not optimally placed. Other residues of the binding pocket are also shown from the three subunits (A, B, C) of the Spike protein. Please note that due to the structural symmetry of the Spike trimer, each docking site, except those that are present at the C_3 central axis location will have symmetry-related locations. Diagram from only one docking site isshown.

Table 2: The highest affinity hits of the docked compounds

Compound	CID	Affinity score (kcal/mol)	Replicate hit count
Caffeine	2519	-6.5	20
Curcumin	969516	-8.82	40
Glycyrrhizin	14982	-10.23	13
Jujuboside B	24721031	-11.6	35
Glucolepidiin	656547	-7.45	79
Linoleic acid	5280450	-6.26	21
Kaempferol	5280863	-8.5	25
Malvone A	135542082	-7.6	34
Allantoin	204	-6.4	68
Vasicine	72610	-7.3	63

4. Discussion

4.1 Adsorption, distribution, metabolism, excretion, toxicity studies

Most drugs are rejected in the discovery or development pipeline because their harmful side effects or poor bioavailability outweigh the benefits expected from the intended therapy. We have done an elaborate study of the molecules by checking their molecular properties as well as their toxicity potential. The molecular weight of the molecules (Table 1) suggests that except for Jujuboside B, all other molecules have a molecular weight of less than 500 g/mol consistent with the proposal by Lipinski's rule (Lipinski *et al*., 2004). If, we look at the hydrogen bonding capacity, Glucolepidiin, Glycyrrhizin and Jujuboside B have 5 or more hydrogen bond donors and 10 hydrogen bond acceptors as stipulated in Lipinski's rule. In terms of lipophilicity, only linoleic acid violates the threshold logP value of 5 as per Lipinski's rule. Lipinski's rule is a qualitative guideline and is more appropriate for screening synthetic compounds. Since all the compounds in our list are from natural sources, Lipinski's guidelines are indicative of their likely bioavailability if taken in purified form. However, when ingested a part of a food product, bioavailability is expected to be higher.

The carcinogenicity of the compounds has been assessed using the National Toxicity Program, with the mouse as a reference. Only Curcumin is showing significant carcinogenic potential, but we know that only under certain conditions, this property is manifested (Lopez *et al*., 2008). This is corroborated by a low score for carcinogenicity. Similarly, Malvone A is showing a marginally high carcinogenicity score for FDA score, but low for NTP in mice and rats. Taking both the NTP and FDA scores together, one may argue that the overall carcinogen score for all the compounds is low. Two more scores that appear high are the Development Toxicity Potential for Jujuboside B and high aerobic biodegradability for Linoleic acid. Therefore, administration of the former may be avoided in pregnant women, while special formulations have to be created or storage conditions stipulated for the preservation of Linoleic acid for increased shelf life. The data confirms the safe ingestion of the compounds and more so if it is eaten as a portion of food from which it is sourced.

4.2 Docking of compounds to Spike protein

The affinity of the compounds to the Spike ectodomain trimeric structure was estimated using affinity scores. We checked if, the highest scoring site is present as the top-rank candidate in the replicate runs that were carried out at different exhaustiveness values. If the same geometry or similar geometry of binding existed, that was noted as well by checking the RMSD value of 5Å or less and a common anchoring residue. The presence of multiple docking hits suggests a higher likelihood of binding at the site even if the absolute value of the docking score is low due to the absence of many hydrogen bonds to fix a specific geometry.

The highest affinity was obtained for Jujuboside B (Table 2, Figure 2), which is expected because it has the highest number of hydrogen bond donors and acceptors as well as the molecular weight (Table 1). In contrast, the least affinity value is from Linoleic acid. It does not have the lowest molecular weight but is among compounds with a low number of hydrogen bond donors and acceptors (Table 1, Figure 2). Vasicine has similar hydrogen bonding interaction, but its affinity is considerably higher. The affinity scores for neem compounds were found between -8.4 to -10.5 kcal/mol by a similar docking method in a recent study testing the *in vitro* inhibition of SARS-CoV-2 (Sarkar *et al*., 2022). Another study with 50 phytochemicals docked to the Spike protein from SARS-CoV-2 Delta and Delta-Plus variant showed an affinity as low as -6.5 and -6.1 kcal/mol, respectively, for hydroxychloroquine. Since the same screening function was used for scoring in these studies as ours, it appears likely from the affinity values that all the compounds are highly capable of binding to the Spike protein. Notwithstanding, there exists no experimental evidence to validate the same, although *in vitro* experiments have shown hydroxychloroquine to inhibit the SARS-CoV-2 virus (Solo *et al*., 2021; Ou *et al*., 2021). The high replicate hit count of docking (Table 2) positively indicates the higher chances of interaction, as docking searches are initiated using a seed-based position and there is no guarantee that the same site will get a hit twice unless the site itself is favorably accessible and compatible both in physical and chemical terms. Interestingly, there is a correlation of 0.67 between the Affinity Score and the Replicate Hit Count, excluding the Linoleic acid. This means that despite lower affinity, there are many replicate hits although the docking pose is not strictly aligned geometrically. In thermodynamics parlance, this increases the likelihood of a strong binding in the physiological condition.

The Spike protein undergoes a conformational change that mediates the process of viral entry. The binding of the inhibitor proteins is expected to stabilize the Spike structure and therefore increase the barrier to the conformational transition to inhibit the viral entry process. While affinity is a good measure of the ability of the compound to inhibit, the location of binding is also of importance. If we look at the binding pockets of docked compounds (Figure 2), Jujuboside B, Linoleic acid, and Allantoin dock at a site where they contact all the three subunits of Spike. Linoleic acid and Allantoin dock at the same site but in a different orientation, and all three compounds fill the groove between the central helix of the trimers of the Spike protein. On the other hand, Glycyrrhizin and Malvone A bind solely to one subunit, and all the remaining compounds to two subunits.

Along similar lines, one can also look at the compounds that bind across the S1 (1-685) and the S2 (686-1273) domains. The activation of the Spike protein is driven by the cleavage process that covalently separates the S1 and S2 domains further to which the conformation transition in the S2 domain causes the viral entry. Binding across the S1 and the S2 domain may inhibit the activation of the Spike protein. Looking at the compounds, Curcumin, Glycyrrhizin, Caffeine, and Glucolepidiin have binding sites contributed by S1 and S2 domain residues. Vasicine has only one residue (1692) in its binding site from the S2 domain, but its proximity to the S1/S2 cleavage site may allow it to affect the cleavage process which in turn may affect the Spike activation process. Malvone A is the only compound that binds only to one subunit and the S1 domain. Since the ACE2 receptor binding site of Spike spans residues 387-516, the effect of Malvone A is expected to be indirect only.

Although, several new molecules have been approved recently for the treatment of COVID-19, the repurposing of known molecules remains an important strategy for the discovery and development of new drugs against this infection. Our overall results show that Spike protein can bind all ten plant products with high affinity, the S2 domain being the primary binding site. Compounds binding at the interface of subunits or the S1/S2 domain are expected to be effective in stabilizing the Spike quaternary structure and thereby prevent its function. Also, the S2 domain is comparatively more conserved than the S1 domain, therefore the efficacy of these compounds is likely to be retained against new variants of the virus that is rapidly evolving. Very few binding interactions are found on the receptor binding domain, which means that topically used of these molecules such as in nasal spray would not be effective. In the ingestible form, the compounds can bind to the Spike molecule and disable it from driving virus-host fusion, its main function. It can thereby limit the cell-to-cell spread of the virus thus enforcing localization and clearance by the host immune system. The ADMET studies suggest that bioavailability could be an issue for some compounds if used in their pure form; therefore, they may be best delivered from the plant source in native or a derived form to allow easy passage for systemic circulation post oral ingestion. In conclusion, the study is expected to give promising new insights into the use of natural ligands for the treatment of COVID-19.

5. Conclusion

The work reveals various facets of the compounds that could be useful in addressing the challenges arising out of COVID-19. If, we focus only on antiviral properties, the best compounds can be chosen based on affinity, *i.e.*, Jujuboside B > Glycyrrhizin > Curcumin > Kaempferol >Malvone A >Glucolepidiin>Vasicine > Caffeine >Allantoin >Linoleic acid. If, these compounds are ingested as part of food then bioavailability may not be an issue. However, if given in the purified form, the bioavailability estimated from the logP values as Allantoin >Glucolepidiin> Caffeine > Vasicine >Jujuboside B >Malvone A > Kaempferol > Glycyrrhizin > Curcumin > Linoleic acid would result in effective antiviral activity as (estimated from the combined rank order of solubility and affinity) Jujuboside B >Glucolepidiin>Glycyrrhizin ~ Allantoin >Kaempferol ~Malvone A ~ Vasicine ~ Caffeine >Curcumin >Linoleic acid. If, we also look at the existing knowledge on how these compounds regulate the inflammatory response in the body, curcumin, Kaempferol, Malvone A, and Vasicine are known to have some effect. Therefore, these compounds can synergize the host's antiviral response along with the compound's direct inhibitory action against the virus. More studies are needed, however, to understand the beneficial aspects of this response since a pro-inflammatory response is needed to raise immunity against the virus while an anti-inflammatory response is required to post its clearance. From this study alone, one can propose Jujuboside B, Glucolepidiin, and Glycyrrhizin as the top three candidates suitable for further trials for COVID-19 mitigation. Linoleic acid need not be considered for any further study.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Nagy, A. and Alhatlani, B. (2021). An overview of current COVID-19 vaccine platforms. Computational and Structural Biotechnology Journal, **19**: 2508-2517.

Acevedo, A.; Brodsky, L. andAndino, R. (2014). Mutational and fitness landscapes of an RNA virus revealed through population sequencing. Nature, **505**(7485):686-690.

Araújo, L. U.; Grabe-Guimarães, A.;Mosqueira, V. C.; Carneiro, C. M. and Silva-Barcellos, N. M. (2010). Profile of wound healing process induced by allantoin. Acta Cirurgicabrasileira, **25**(5):460-466.

Chainani-W.u., N. (2003). Safety and anti-inflammatory activity of curcumin: A component of tumeric (*Curcuma longa*). Journal of Alternative and Complementary Medicine (New York, N.Y.), **9**(1): 161-168.

Devi, K. P.; Malar, D. S.;Nabavi, S. F.;Sureda, A.; Xiao, J.;Nabavi, S. M. andDaglia, M. (2015). Kaempferol and inflammation: From chemistry to medicine. Pharmacological Research, **99:**1-10.

Duffy, S.;Shackelton, L. A. and Holmes, E. C. (2008). Rates of evolutionary change in viruses: Patterns and determinants. Nature reviews. Genetics, **9**(4):267-276.

Farag, M.; Pathan, A. andAldoaij, N. (2021). Literature review of 10 plants products for their anti-inflammatory, antioxidant, immuno-modulatory, and antiviral properties Neuro Pharmac Journal, 4: 241-247.

Graham, M. S.; Sudre, C. H.; May, A.; Antonelli, M.; Murray, B.; Varsavsky, T.; Kläser, K.; Canas, L. S.; Molteni, E.; Modat, M.; Drew, D. A.; Nguyen, L. H.; Polidori, L.; Selvachandran, S.; Hu, C.; Capdevila, J.; Hammers, A.; Chan, A. T.; Wolf, J. and Ourselin, S. (2021). COVID-19 genomics UK (COG-UK) consortium, changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: An ecological study. The Lancet. Public Health, 6(5):e335-e345.

Hall, S.; Desbrow, B.; Anoopkumar-Dukie, S.; Davey, A. K.; Arora, D.; McDermott, C.; Schubert, M. M.; Perkins, A. V.; Kiefel, M. J. and Grant, G. D. (2015). A review of the bioactivity of coffee, caffeine and key coffee constituents on inflammatory responses linked to depression. Food Research International (Ottawa, Ont.), **76**(3):626-636.

Jandacek, R. J. (2017). Linoleic acid: A nutritional quandary. Healthcare (Basel, Switzerland), **5**(2):25.

Gulati, K.; Rai, N.; Chaudhary, S. and Ray, A. (2016). Chapter 6 - nutraceuticals in respiratory disorders, Editor(s): Ramesh C. Gupta, Nutraceuticals, Academic Press, pp:75-86, ISBN 9780128021477.

Kustin, T.; Harel, N.; Finkel, U.; Perchik, S.; Harari, S.; Tahor, M.; Caspi, I.; Levy, R.; Leshchinsky, M.; Ken Dror, S.; Bergerzon, G.; Gadban, H.; Gadban, F.; Eliassian, E.; Shimron, O.; Saleh, L.; Ben-Zvi, H.; Keren Taraday, E.; Amichay, D.; Ben-Dor, A. and Stern, A. (2021). Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. Nature Medicine, **27**(8):1379-1384.

Lipinski C. A. (2004). Lead-and drug-like compounds: The rule-of-five revolution. Drug discovery today. Technologies, **1**(4):337-341.

Lippi, G.; Mattiuzzi, C. and Henry, B. M. (2021). Updated picture of SARS-CoV-2 variants and mutations. Diagnosis (Berlin, Germany), **9**(1):11-17.

López-Lázaro M. (2008). Anticancer and carcinogenic properties of curcumin: considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent. Molecular Nutrition and Food Research, 52 Suppl 1:S103-S127.

Luo, P.; Liu, D. and Li, J. (2020). Pharmacological perspective: glycyrrhizin may be an efficacious therapeutic agent for COVID-19. International Journal of Antimicrobial Agents, **55**(6):105-995.

McEwen, A. E.; Cohen, S.; Bryson-Cahn, C.; Liu, C.; Pergam, S. A.; Lynch, J.; Schippers, A.; Strand, K.; Whimbey, E.; Mani, N. S.; Zelikoff, A. J.; Makarewicz, V. A.; Brown, E. R.; Bakhash, S.; Baker, N. R.; Castor, J.; Livingston, R. J.; Huang, M. L.; Jerome, K. R.; Greninger, A. L. and Roychoudhury, P. (2022). Variants of concern are overrepresented among postvaccination breakthrough infections of severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) in Washington State. Clinical infectious diseases : An official publication of the Infectious Diseases Society of America, **74**(6):1089-1092.

Mousavi, S. M.; Hashemi, S. A.; Behbudi, G.; Mazraedoost, S.; Omidifar, N.; Gholami, A.; Chiang, W. H.; Babapoor, A. and Pynadathu Rumjit, N. (2021). A review on health benefits of *Malva sylvestris* L. nutritional compounds for metabolites, antioxidants, and anti-Inflammatory, anticancer, and antimicrobial applications. Evidence-Based Complementary and Alternative Medicine:eCAM, 2021, 5548404.

Ninave, P. B. and Patil, S. D. (2019). Antiasthmatic potential of *Zizyphus jujuba* Mill and Jujuboside B. - Possible role in the treatment of asthma. Respiratory Physiology and Neurobiology, **260**:28-36.

Ou, T.; Mou, H.; Zhang, L.; Ojha, A.; Choe, H. and Farzan, M. (2021). Hydroxychloroquine-mediated inhibition of SARS-CoV-2 entry is attenuated by TMPRSS2. PLoS Pathogens, **17**(1):e1009212.

Pal, D. (2021). Spike protein fusion loop controls SARS-CoV-2 fusogenicity and infectivity. Journal of Structural Biology, **213**(2):107713.

Solo, P. and Doss, M. A. (2021). Potential inhibitors of SARS-CoV-2 (COVID 19) spike protein of the delta and delta plus variant: *In silico* studies of medicinal plants of North-East India. Current Research in Pharmacology and Drug Discovery, **2**:100065.

Qomara, W. F.; Primanissa, D. N.; Amalia, S. H.; Purwadi, F. V. and Zakiyah, N. (2021). Effectiveness of remdesivir, lopinavir/ritonavir, and favipiravir for COVID-19 treatment: A systematic review. International Journal of General Medicine, **14**:8557-8571.

Romeo, L.; Iori, R.; Rollin, P.; Bramanti, P. and Mazzon, E. (2018). Isothiocyanates: An overview of their antimicrobial activity against human infections. Molecules (Basel, Switzerland), **23**(3):624.

Sarkar, L.; Oko, L.; Gupta, S.; Bubak, A. N.; Das, B.; Gupta, P.; Safiriyu, A. A.; Singhal, C.; Neogi, U.; Bloom, D.; Banerjee, A.; Mahalingam, R.; Cohrs, R. J.; Koval, M.; Shindler, K. S.; Pal, D.; Nagel, M. and Sarma, J. D. (2022). *Azadirachta indica* A. Juss bark extract and its Nimbin isomers restrict β-coronaviral infection and replication. Virology, **569**:13-28.

Seo, E. J.; Lee, S. Y.; Kang, S. S. and Jung, Y. S. (2013). *Zizyphus jujuba* and its active component jujuboside B inhibit platelet aggregation. Phytotherapy Research : PTR, **27**(6):829-834.

Trott, O. and Olson, A. J. (2010). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry, **31**(2):455-461.

Tu, Y. F.; Chien, C. S.; Yarmishyn, A. A.; Lin, Y. Y.; Luo, Y. H.; Lin, Y. T.; Lai, W. Y.; Yang, D. M.; Chou, S. J.; Yang, Y. P.; Wang, M. L. and Chiou, S. H. (2020). A review of SARS-CoV-2 and the ongoing clinical trials. International Journal of Molecular Sciences, **21**(7):2657.

Walls, A. C.; Park, Y. J.; Tortorici, M. A.; Wall, A.; McGuire, A. T. and Veesler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell, **181**(2):281-292.

Ward, H.; Whitaker, M.; Flower, B.; Tang, S. N.; Atchison, C.; Darzi, A.; Donnelly, C. A.; Cann, A.; Diggle, P. J.; Ashby, D.; Riley, S.; Barclay; W. S.; Elliott, P. and Cooke, G. S. (2022). Population antibody responses following COVID-19 vaccination in 212,102 individuals. Nature Communications, **13**(1):907.

Xia, S.; Liu, M.; Wang, C.; Xu, W.; Lan, Q.; Feng, S.; Qi, F.; Bao, L.; Du, L.; Liu, S.; Qin, C.; Sun, F.; Shi, Z.; Zhu, Y.; Jiang, S. and Lu, L. (2020). Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. Cell Research, **30**(4):343-355.

Yi, K.; Kim, S. Y.; Bleazard, T.; Kim, T.; Youk, J. and Ju, Y. S. (2021). Mutational spectrum of SARS-CoV-2 during the global pandemic. Experimental and Molecular Medicine, **53**(8):1229-1237.

Zhao, Y.; Zhang, X.; Li, J.; Bian, Y.; Sheng, M.; Liu, B.; Fu, Z.; Zhang, Y. and Yang, B. (2016). Jujuboside B reduces vascular tension by increasing Ca2+ influx and activating endothelial nitric oxide synthase. PloS One, **11**(2):e0149386.

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