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Molecular docking study reveals naringenin and hesperetin from desert truffles as promising potential inhibitors for coronavirus (COVID-19)

Medicinal impact of desert truffles

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Abstract
Aim: In silico methods such as network analysis and screening have been commonly used to investigate the pharmacological functions of typical medicinal plants. The aim of the current research is to use pharmacological and binding affinity methods to test desert truffle compounds as bioactive constituents' inhibitors for COVID-19.
Material and Methods: Forty-four compounds, as well as lopinavir and indinavir, were examined for molecular docking and pharmacokinetics (ADMET) against the 3CLpro and Nsp15 proteins of COVID-19.
Results: Ten compounds out of 44 phytoconstituents (homogentisic acid, catechin hydrate, caffeic acid, syringic acid, epicatechin, trans-cinnamic acid, luteolin, quercetin, naringenin and hesperetin) demonstrated outstanding pharmacokinetics (ADMET) and drug-like properties as HIV inhibitors Lopinavir and Indinavir. Interestingly, the Swiss ADME prediction BOILED-Egg model showed that only three compounds (catechin hydrate, naringenin and hesperetin) were able, like the controls, to bind to the P-glycoprotein substrate
Discussion: The pharmacokinetic prediction analysis has already shown that catechin hydrate, naringenin, and hesperetin have excellent inhibitor-like profiles. Naringenin and hesperetin were able to form strong H-bonds with the main amino acids (residues that may be responsible for destroying protein activity) HIS41 and/or CYS145 of 3CLpro and THR341 of Nsp15, as well as the HIV-inhibitors, which gives hope to be novel coronavirus inhibitors.

Keywords
Deseret truffles; COVID-19; ADMET screening; Naringenin; Hesperetin

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Introduction

In 2019, the novel Covid Disease (COVID-19) arose spontaneously as the causative specialist of Extreme and Acute Respiratory Syndrome (SARS-CoV-2) Researchers in China rapidly sequenced the viral genome and made it unreservedly available to all. Sixty-seven druggable human proteins or hosts have been identified and used as a focal point for 69 current FDA-confirmed drugs, drugs in clinical trials as well as preclinical mixtures. In either case, using the COVID- 19 genomic grouping, researchers have distinguished novel, helpful drugs against COVID -19 [1-3].

Medicinal mushrooms are a rich source of polysaccharides with antitumor, antibacterial and immunostimulating-like medicinal benefits. Recent studies related to hypogeous fungi and the so-called desert truffles have been carried out in addition to the traditional studies of epigenous higher basidiomycetes [4]. A possible drug target named (Nsp15 and Mpro) was recently determined in SARS-CoV-2 [5]. These enzymes have played a significant role to play in the production of translated polyproteins. This protein is 89% indistinguishable from the previous SARS-CoV flare-up protein [4]. Nsp15 obstruction has been reported to reduce viral replication [6].

Various therapeutic protocols, including anti-HIV, anti-influenza, and antimalarial drugs in a single or in combination regimens, have been adopted by the researchers to fight against COVID-19. These drugs, however, cannot respond to the sophisticated coronaviral attacks continuously. Phytochemicals were reported in the literature to have potent antiviral activity, which could be recruited to suppress the high rate of coronavirus replication process [7-10].

In vivo, it has been found that antagonistic reaction to protein or enzyme inhibitors does not promise that the inhibitor is suitable as a potential drug. In drug discovery, the pharmacokinetic profile (absorption, distribution, metabolism, and excretion) of the inhibitor including drug-likeness analyses is important to determine whether the inhibitor can be administered to a biological system. Poor pharmacokinetics properties of candidate inhibitors with highly toxic effects on cells are the major cause to stop the continuation of the clinical phases. The number of atoms (20-70), including heteroatoms, and molar refractivity between 40-130, is an important factor in the success of an inhibitor [11-17].

Accordingly, the present study attempted to screen and evaluate the possible inhibitory effect of desert truffles derived compounds against SARS-CoV-2 (3CLpro and Nsp15), which would in turn provide the possibility to know new compounds against the novel pandemic coronavirus disease (COVID-19).

Material and Methods

This study was conducted at the Pharmacy college in Hafr Al-Batin University, Hafr Al-Batin, Saudi Arabia in December 2020.

Pharmacokinetics prediction by Swiss-ADME

In the current study, we used the Swiss-ADME free web tool to predict the pharmacokinetics and the drug-likeness of the small molecules that are important to know before turning to clinical trials [18]. The 2D structures (SDF format) of the compounds were imported and turned into a SMILES format, then the docking process was run.

Molecular docking simulation

This part was achieved using the AutoDock 4.2 software (Forli W, Halliday S, Belew R, Olson A. AutoDock Version 4.2. Citeseer. 2012) for selected bioactive compounds of desert truffles and two inhibitors against 3CLpro enzyme (PDB ID: 6LU7) and the non-structural endoribonuclease protein Nsp15 (PDB ID: 6VWW). 3Clpro and Nsp15 to predict their potential activity in halting the viral replications [19]. All rotatable bonds of the selected compounds were set randomized as completely flexible during the simulation process. Grid box size was set to 40*40*40 for the active binding sites, coordinates (as x, y, z respectively). The binding site of the 3Clpro was -10.2439, 17.966, 66.5084 and it was -94.65, 19.58, and -28.99 for Nsp15 [20]. A maximum number of 100 runs were chosen for each independent Lamarckian genetic algorithm. The rest of parameters were kept as default. 2D and 3D models of interactions were visualized and analyzed by the Biovia Discovery Studio Visualizer 19, to easily observe hydrogen bonds and the hydrophobic interactions.

Results

In silico ADMET /Pharmacokinetic Predictions

The ADME properties of the bioactive compounds of desert truffles and two FDA-approved HIV inhibitors are presented in Table 1 to illustrate and identify the good pharmacokinetic properties of the promising candidates from the desert truffles. In addition, hepatotoxicity, AMES toxicity, inhibition of hERG, and skin sensitization have been predicted in order to identify the toxic effects of the inhibitors. These criteria have been measured and tested for conformity with their normal ranges. Furthermore, the drug-likeness properties of the bioactive compounds with their bioavailability scores have been investigated in Table 1 to identify which of these molecules have properties close to those of known HIV-inhibitors. Subsequently, the pharmacokinetic properties of the truffle phytoconstituents were analyzed using the BOILED-Egg model, which enables an intuitive assessment of passive gastrointestinal absorption (GIA) and blood brain barrier (BBB) penetration according to the molecular position in the LOG P vs. TPSA (Figure 1).

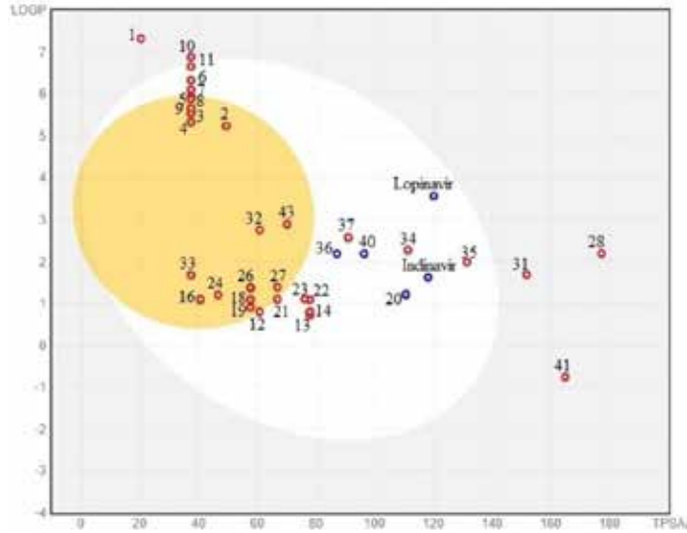

Figure 1. BOILED-Egg Model of the 44-desert truffle phytoconstituents and two FDA approved HIV inhibitors (Lopinavir and indinavir), generated by the Swiss-ADME web tool.

Table 1. Drug-likeness properties of the 44-desert truffle bioactive compounds and two FDA approved HIV inhibitors (Lopinavir and Indinavir), calculated by the SwissADME web tool

Group	S. No.	Compounds	Drug-Likeness							
			M.W g/mol	R. bonds	A.H-bond	D.H-bond	MR	TPSA	LOGP	Bioavailability Score
Desert truffle bioactive compounds	1	Ergosterol	396.65	4	1	1	127	20.23	6.33	0.55
	2	Anandamide	347.53	17	2	2	110	49.33	3.91	0.55
	3	Palmitic acid	256.42	14	2	1	81	37.3	4.19	0.85
	4	Palmitoleic acid	254.41	13	2	1	80	37.3	4.09	0.85
	5	Heptadecanoic acid	270.45	15	2	1	86	37.3	4.44	0.85
	6	Stearic acid	284.48	16	2	1	90	37.3	4.67	0.85
	7	Oleic acid	282.46	15	2	1	90	37.3	4.57	0.85
	8	Linoleic acid	280.45	14	2	1	89	37.3	4.47	0.85
	9	Linolenic acid	278.43	13	2	1	88	37.3	4.38	0.85
	10	cis-11-eicosenoic acid	310.51	17	2	1	99	37.3	5.03	0.85
	11	Cis-11,14-eicosadienoicacid	308.5	16	2	1	99	37.3	4.93	0.85
	12	Pyrogallol	126.11	0	3	3	32	60.69	0.18	0.55
	13	Homogentisic acid	168.15	2	4	3	42	77.76	0.47	0.56
	14	Protocatechuic acid	154.12	1	4	3	37	77.76	0.4	0.56
	15	Gentisic acid	154.12	1	4	3	37	77.76	0.4	0.56
	16	Pyrocatechol	110.11	0	2	2	30	40.46	0.79	0.55
	17	Galanthamine	110.11	0	2	2	30	40.46	0.79	0.55
	18	p-Hydroxy-benzoic acid	138.12	1	3	2	35	57.53	0.99	0.85
	19	Dihydroxybenzaldehyde	138.12	1	3	2	35	57.53	0.18	0.55
	20	Catechin hydrate	290.27	1	6	5	74	110.38	0.24	0.55
	21	Vanillic acid	168.15	2	4	2	41	66.76	0.74	0.85
	22	Caffeic acid	180.16	2	4	3	47	77.76	0.7	0.56
	23	Syringic acid	198.17	3	5	2	48	75.99	0.49	0.56
	24	Vanillin	152.15	2	3	1	40	46.53	0.51	0.55
	25	Epicatechin	290.27	1	6	5	74	110.38	0.24	0.55
	26	p-Coumaric acid	164.16	2	3	2	45	57.53	1.28	0.85
	27	Ferulic acid	194.18	3	4	2	51	66.76	1	0.85
	28	Catechin gallate	442.37	4	10	7	110	177.14	0.05	0.55
	29	Rutin	610.52	6	16	10	141	269.43	-3.89	0.17
	30	Trans-2-hydroxy-cinnamic	164.16	2	3	2	45	57.53	1.28	0.85
	31	Myricetin	318.24	1	8	6	80	151.59	-1.08	0.55
	32	Resveratrol	228.24	2	3	3	67	60.69	2.26	0.55
	33	Trans-Cinnamic acid	148.16	2	2	1	43	37.3	1.9	0.85
	34	Luteolin	286.24	1	6	4	76	111.13	-0.03	0.55
	35	Quercetin	302.24	1	7	5	78	131.36	-0.56	0.55
	36	Naringenin	272.25	1	5	3	71	86.99	0.71	0.55
	37	Genistein	270.24	1	5	3	73	90.9	0.52	0.55
	38	Apigenin	270.24	1	5	3	73	90.9	0.52	0.55
	39	Kaempferol	286.24	1	6	4	76	111.13	-0.03	0.55
	40	Hesperetin	302.28	2	6	3	78	96.22	0.41	0.55
	41	Chlorogenic acid	354.31	5	9	6	83	164.75	-1.05	0.11
	42	Gallic acid	170.12	1	5	4	39	97.99	-0.16	0.56
	43	Chrysin	254.24	1	4	2	71	70.67	1.08	0.55
	44	Rhamnetin	316.26	2	7	4	82	120.36	-0.31	0.55
HIV Inhibitors	1	Lopinavir	628.8	17	5	4	188	120	2.93	0.55
	2	Indinavir	613.79	14	7	4	183	118.03	1.33	0.55

M.W: Molecular weight, R. bonds: Rotatable bonds, A.H-bond: Acceptor hydrogen bond, D.H-bond: Donor hydrogen bond, MR: Molar refractivity, TPSA: Topological polar surface area

Table 2. Binding interaction F.B.E (Kcal/mol) scores and the inhibition constant Ki (Kcal/mol) for the 44-desert truffle phytoconstituents and two FDA approved HIV inhibitors (Lopinavir and Indinavir) with 3CLpro and Nsp15

	S. No.	Compounds	6LU7 (F.B.E)	KI	6VWW (F.B.E)	Ki
Desert truffle bioactive compounds	1	Ergosterol	-4.83	288.34 uM	-7.07	6.57 uM
	2	Anandamide	-3.61	2.28 mM	-4.66	386.44 uM
	3	Palmitic acid	-3.01	6.26 mM	-5.23	146.76 uM
	4	Palmitoleic acid	-3.08	5.50 mM	-5.58	81.06 uM
	5	Heptadecanoic acid	-2.60	12.41 mM	-5.32	125.25 uM
	6	Stearic acid	-2.42	16.94 mM	-5.00	217.95 uM
	7	Oleic acid	-3.16	4.83 mM	-5.40	110.44 uM
	8	Linoleic acid	-3.24	4.20 mM	-5.35	120.67 uM
	9	Linolenic acid	-3.43	3.07 mM	-5.84	52.38 uM
	10	cis-11-eicosenoic acid	-2.65	11.51 mM	-5.38	114.12 uM
	11	cis-11,14-eicosadienoic acid	-2.78	9.12 mM	-5.50	93.02 uM
	12	Pyrogallol	-3.22	4.38 mM	-5.49	94.72 uM
	13	Homogentisic acid	-4.02	1.13 mM	-6.23	27.13 uM
	14	Protocatechuic acid	-3.72	1.88 mM	-4.91	253.67 uM
	15	Gentisic acid	-3.46	2.91 mM	-4.91	252.22 uM
	16	Pyrocatechol	-4.29	712.51 uM	-3.78	1.69 mM
	17	Galanthamine	-4.29	712.77 uM	-3.78	1.69 mM
	18	p-Hydroxybenzoic acid	-3.70	1.94 mM	-4.87	268.14 uM
	19	Dihydroxybenzaldehyde	-4.30	699.20 uM	-4.84	282.47 uM
	20	Catechin hydrate	-7.11	6.95 uM	-8.03	1.92 uM
	21	Vanillic acid	-3.69	1.98 mM	-4.84	281.61 uM
	22	Caffeic acid	-4.11	975.87 uM	-5.86	50.45 uM
	23	Syringic acid	-3.44	2.99 mM	-5.06	195.40 uM
	24	Vanillin	-3.98	1.21 mM	-4.67	374.88 uM
	25	Epicatechin	-5.12	177.11 uM	-6.42	19.69 uM
	26	p-Coumaric acid	-4.22	804.41 uM	-5.99	40.44 uM
	27	Ferulic acid	-4.18	869.30 uM	-5.80	56.21 uM
	28	Catechin gallate	-5.44	103.01 uM	-8.15	1.06 uM
	29	Rutin	-6.78	10.64 uM	-6.84	9.65 uM
	30	trans-2-hydroxycinnamic	-4.48	517.72 uM	-6.81	10.23 uM
	31	Myricetin	-5.79	57.47 uM	-7.62	2.60 uM
	32	Resveratrol	-6.79	10.61 uM	-6.20	28.30 uM
	33	trans-Cinnamic acid	-4.16	895.80 uM	-5.90	47.31 uM
	34	Luteolin	-6.75	11.70 uM	-6.69	12.52 uM
	35	Quercetin	-5.90	47.33 uM	-7.45	3.47 uM
	36	Naringenin	-7.82	2.01 uM	-8.68	433.04 nM
	37	Genistein	-6.05	36.76 uM	-6.33	22.95 uM
	38	Apigenin	-6.71	12.05 uM	-6.92	8.48 uM
	39	Kaempferol	-5.79	56.89 uM	-6.77	10.97 uM
	40	Hesperetin	-7.23	6.02 uM	-8.15	1.06 uM
	41	Chlorogenic acid	-5.61	77.45 uM	-7.45	3.45 uM
	42	Gallic acid	-3.74	1.83 mM	-4.59	432.67 uM
	43	Chrysin	-5.85	51.79 uM	-6.37	21.55 uM
	44	Rhamnetin	-5.87	49.81 uM	-7.66	2.42 uM
HIV Inhibitors	1	Lopinavir	-7.79	1.94 uM	-7.86	1.89 uM
	2	Indinavir	-8.12	1.12 uM	-7.09	7.04 uM

The white area has a high probability of passive absorption by the gastrointestinal tract, and the yellow area has a high probability of BBB permeability. A blue dot indicates that the drug is not able to inhibit the P-gp substrate, while the red is its inhibitor.

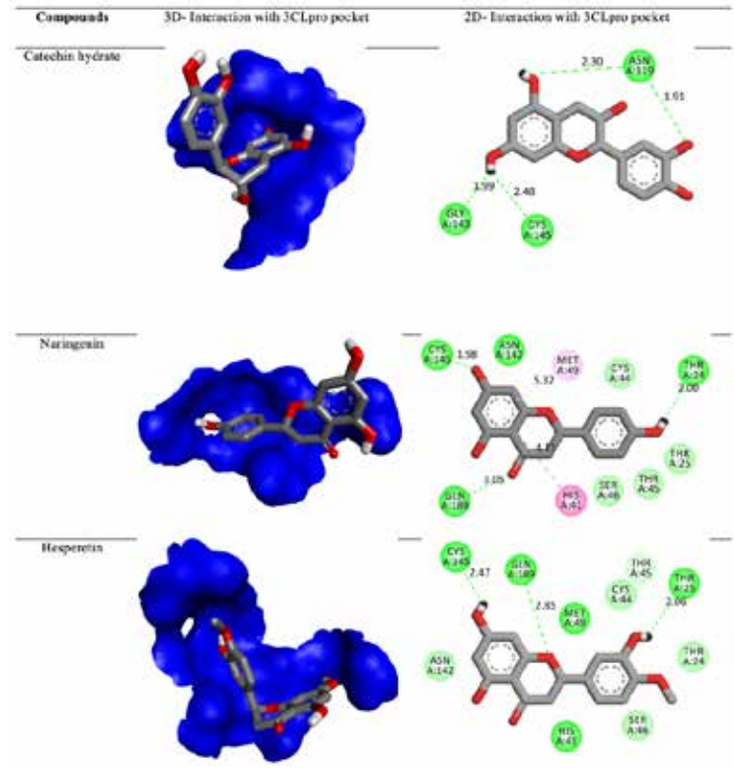

Figure 2. 3D & 2D binding interaction model of catechin hydrate, naringenin, hesperetin, lopinavir and indinavir with the main protease 3CLpro pocket (PDB ID: 6LU7)

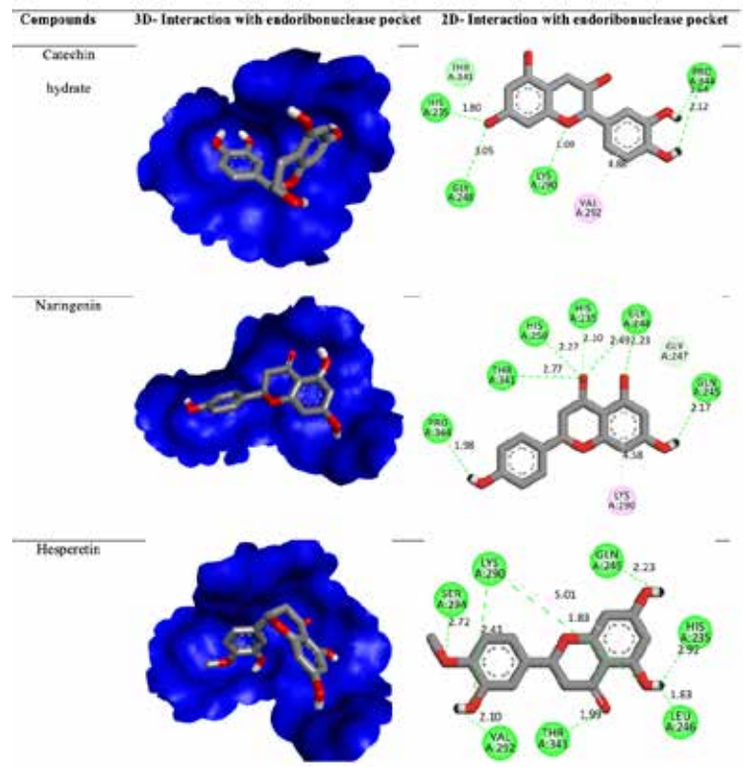

Figure 3. 3D & 2D binding interaction model of catechin hydrate, naringenin, hesperetin with the Nsp15 endoribonuclease pocket (PDB ID: 6VWW)

Molecular Docking

Recent literature reported that the key amino acids in the active binding site of 3CLpro were HIS41 and CYS145, as well as THR341 in Nsp15 [21-23]. Accordingly, there is broad consensus among researchers that promising new antiviral activity drugs need to interact with these enzymes, which may help to stop protein activity in viral replication.

In our study, the molecular docking analysis was carried to evaluate the interaction of desert truffle-derived compounds with the two target SARS-CoV-2 proteins (3CLpro and Nsp15). Then, the best binding affinity of the interacting compounds to the active site residues (CYS145 and HIS 41) of 3CLpro and THR341 of Nsp15 were also calculated. Two commonly used anti-viral medications lopinavir and indinavir were also docked for further comparisons. Table 2 and Figure 2 display the computed docking scores between SARS-CoV-2 proteins (3CLpro and Nsp15) and the 44 phytoconstituents compounds of truffles (ligands), as well the HIV-inhibitors (Lopinavir and indinavir).

Discussion

Truffle phytoconstituents have good pharmacological properties, as do the HIV inhibitors (Lopinavir and Indinavir) All of these compounds have high water solubility and gastrointestinal absorption. They smoothly excrete from the body without bounding with the renal OCT2 substrate, and also cannot cross the BBB. In addition, the toxicity profiles of these phytoconstituents revealed there are no undesirable characteristics, and all of them appear to be almost identical to the inhibitors (controls). Interestingly, the BOILED-Egg model (Figure 1) showed that, like lopinavir and indinavir, the compounds catechin hydrate, naringenin and hesperetin only have the ability to bind to the P-GP substrate, suggesting that these compounds may be promising and safer for COVID-19. In silico, pharmacokinetic tools along with the drug-likeness prediction, provide an array of opportunities to accelerate the discovery of new potential compounds with predicted biological activity.

The docking simulation was carried out for all the selected ligands with two COVID-19 proteins (Table 2 and Figures 2 and 3). The findings of this study showed that some phytoconstituent compounds tend to enzyme more than others. The free binding energies of drugs containing more negative values than -6.5 kcal/mol are assumed to show strong interactions and may significantly impair enzymatic activities. Six compounds showed a more negative binding affinity than - 6.50 Kcal/mol for the main protease (3CLpro) and endoribonuclease (Nsp15). Lopinavir and indinavir [25] revealed strong binding affinity for both proteins, and the scores were close to the most negative compounds. However, the analysis also showed violations of drug-like properties by rutin, while luteolin and apigenin had good pharmacological predictive values. Therefore, the docked structures of catechin hydrate, naringenin, hesperetin and control complexes of HIV-inhibitors (Lopinavir and indinavir) with main protease (PDB: 6LU7) and endoribonuclease (PDB: 6VWW) of SARS CoV-2 were presented in Figure 2 and Figure 3, respectively, to recognize key amino acid interactions in the pockets and evaluate inhibitory effects on viral replications.

Strikingly, the findings exhibited the ability of naringenin and hesperetin to form strong H-bonds with key amino acids of the main protease (CYS145) from the hydroxy group of naringenin and hesperetin at the distances of 1.98A and 2.47A, respectively, and also, H-bonds with the key residue THR341of the Nsp15 at distances of 2.77A and 1.99A, respectively. This indicates that both may be potent drugs to inhibit the viral replication of COVID-19 by halting the activity of the two essential proteins.

Conclusion

The results of the ADMET and drug-like properties have shown that the truffle phytoconstituents (catechin hydrate, naringenin and hesperetin) have excellent properties like inability to cross the BBB and high GI absorption when taken orally. They are expected to be safe and have a strong bioavailability score. In addition, the free binding energy (Molecular Docking) of all compounds on the active site of 3CLpro and Nsp15 was measured to confirm their affinity to interact and to classify potential lead drugs according to their affinity and pharmacological properties. Docking scores revealed that catechin hydrate, rutin, luteolin, naringenin, apigenin and hesperetin have more negative free binding energy than -6.50 kcal/mol for both proteins. The analysis of the interactions of catechin hydrate, naringenin and hesperetin with the key amino acids in 3CLpro (HIS41 and/or CYS145) and Nsp15 (THR341) showed that naringenin and hesperetin are able to form strong H-bonds with proteins, which provide potential compounds to be novel inhibitors to COVID-19. In order to confirm the computational findings, the findings of this study need further in vitro and in vivo investigations.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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