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In Silico Approach to Search Various Phytochemicals as Potential Therapeutics Against the Spike Protein from Alpha Variant Strain (B.1.1.7) of SARS-CoV-2

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Abstract: Scientists have indeed been attempting to examine many active chemicals identified in plants that would have the effect of restricting the multiplication of SARS-CoV-2 since the onset of the COVID-19 widespread. The worldwide healthcare system has been trying to discover an efficient therapeutic solution because there are no therapeutically authorised medications. Testing of botanical pharmaceuticals could be a feasible method that fight COVID-19 during this crucial moment. The research focused upon the spike protein of SARSCoV2's novel alpha strain, which was initially found in the United Kingdom. The objectives of this paper was to use a molecular docking approach to analyse pharmacological chemicals discovered in plants in order to prohibit the major protease (7DDN) of the SARS-CoV2 alpha variant strain (B.1.1.7). The binding affinity computed with PyRx virtual screening tool, which employed AutoDock Vina as a docking processor, were evaluated. All total 33 phytochemicals were analysed in this research. Hesperidin and broussochalcone A, according to findings of this study, had the strongest interaction (-8.7 Kcal/mol) with 7DDN spike protein. Pectolinarin has the second highest binding affinity (-8.3 Kcal/mol). Rhoifolin had the third highest interaction (-8.2 Kcal/mol), followed by Epigallocatechin, Cannabidiol, and Morin, which all had a docking score of -7.9 Kcal/mol. This study, which aimed to predict the suppressive activities of compounds obtained from plants specifically address 7DDN proteins, discovered a number of things, including that the pharmaceutical is having a significant posture and binding affinity than hydroxychloroquine. Furthermore, *in silico* drug likeness and ADMET analyses of the phytochemicals demonstrated significant therapeutic advantages. As a conclusion, the present investigation would serve as a springboard for much more exploration to assess the phytocompounds' effectiveness.

Keywords: Healthcare system, Molecular docking, Binding affinity, Phytochemicals, Druglikeness

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Introduction

According to WHO, the global COVID-19 catastrophe involving countless deaths were caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) (Salvatore *et al.*, 2021). Rapidly spreading of the illness had forced implementation of additional pharmacological therapies. Palliative therapy and illness alleviation seem to be the mainstays of modern therapy. There may be a critical necessity of innovative treatment modality towards COVID-19 owing to the unavailability of any effective and direct medications (Sarkar, 2021). With a five-day

gestation period, COVID-19 disease causes acute respiratory distress symptoms such as nausea, chest infection, with breathing difficulty. If SARS-CoV2 is not addressed promptly and effectively, it can create serious respiratory problems and ultimately fatal (Prakash, 2021). Since the outbreak of the COVID-19 catastrophe, de novo mutations of SARS-CoV-2 have originated and disseminated over the universe. Because extremely detrimental changes being swiftly purged, majority of alterations were found in migrating SARS-CoV-2 virions' sequences which appear likely to be harmless or modestly catastrophic (Sarkar, 2021). It is indeed unclear to what level of mutations changing the antigenic nature of SARS-CoV-2 should allow variations to bypass protection given by natural exposure to an antigen (Omotayo, 2021). Moreover, there has been substantial evidence indicating mutations that alter the antigenic character of SARS-CoV-2 which have been persisting but also affecting immune surveillance to the point where prompt action needs to be taken. As a result, changes which alter the antigenicity of the spike protein remain highly pertinent (Gurung *et al.*, 2020). Molecular investigations reveal a shift in the cultural context as well as indications of heightened beneficial mutations operating on immunologically relevant SARS-CoV-2 genes in patients (Andréa, 2021). The research is concentrated upon the spike protein (7DDN) of SARSCoV2's novel alpha strain, which was initially identified in the United Kingdom.VUI 202012/01 was the name given to it. The alpha strain of the Covid-19 virus encompasses twenty-three variants. Eight of these were discovered within the spike protein.

SARS-CoV2 seems to be single-stranded with positive mode RNA virus. They fall towards the Coronaviridae family (Sarkar, 2022).The virion dimension of SARS-CoV2 ranges 50–200 nm. Total number of nucleotide present in genomic RNA is twenty-nine thousand eight hundred and eleven (Muhammad Tahir, 2020). There is total one hundred and twenty number of ORF found in entire genome and translating twenty-nine proteins, that found to have various functions such as engaged for viral pathogenicity, genome replication plus provide survivability factors of the virus inside host (Prakash, 2021). The major four structural proteins are found to have S i.e. spike protein, M, membrane protein, E, envelope protein as well as N i.e. nucleocapsid protein. Among these four protein molecules, N protein is required for genome packaging, whereas protein S, E and M seems to be involved in making coat of the virus as well as receptor for interaction with host cell surface protein (Dwight *et al.*, 2021). The spike protein, which aids the virus's entrance into the host cell, is extensively glycosylated and having transmembrane fashion. The spike protein has a molecular weight of 180-200 kDa. It is made up of 1200 number of amino acids (Seema *et al.*, 2020). Coronavirus spike protein encompasses three distinct domains. The first domain is a N-terminal domain which is present extracellularly, for anchoring in the virus envelope having a second transmembrane domain and third domain is a short intracellular C-terminal portion (Arora *et al.*, 2020). SARSCoV2 targets and causes disease in four stages including undiagnosed, intermediate, acute, and pathological. Infection originates inside the lower respiratory tract, then invades pulmonary epithelial cells that hijacks the whole host cell function (Muhammad Tahir *et al.*, 2020). There has been still no clinically authorised medication to combat COVID-19 with SARS-CoV2. Numerous medications with minimal clinical expertise are being employed in clinical studies and guidelines depending on *in vitro* research towards SARS-CoV-2 or comparable viruses; nevertheless, the efficacy of medication for any class of drug was not shown (Dwight *et al.*, 2020). Multiple investigators propose testing the efficiency of adapting current antiviral medicines against SARS-CoV2. The coronaviruses $3CL^{pro}$ as well as PL^{pro} have been thought to be critical candidates for COVID-19 control among the many drug targets. ORF-1 of the viral RNA genome codes $3CL^{pro}$along with PL^{pro}, which would be involved in the conversion of silent polyproteins i.e., pp1a plus pp1ab, becoming active non-structural

components i.e., nsps (Namisha *et al.*, 2020). Considering corona virus infection was a global prevalentand having health implications across the globe, more investigation seems warranted, as well as the development of specific therapy treatments to reduce mortality and morbidity (Ziyad Tariq *et al.*, 2020).

Numerous phytochemical molecules have been discovered to possess fighting spirit and stop spreading of fungal, microbial with viral diseases (Venkateshan *et al.*, 2020). By use of computer-assisted structure-based drug design (SBDD) to address this problem, rather than the conventional practice of pharmaceutical research, has been the major issue. Herbal medicines, which also have documented health advantages and low toxicity, may be explored as novel therapeutics for lowering disease forecast including inhibiting the viral life span (Khare *et al.*, 2020). Molecular docking is being used to anticipate whether bioactive substances (ligands or drug) interface with receptor proteins (Wathore *et al.*, 2020). Considering the significance of early look for bioactive compounds' propensity to uncover therapeutic possibilities or combat fungus, bacteria and viruses, present research work used a molecular docking approach in analysing biologically active chemicals which is found in several community known plants. In addition, this study also looked into the phytochemicals in silico drug likeness as well as ADMET qualities. The findings of the research have been intended to be used as a starting point for even further investigation into specific treatments for overcoming COVID-19.

Materials and Methods

Selection and preparation of protein for docking:

From the protein data bank (https://www.rcsb.org), the author acquired accessible three-dimensional structure of spike protein whose PDB ID was 7DDN and molecular weight was found 420.17 kDa (Fig. 1). The SARS-CoV2 spike protein's most extensive electron microscopic architecture was chosen initially. This protein found to have total 1261 amino acids with three chain denoted as A, B and C. Resolution was found as 6.30 Å. All of the connected ligands, water molecules as well as chains B and C, were deleted. For molecular docking, energy minimisation was carried out by utilizing SPBDV 4.1.3 software and then transformed to pdbqt format employing auto dock (Kanchanok *et al.*, 2020). The Autodock tools were used to create the Grid Parameter File (Gurung *et al.*, 2020).

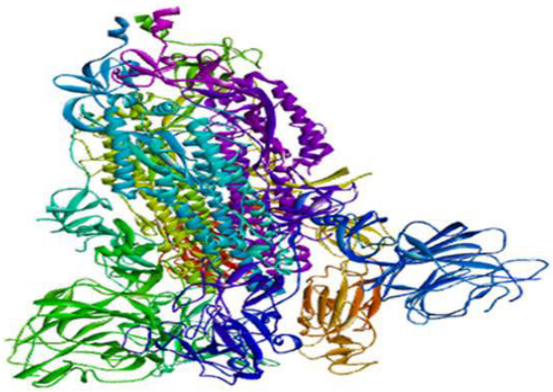


Fig. 1: 3D Structure of SARS CoV 2 (alpha variant strain B.1.1.7) spike protein (PDB ID: 7DDN).

Selection of phytochemicals and preparation of ligand:

A total of 33 phytochemical constituents which have been reported to be possess protease inhibiting properties were gathered from various sources. The name of the chemicals, PubChem ID and the chemical formula are documented in Table 1. Sdf form of all phytochemicals were accessible directly from PubChem database (https://pubchem.ncbi.nlm.nih.gov). Downloaded sdf form later were converted into mol.2 form by using Discovery Studio software. Using the UCSF Chimera v1.14 force field, the energy of phytochemicals (ligand) was minimised (Dwarka *et al.*, 2020). The SWISSADME predictor (http://www.swissadme.ch/) was used to compute the attributes of active compounds using Lipinski's rule of five (Kuppuswamy *et al.*, 2020).

Molecular docking study:

Molecular docking activity conducted with SARSCoV2 spike protein 7DDN by using PyRx

Table 1: List of various phytochemicals used in this study with their molecular formula along with PubChem ID

S. No.	Name of the Phytochemicals	Molecular formula	PubChem ID
1	Quinine	$C_{20}H_{24}N_2O_2$	3034034
2	Cannabidiol	$C_{21}H_{30}O_2$	644019
3	Hesperidin	$C_{28}H_{34}O_{15}$	10621
4	Rhoifolin	$C_{27}H_{30}O_{14}$	5282150
5	Pectolinarin	$C_{29}H_{34}O_{15}$	168849
6	Morin	$C_{15}H_{10}O_7$	5281670
7	Epigallocatechin gallate	$C_{22}H_{18}O_{11}$	65064
8	Herbacetin	$C_{15}H_{10}O_7$	5280544
9	Ethyl cholate	$C_{26}H_{44}O_5$	6452096
10	Kaempferol	$C_{15}H_{10}O_6$	5280863
11	Tangeretin	$C_{20}H_{20}O_7$	68077
12	Chalcone	$C_{15}H_{12}O$	637760
13	Nobiletin	$C_{21}H_{22}O_8$	72344
14	Bis (3, 5, 5-trimethylhexyl) phthalate	$C_{26}H_{42}O_4$	34277
15	6-gingerol	$C_{17}H_{26}O_4$	442793
16	6-shogaol	$C_{17}H_{24}O_3$	5281794
17	Hydroxychloroquine	$C_{18}H_{26}ClN_3O$	3652
18	Myristicin	$C_{11}H_{12}O_3$	4276
19	Eugenol	$C_{10}H_{12}O_2$	3314
20	Sinigrin	$C_{10}H_{16}KNO_9S_2$	23682211
21	Xanthoangelol	$C_{25}H_{28}O_4$	643007
22	Savinin	$C_{20}H_{16}O_6$	5281867
23	Pristimerin	$C_{30}H_{40}O_4$	159516
24	Apigenin	$C_{15}H_{10}O_5$	5280443
25	Curcumin	$C_{21}H_{20}O_6$	969516
26	Cryptotanshinone	$C_{19}H_{20}O_3$	160254
27	Broussochalcone A	$C_{20}H_{20}O_5$	6438825
28	Epigallocatechin	$C_{15}H_{14}O_7$	72277
29	Baicalein	$C_{15}H_{10}O_5$	5281605
30	Ellagic acid	$C_{14}H_6O_8$	5281855
31	Cinnamamide	C_9H_9NO	5273472
32	6,8-Diprenylgenistein	$C_{25}H_{26}O_5$	480783
33	Polygalacin	$C_{29}H_{34}O_{16}$	5464499

software (Balaji *et al.*, 2020). For docking, this utility made use of Auto Dock. In this study, the protein structure was uploaded as a macromolecule first, and then all of the bioactive chemicals one by one (ligand). The software reduced the energy of the ligand before converting it to the Auto Dock ligand format (pdbqt). Finally, after covering the complete protein structure with a grid box, docking began to screen the best-fitting bioactive chemicals based on energy value. Each simulation was run ten times in total, yielding ten docked conformations. As a result, the lowest energy configurations had been chosen to have the best binding configuration. Hydrophobic correlations, hydrogen bonds, van der Waals interactions, and intra-molecular relationships with such a single bioactive molecule have all been thoroughly investigated utilising Discovery Studio software.

Results and Discussion

The worldwide coronavirus illness outbreak has been caused by the SARS-CoV-2 (Salvatore *et al.*, 2021; Sarkar *et al.*, 2021). Several drugs with little

clinical experience have been used in epidemiological practice and recommendations based on wet lab research towards SARS-CoV-2 or similar viruses; unfortunately, the benefit of any type of treatment has not been demonstrated (Jayalakshmi *et al.*, 2020). In this study, a molecular docking approach was employed to examine physiologically active compounds discovered in a variety of botanicals. Table 1 listed all 33 phytochemical compounds used during the *in silico* study. Every compound has been utilised to explore the fundamental origins of the medications utilising the SWISS ADME once they were formulated. Table 2 illustrates the fitness of the Lipinski 'Rule of Five of all 33 compounds.

The much more difficult as well as critical challenge confronting by global researchers right now is the search for drugs and vaccines to combat the COVID-19 outbreak (Kumar *et al.*, 2020). In this study 33 phytochemicals were evaluated from various medicinal plants that have been documented to have anti-protease properties as part of this drug discovery effort. *In vitro* protease inhibitory activities have been documented for all of the phytocompounds studied. Inhibitory action was discovered against 7DDN protein of SARSCoV2. Considering this has been the latest structure available in PDB at the time, and the same spike protein has been adopted for investigation to reflect a prevalent alpha strain of SARS CoV2. The spike protein has been in an open state in this configuration, when no substrates or antagonists linked towards it. The similar principal protease is required for coronavirus multiplication, and the interface glycoprotein i.e., spike protein is needed for virus-cell cell fusion via the cellular receptor named ACE2 (Balmeh *et al.*, 2020). Since the spike protein on the virus's interface connects very well to ACE2 on the outer face cells, SARS-Cov-2 has been easily transferred (Kuppuswamy *et al.*, 2020). The most popular and highly utilised methodologies for assessing the connection between ligand-protein structures at the atoms seem to be molecular docking with molecular dynamics modelling (Li *et al.*, 2020). Breakthrough antagonists targeting disease-causing molecular targets can always be created utilising such strategies. This study evaluated the 7DDN protein antagonistic capability of 33 phytocompounds which have already been indicated to have anti-protease function by numerous studies. Among the 33-phytochemical utilized, we found two molecule named Hesperidin (Fig. 4) and Broussochalcone A (Fig. 28) both delineated highest interaction with 7DDN spike protein. Both found to have interaction energy -8.7 Kcal/mol (Table 3). Hesperidin is indeed a bioflavonoid, a category of plant pigmentation mostly in citrus fruit that has antioxidant and anti-inflammatory properties (Berretta *et al.*, 2020). Hesperidin has been found in oranges, grapefruit, lemons, plus tangerines, although it is offered as a supplementation (Seema *et al.*, 2020). Broussochalcone A is a herbal medicine. This is an alkaloid extracted from *Stephania tetrandra* (Mubarak *et al.*, 2020). In patient carcinoma cells, Broussochalcone A suppresses cell proliferation by triggering NR4A1-mediated signalling pathway (Gurung *et al*., 2020). Broussochalcone A is really a possible chemotherapeutic agent that targets the NR4A1 gene, which is upregulated in many types of malignancies in humans (Víctor *et al.*, 2020). Second highest binding affinity was found for Pectolinarin (-8.3 Kcal/mol). Number of hydrogen bond during interaction was found 1 (Table 3, Fig. 6). Because of its occurrence in many therapeutic plants, Pectolinarin, which belongs to the flavone family, had received much interest. It already has proven to be a useful biological drug, with antioxidant, anti-inflammatory, antidiabetic, as well as anticancer properties that have been tested both *in vitro* and *in vivo* (Azim *et al.*, 2020). In this study, Rhoifolin showed third highest interaction (-8.2 Kcal/mol) with 7DDN (Table 3, Fig. 5). Rhoifolin is really a flavone that could be found in *Boehmeria nivea*, China grass, *Citrus limon*, *Canton lemon* as well as in *Citrus x aurantium* (Chidambaram *et al.*, 2020). Rhoifolin has been found in clinical studies to exhibit a wide spectrum of biological actions involving antioxidant, anti-inflammatory, antibacterial,

Table 2: Lipinski rule related information of selected phytocompounds studied along with reference compound Hydroxychloroquine. Given emphasis on molecular weight, number of hydrogen bond donor as well as acceptor, along with Log $P_{o/w}$ and Log S value of the phytocompounds

S. No.	Phytochemicals	Molecular Weight (g/mol)	No. of H bond donor	No. of H bond acceptor	Log $P_{o/w}$	Log S	Lipinski Rule violation
1	Quinine	356.67	1	4	1.40	-1.73	0
2	Cannabidiol	350.75	2	2	4.83	-5.61	1
3	Hesperidin	610.56	8	15	-0.72	-3.28	3
4	Rhoifolin	346.42	0	5	3.38	-4.43	0
5	Pectolinarin	622.57	7	15	-0.43	-3.74	3
6	Morin	319.37	5	7	-0.93	-0.48	0
7	Epigallocatechin Gallate	482.66	8	11	-0.92	-1.49	2
8	Herbacetin	319.37	5	7	-0.72	-1.02	0
9	Ethyl cholate	436.62	3	5	3.52	-3.86	0
10	Kaempferol	286.24	4	6	1.70	-3.31	0
11	Tangeretin	404.62	0	7	1.30	-2.37	0
12	Chalcone	234.46	0	1	3.78	-4.22	0
13	Nobiletin	436.66	0	8	1.00	-2.22	0
14	Bis (3, 5, 5-trimethylhexyl) phthalate	418.61	0	4	6.48	-6.90	1
15	6-gingerol	322.61	2	4	2.88	-2.80	0
16	6-shogaol	305.60	1	3	3.65	-3.63	0
17	Hydroxychloroquine	364.09	2	4	1.33	-0.97	0
18	Myristicin	210.35	0	3	1.17	-1.70	0
19	Eugenol	183.35	1	2	1.75	-2.20	0
20	Sinigrin	372.48	4	10	-1.10	-0.64	0
21	Xanthoangelol	433.81	3	4	4.50	-5.24	0
22	Savinin	378.54	0	5	1.03	-1.64	0
23	Pristimerin	464.64	1	4	5.57	-6.54	1
24	Apigenin	291.40	3	5	0.36	-1.45	0
25	Curcumin	398.62	2	6	2.56	-2.92	0
26	Cryptotanshinone	300.39	0	3	2.96	-3.04	0
27	Broussochalcone A	370.61	4	5	2.46	-3.56	0
28	Epigallocatechin	324.41	6	7	-0.72	-0.92	1
29	Baicalein	291.40	3	5	0.46	-1.80	0
30	Ellagic acid	312.27	4	8	-0.47	-1.09	0
31	Cinnamamide	164.31	1	1	1.65	-2.03	0
32	6,8-Diprenylgenistein	443.76	3	5	3.48	-4.37	0
33	Polygalacin	638.57	8	16	-0.34	-3.74	3

hepatoprotective, as well as anticancer properties (Gurung *et al.*, 2020). Three phytochemicals named as Cannabidiol, Morin and Epigallocatechin found to have same interaction energy – 7.8 Kcal/mol with 7DDN in this study (Table 3, Figs. 3, 7, 29). Among them Cannabidiol and Epigallocatechin showed having 1 hydrogen bond during interaction, while Morin did not show forming hydrogen bond during interaction with 7DDN. One of the key ingredients discovered in

Table 3: Molecular docking study with various phytochemicals used and their interaction study with 7DDN. Interaction energy, interaction residues as well as number of hydrogen bond involved in interaction is also depicted

S. No.	Phytochemicals	Interaction energy (Kcal/mol)	Interacting residues	No. of H Bonds in interaction	Fig. No.
1	Quinine	-6.9	Asp 290, Leu 293, Asp 294, Arg 273, Cys 291, Leu 291	2	2
2	Cannabidiol	-7.8	Ala 944, Leu 945, Asp 950, Gln 949, Lys 947, Leu 948, Ser 943	2	3
3	Hesperidin	-8.7	Gly 1124, Phe 1089, Phe 1121, Val 1122, Ala 1087, Asn 1125	1	4
4	Rhoifolin	-8.2	Leu 270, Asp 53, Tyr 37, Ile 197, Leu 54, Lys 202, Asn 196, Lys 202, Phe 201, Tyr 200, Gly 89, Phe 86	0	5
5	Pectolinarin	-8.3	Thr 1076, Phe 1075, Ile 712, Thr 1076, Ser 708, Asn 709, Thr 1077	1	6
6	Morin	-7.8	Phe 515, Cys 391, Leu 518, His 519, Phe 392, Leu 390, Glu 516, Leu 518	0	7
7	Epigallocatechin gallate	-7.8	Gly 502, Val 503, Asn 437, Asn 439, Tyr 508, Asn 501, Ile 402, Tyr 505, Arg 403, Gly 404, Pro 507	3	8
8	Herbacetin	-7.3	Val 320, Phe 592, Val 551, Thr 549, Gly 550, Thr 588, Pro 589, Ser 591	0	9
9	Ethyl cholate	-6.7	Tyr 1110, Gln 1106, Pro 715, Arg 1107, Thr 1105, Val 1094, Phe 1075, Thr 716, Ile 712, Glu 1072, Val 1096, Lys 1073	0	10
10	Kaempferol	-7.9	Gly 89, Ile 197, Asp 88, Tyr 37, Leu 270, Phe 55, Pro 272, Gln 271, Lys 195, Asp 53	2	11
11	Tangeretin	-6.6	Ala 944, Leu 945, Asp 950, Lys 947, Gln 949, Leu 948, Ser 943, Leu 945	2	12
12	Chalcone	-6.3	Thr 315, Cys 301, Leu 303, Lys 304, Thr 299, Lys 300, Glu 298	2	13
13	Nobiletin	-6.4	Val 1096, Val 1104, Phe 1095, Thr 1105, Pro 1090, Ile 712, Ile 714, Arg 1107, Gly 1093	1	14
14	Bis (3, 5, 5-trimethylhexyl) phthalate	-5.8	Val 1129, Ala 1087, Ala 1080, Ser 1123, Pro 1090, Phe 1095, Phe 1121, Arg 1091, Thr 1120, His 1088	1	15
15	6-gingerol	-5.9	Thr 302, Val 308, Lys 304, Tyr 313, Ser 305, Lys 300, Cys 301,	1	16
16	6-shogaol	-5.8	Asn 317, Thr 315, Gly 594, Val 595	2	17
17	Hydroxychloroquine	-5.6	Val 62, Ala 27, His 66, Arg 78, Phe 65, Thr 63, Tyr 28, Tyr 266	2	18
18	Myristicin	-4.5	Ile 712, Thr 1105, Tyr 1077, Val 1096, Phe 1103, Val 1094, Trp 1102, Ile 1081, Ala 1080, His 1088, Phe 1089, Pro 1099, Thr 1120, Ile 1115, Val 1104	1	19
19	Eugenol	-4.9	Thr 1017, Val 1096, Arg 1107, Ala 713, Lys 1073, Ile 714, Asn 1074, Val 1094, Phe 1075, Ser 711	1	20
20	Sinigrin	-5.9	Phe 543, Leu 546, Thr 573, Val 576,	1	21

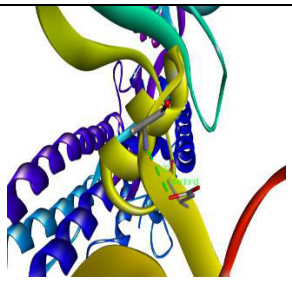
			Thr 549, Ile 587, Asn 542, Thr 547, Gly 548, Leu 552, Ile 326, Val 539		
21	Xanthoangelol	-6.9	Ala 672, Gln 607, Ala 609, Ile 598, Thr 599, Val 608, Pro 600, Ile 693, Gly 652, Glu 654, Ala 653, Ser 691, Ser 673, Tyr 674	1	22
22	Savinin	-7.2	Gln 1106, Val 911, Gly 910, Tyr 1047, Ile 909, Tyr 1067, Phe 1109, Pro 715, Arg 1107	2	23
23	Pristimerin	-6.9	Leu 276, Val 289, Glu 298, Cys 285, Cys 291, Ser 297, Thr 299, Leu 303, Lys 304, Lys 300, Thr 302	2	24
24	Apigenin	-7.4	Pro 57, Pro 272, Arg 273, Leu 270, Leu 54, Phe 55	2	25
25	Curcumin	-7.9	Val 1129, His 1088, Thr 1120, Arg 1091, Phe 1121, Phe 1095, Pro 1090, Ser 1123, Ala 1080, Ala 1087	1	26
26	Cryptotanshinone	-7.5	Phe 541, Asn 540, Thr 549, Thr 547	1	27
27	Broussochalcone A	-8.7	Thr 302, Val 308, Thr 299, Cys 301, Lys 300, Ser 305, Tyr 313, Lys 304	2	28
28	Epigallocatechin	-7.8	Thr 299, Val 608, Thr 599, Ile 598, Ile 312, Tyr 313, Ala 609, Leu 611, Val 610, Ser 596, Thr 315, Pro 295	1	29
29	Baicalein	-7.0	Glu 1111, Gly 1093, Arg 1107, Gly 910, Glu 1092, Val 911, Thr 912, Thr 1105, Asn 1108, Ile 714, Phe 1109, Val 1094	3	30
30	Ellagic acid	-7.2	Gly 648, Thr 645, Phe 643, Ala 653, Ile 598, Leu 611, Ala 609, Asn 641, Gly 652, Val 642, Ile 651, Ile 666, Gln 644	1	31
31	Cinnamamide	-5.2	Leu 368, ser 371, Asn 370, Tyr 369, Ser 366, Tyr 365, Asp 364	1	32
32	6,8-Diprenylgenistein	-7.5	Asn 953, Gln 954, Thr 961, Leu 962, Ala 958, Ala 956, Asn 960, Leu 959, Asn 955	2	33
33	Polygalacin	-7.1	Ser 1123, Ala 1087, Phe 1121, His 1088, Lys 1086	0	34

hemp plants is cannabidiol (Sharma *et al.*, 2020). Cannabidiol is perhaps the world's least extensively employed banned narcotic, and its usage was already linked to a variety of mental health issues, specifically among teenagers (Seema *et al.*, 2020). Epicatechin is indeed a flavonoid. Spondias mombin green tea (*Camellia sinensis*) with dark chocolate have been found as the extensive source for this (Venkateshan *et al.*, 2020). Morin seems to be a yellow chemical substance that could be extracted from the leaves of common guava, osage orange, with old fustic (Gurung *et al.*, 2020). -7.9 Kcal/mol was found the interaction energy for both kaempferol (Table 3, Fig. 11) plus curcumin (Table 3, Fig. 26). Kaempferol outlined 2 hydrogen bond during interaction, whereas curcumin showed only 1 hydrogen bond in the interaction. Kaempferol is just a type of flavonoid naturally occurring in kale, beans, tea, spinach, even broccoli, among other vegetables as well as plant-derived foodstuffs (Balaji *et al.*, 2020). Kaempferol has antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, neuroprotective, antidiabetic, antiosteoporotic, estrogenic, anxiolytic, analgesic, as well as antiallergic activities, according to

countless laboratory studies (Wathore *et al.*, 2020). Curcumin has been the major phenolic ingredient of *Curcuma longa*, an ancient Chinese herb sometimes characterized as turmeric, safflower, as well as yellow ginger (Chidambaram *et al*., 2020). Xanthoangelol is just a powerful dopamine-hydroxylase (DBH) antagonist and then a nonselective MAO blocker (Wathore *et al*., 2020) (Table 3, Fig. 22) and Pristimerin which is atriterpene compound (Kushwaha *et al.*, 2021)(Table 3, Fig. 24) both exhibited same interaction energy i.e., -6.9 Kcal/mol. Pristimerin would be a protein derived from plant preparations that has anticancer, antioxidant, plus anti-inflammatory properties (Mubarak *et al.*, 2020). Angelica plants produce Xanthoangelol, which really is a natural chalcone (Sharma *et al.*, 2020). Similarly, Tangeretin showed interaction energy -6.6 Kcla/mol (Table 3, Fig. 12), Chalcone showed interaction energy -6.3 Kcal/mol (Table 3, Fig. 13) and Nobiletin found to have interaction energy -6.4 Kcal/mol (Table 3, Fig. 14). This investigation, which intended to forecast the inhibitory activity of chemicals produced by plants targeting 7DDN proteins, yielded various findings, such that the drug have a better docking pose than hydroxychloroquine (Table 3, Fig. 18). Many other phytochemical related detail information has been provided in Table 3 and Figure 2 to 34, respectively. The observations of the connection here between 7DDN protein and indeed the selected phytochemicals reveal that there can be unfavourable donor-donor bonds, indicating that perhaps the two molecules repel each other. The development of that kind of bond can alter the stabilization of ligands that would be employed as therapeutic candidates by reducing the durability of other kinds of bonds (Zhang *et al.*, 2020). Hesperidin, nabiximols, pectolinarin, epigallo-catechin gallate, and rhoifolin displayed lower binding free energies towards 7DDN protein of SARS-CoV-2, according to findings of this study. These compounds have the ability to act as antiviral phytochemicals, preventing the virus from replicating (Padmini *et al.*, 2020; Li *et al.*, 2020; Khare *et al.*, 2020). These results constitute merely a preliminary examination to aid later tests, which will begin in animal models or human clinical trials.

Docking is a computerized methodology for anticipating the favoured orientation of one molecule to another when they should be linked together so that to form a stable complex (Kumar *et al.*, 2020). Although simulating a drug's interaction with a receptor would be a difficult task. Intermolecular interaction involves hydrophobic, dispersion, or Van der Waals forces, H bonding, and electrostatic forces (Padmini *et al.*, 2020). Hydrophobic interactions seem to be the dominating power for binding, whereas hydrogen bonding and electrostatic interactions likely to influence the precision of the complexation (Nag *et al.*, 2021). As there are so many degrees of variation and little information of the effect of environment on the binding relationship, modelling the intermolecular interactions in a ligand-protein compound has been challenging. Besides connecting complementary properties, molecular docking aims to organise molecules into suitable topologies (Balmeh *et al.*, 2020). The protein 3-D structure is necessary for docking research, which would be typically available and easily accessible for every protein from the PDB database.

ADMET determinant would be a machine learning application which estimates over 175 attributes, spanning solubility, logP, pKa, CYP metabolism sites, as well as Ames teratogenicity, fast but rather correctly (Azim *et al.*, 2020; Mahmoud *et al.*; 2020). Each of the optimal ligands chosen for this research has a distinctive number of hydrogen bonds and has been attached to a distinct amino acid residue. For Drug likeness, the present study (Table 2) extensively focussed on Lipinski rule-of-five filter, which contains five-rules or criteria: (i) Molecular weight should be less than 500 Daltons; (ii) lipophilicity must be high and that should express as logP , which is an octanol-water partitions coefficient and never exceed value 5; (iii) The total number of Nitrogen, Hydrogen, and Oxygen - H bonds must be less than



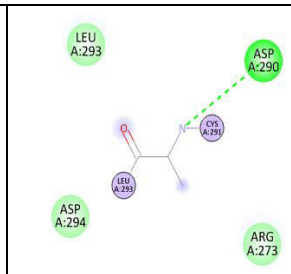
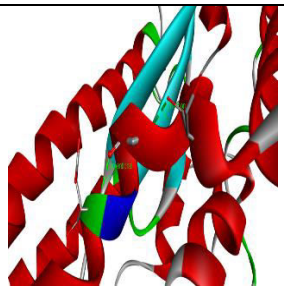


Fig. 2: 3D and 2D interaction between 7DDN and Quinine.



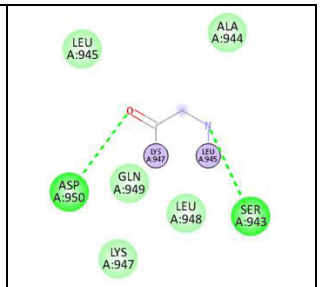
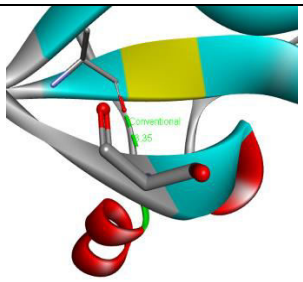


Fig. 3: 3D and 2D interaction between 7DDN and Cannabidiol.



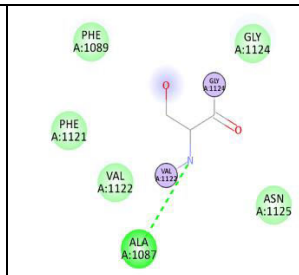
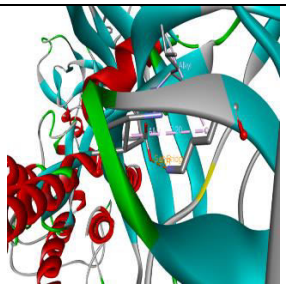


Fig. 4: 3D and 2D interaction between 7DDN and Hesperidin.



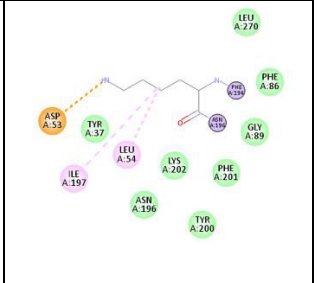
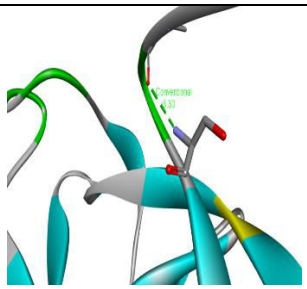


Fig. 5: 3D and 2D interaction between 7DDN and Rhoifolin.



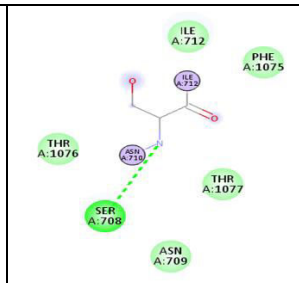
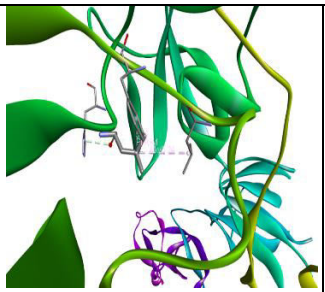


Fig. 6: 3D and 2D interaction between 7DDN and Pectolinarin.



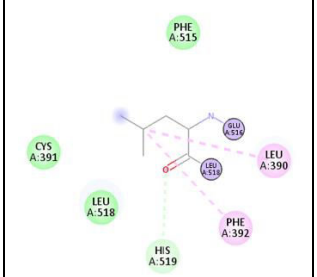
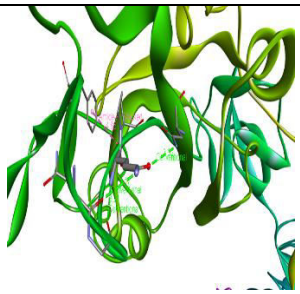


Fig. 7: 3D and 2D interaction between 7DDN and Morin.



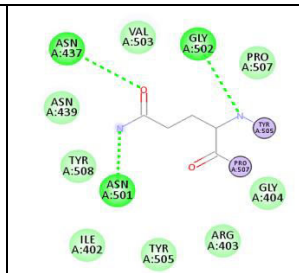
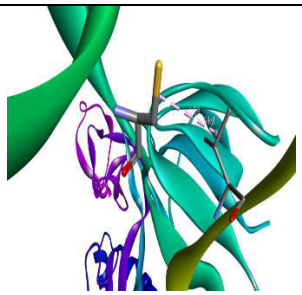


Fig. 8: 3D and 2D interaction between 7DDN and Epigallocatechin gallate.



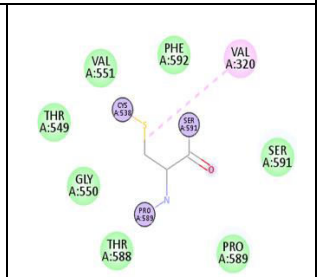


Fig. 9: 3D and 2D interaction between 7DDN and Herbacetin.

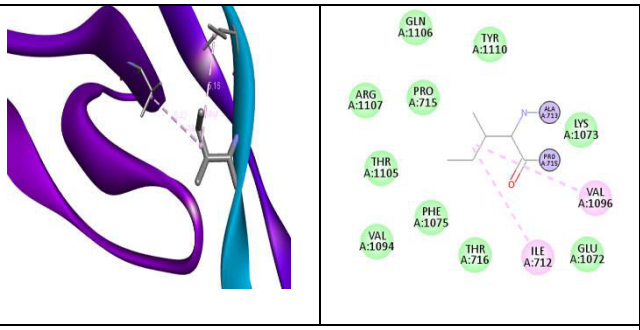


Fig. 10: 3D and 2D interaction between 7DDN and Ethyl cholate.

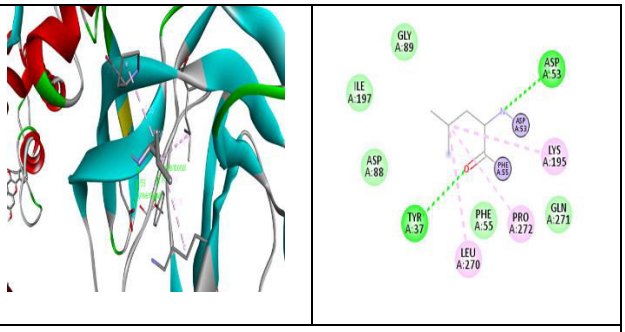


Fig. 11: 3D and 2D interaction between 7DDN and Kaempferol.

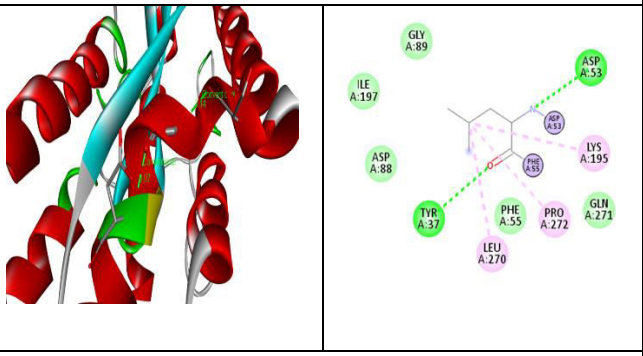


Fig. 12: 3D and 2D interaction between 7DDN and Tangeretin.

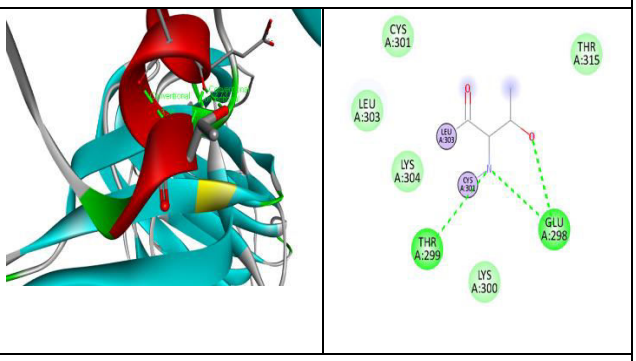


Fig. 13: 3D and 2D interaction between 7DDN and Chalcone.

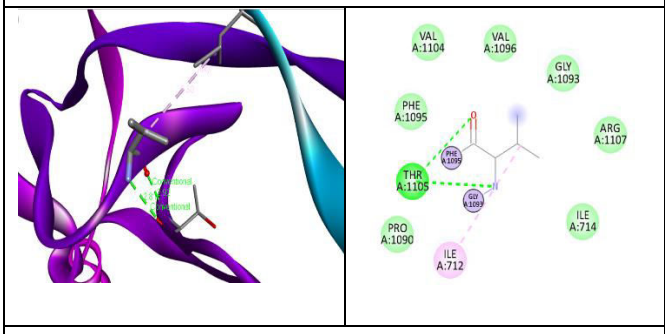


Fig. 14: 3D and 2D interaction between 7DDN and Nobiletin.

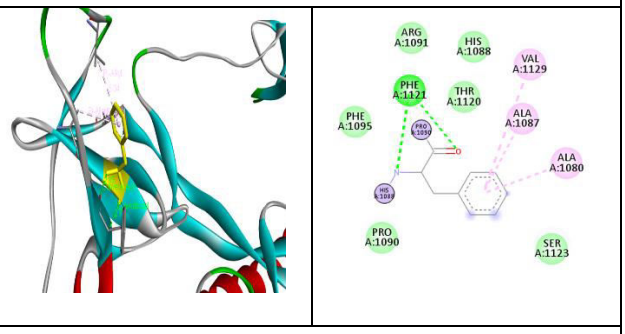


Fig. 15**:** 3D and 2D interaction between 7DDN and Bis (3,5,5-trimethylhexyl) phthalate

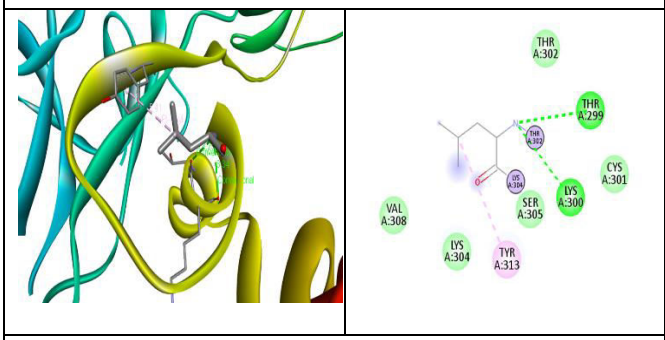


Fig. 16: 3D and 2D interaction between 7DDN and 6-gingerol.

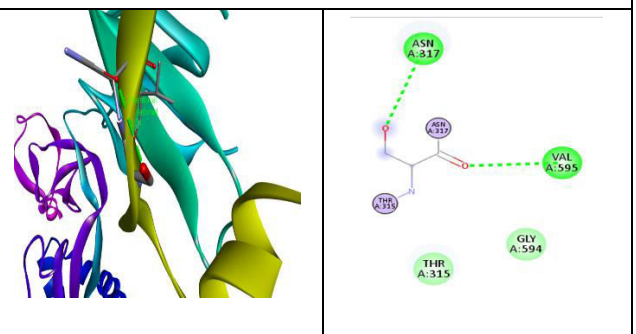


Fig. 17: 3D and 2D interaction between 7DDN and 6-shogaol.

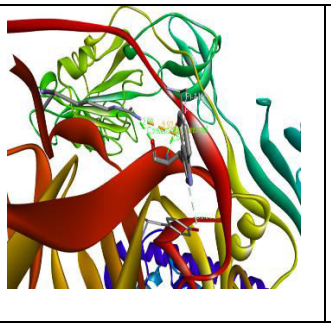
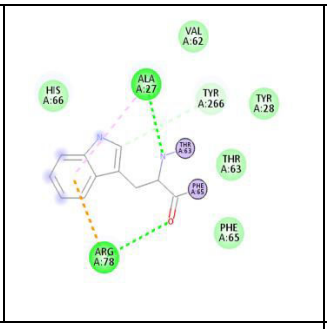



Fig. 18: 3D and 2D interaction between 7DDN and Hydroxychloroquine.

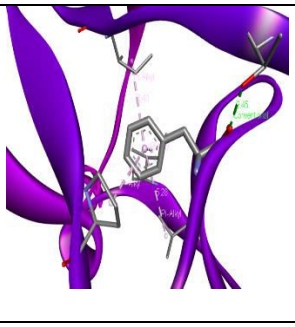
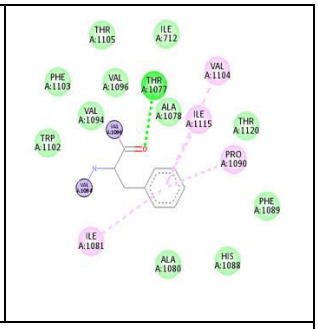



Fig. 19: 3D and 2D interaction between 7DDN and Myristicin.

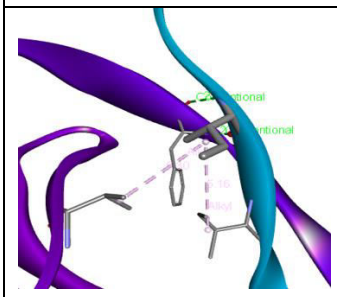
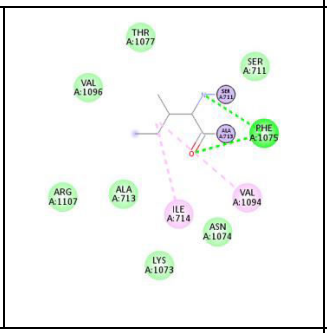



Fig. 20: 3D and 2D interaction between 7DDN and Eugenol.

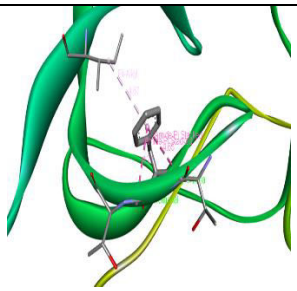
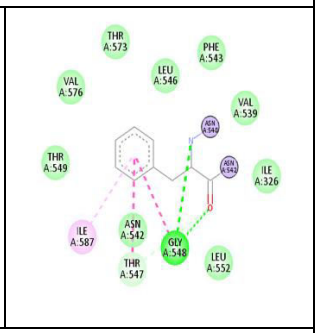



Fig. 21: 3D and 2D interaction between 7DDN and Sinigrin.

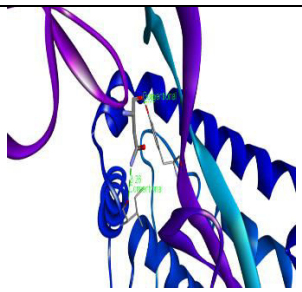
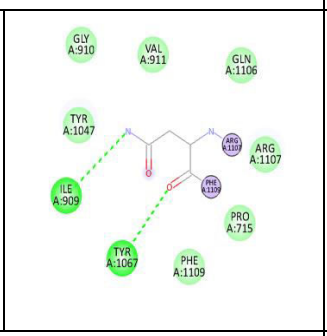



Fig. 22: 3D and 2D interaction between 7DDN and Xanthoangelol.

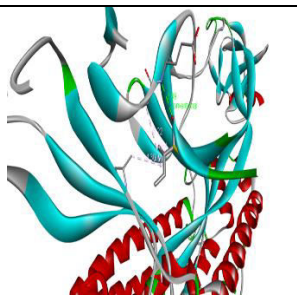
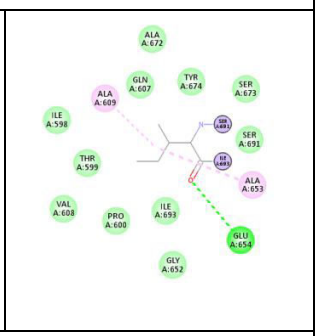



Fig. 23: 3D and 2D interaction between 7DDN and Savinin.

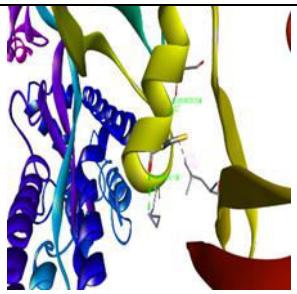
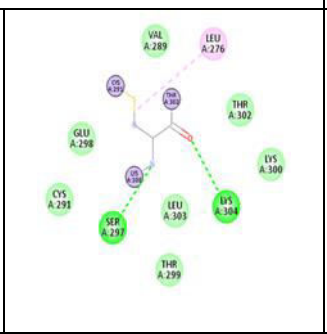



Fig. 24: 3D and 2D interaction between 7DDN and Pristimerin.

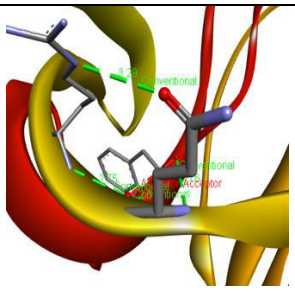
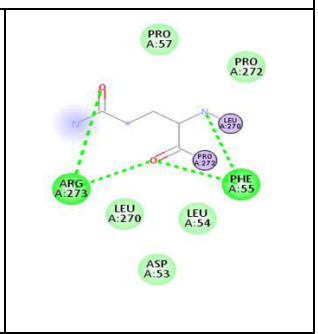



Fig. 25: 3D and 2D interaction between 7DDN and Apigenin.

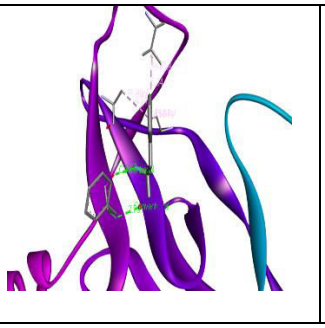
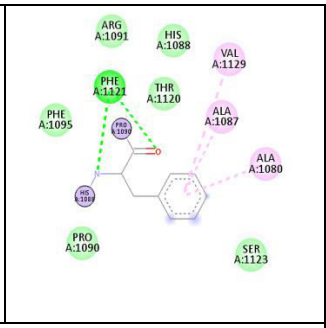



Fig. 26: 3D and 2D interaction between 7DDN and Curcumin.

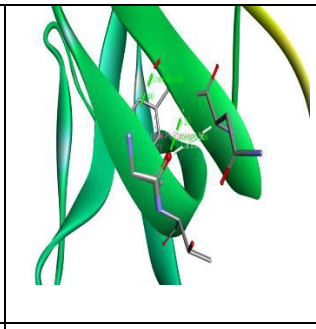
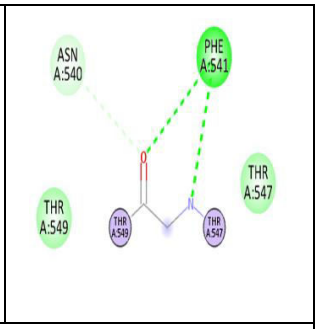



Fig. 27: 3D and 2D interaction between 7DDN and Cryptotanshinone.

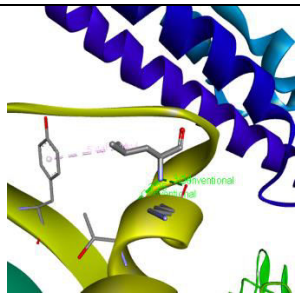
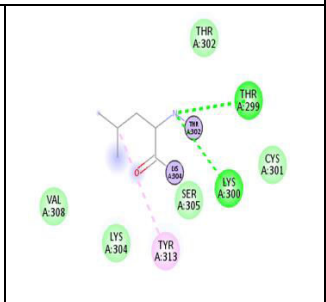



Fig. 28: 3D and 2D interaction between 7DDN and Broussochalcone A.

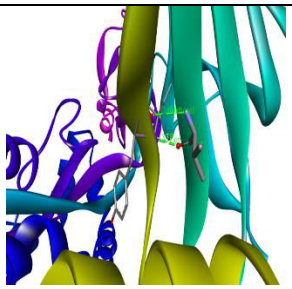
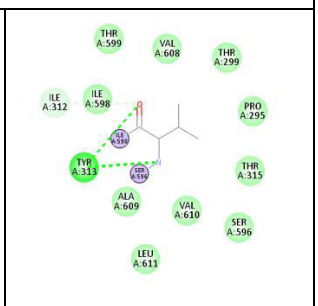



Fig. 29: 3D and 2D interaction between 7DDN and Epigallocatechin.

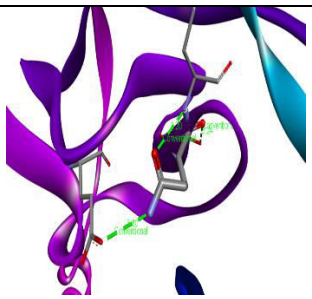
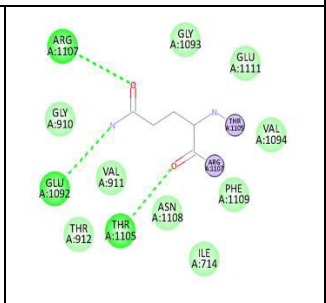



Fig. 30: 3D and 2D interaction between 7DDN and Baicalein.

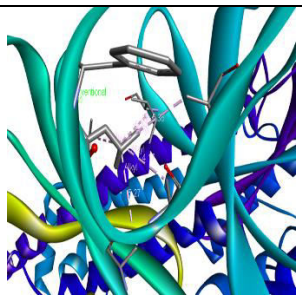
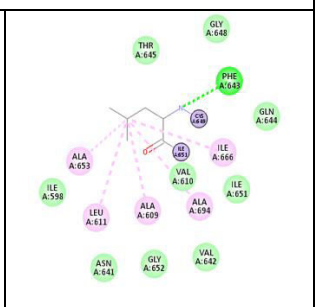



Fig. 31: 3D and 2D interaction between 7DDN and Ellagic acid.

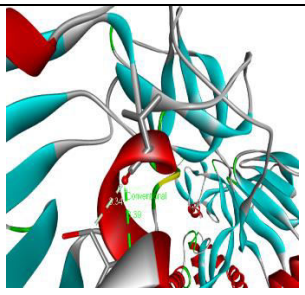
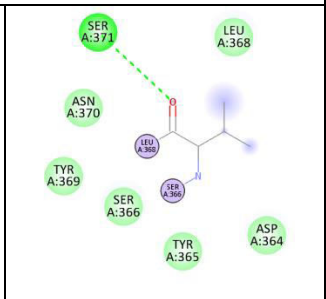



Fig. 32: 3D and 2D interaction between 7DDN and Cinnamamide.

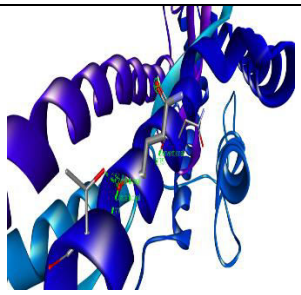
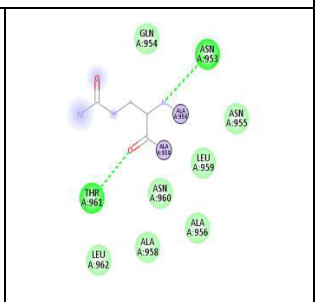



Fig. 33: 3D and 2D interaction between 7DDN and 6,8-Diprenylgenistein.

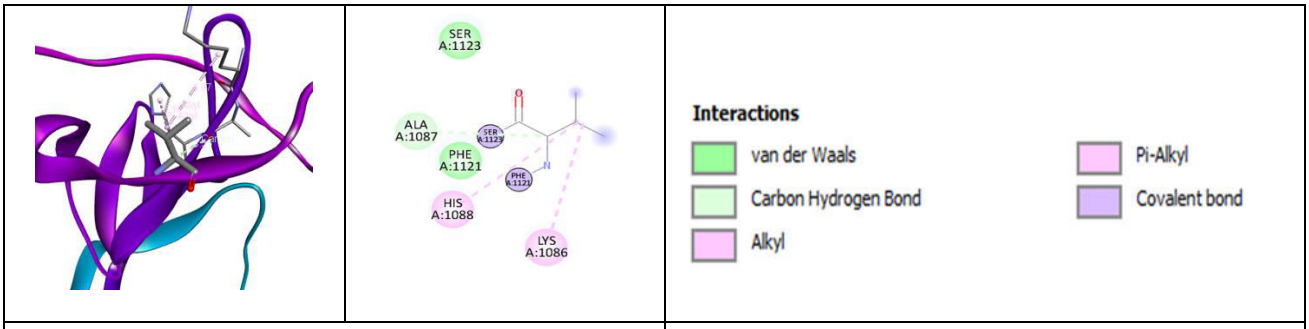


Fig. 34: 3D and 2D interaction between 7DDN and Polygalacin.

NOTE: Colour in the 2D interaction in all picture indicates respective bonds involved in interaction .

5 and considered it as H-bond donors ; (iv) All Nitrogen or Oxygen atoms together less than 10 H-bond acceptors; and (v) The range of molar refractivity should lie between 40 and 130 (Kumar *et al.*, 2020). However, many variables, including pharmacokinetics, can impact a drug's therapeutic efficacy. The flow of drugs into, across, and be out of the body is referred to as pharmacokinetics. The travel of a drug through all the body is called pharmacokinetics, and it has been divided into four phases: absorption, distribution, metabolism, and excretion (ADME) (Akella *et al.*, 2020; Balaji *et al.*, 2020). The Swiss ADME server was used to assess these drugs' ADME prediction, pharmacokinetics, drug-likeness, as well as medicinal chemistry acceptability. ADMET assessment would be required to establish whether or not some drug seems to be ready for clinical testing (Sharma *et al.*, 2020).

Phytochemicals are produced by plants to help them resist diseases caused by fungi, bacteria, and plant viruses, as well as to be ingested by insects and other animals. Long-term health advantages can be obtained by ingesting foods such as fruits, vegetables, grains, legumes, and plant-based beverages, however, there is no possibility of taking vitamins and supplements containing non-nutrient phytochemicals produced from plants which would have the same effect (Mahmoud *et al.*, 2020). Multiple phytochemicals have been found as having bioactivity, either speculative and documented. The consequences of taking a complete plant as medication, although, seem to be unknown because a single species has a vast range of chemicals (Balmeh *et al.*, 2020). Herbal medicines are being employed both as conventional medicine and traditional medicine with said goal for preserving health and/or treating a rare disease (Akella *et al.*, 2020). Despite solid data, the World Health Organization believes that approximately billion people in the world seem to be predominantly dependant on herbal remedies (Sarkar, 2021). In industrial nations, the usage of plant-based components, such as botanical or traditional pharmaceuticals offering alleged health advantages, have been on the rise. Many therapeutic vegetation includes alkaloids, which are bitter-tasting compounds which have been found worldwide yet often hazardous (Kushwaha *et al.*, 2021; Seema *et al.*, 2020). Glycosides comprise potent medications pharmacologically active such as foxglove as well as lily of the hill (Padmini *et al.*, 2020). Medications comprise digoxin but also digitoxin, which together help the heart rhythm thus function effective antihypertensive (Azim *et al.*, 2020). Polyphenols come in a variety of subclasses that play a lot of functions in plant protection towards infections and enemies (Akella *et al.*, 2020). Hormone-mimicking phytosterols including astringent tannins are among them (Omotayo *et al.*, 2021). Terpenes including terpenoids of various types can be found in a range of herbal medicines, as well as resinous

species like conifers. Those having a characteristic odour are used to prevent predators (Dwarka *et al.*, 2020). Spike protein is being studied as a potential subject for novel medication development. Medicinal herbs have indeed been demonstrated to block viral protease (PR), an enzymatic required for the proteolytic cleavage of polyprotein precursors producing proteins required for viral particle formation (Balmeh *et al.*, 2020). The physiological processes, behind plant preparations' antiviral activities, could varied between viruses (Zhang *et al.*, 2020). Furthermore, the opportunities of aqueous extract to enhance human body's intrinsic antiviral protection, especially incorporates a complex immunity, could use overlapping networks (Dwarka *et al.*, 2020). Aside from the immunomodulatory impact, the wide-ranging antiviral feature of medicinal plants has also been fascinating (Kushwaha *et al.*, 2021). The prevailing research literature on pharmaceutical companies' antiviral capabilities has been based on qualitative. Vegetation with antiviral capabilities, for reference, or phytoconstituents evaluated goods somewhat on qualities of recently discovered phytocomponents, represent possibilities (Dwight *et al.*, 2020). When investigating the use of plants to effectively treat viral infections, it is indeed important to keep in mind that most viral immunizations were also made up of regressed or downregulated virions (Muhseen *et al.*, 2020).In this study, we emphasized on numerous phytoconstituents that could be promising as competent pharmacological ingredients in the treatment of SARS-CoV-2 illness, taking into account the antiviral properties of herbal medicines.

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References

Akella M and Malla R. (2020) Molecular modeling and in vitro study on pyrocatechol as potential pharmacophore of CD151 inhibitor. J Molec Graphics Modelling 100: 107681.

Andréa DF. (2021) An overview of the anti-SARS-CoV-2 properties of *Artemisia annua*, its antiviral action, protein-associated mechanisms, and repurposing for COVID-19 treatment, J Integrative Med. 19(5): 375-388.

Arora S, Govind L, Keshav M, Shah S and Yende S. 92020) Identification of potential flavonoid inhibitors of the SARS-CoV-2 main protease 6YNQ: A molecular docking study. Digital Chinese Med. 3(4): 239-248.

Azim KF, Sheikh RA, Anik B, Khan MMR, Deb A and Saneya RS. (2020) Screening and druggability analysis of some plant metabolites against SARS-CoV-2: An integrative computational approach. Informatics Med Unlocked 20: 100367.

Balaji GV, Deepthi R, Annu J, Jayadharini JP and Tharanikkarasu K. (2020) *In silico* pharmacokinetic and molecular docking studies of natural flavonoids and synthetic indole chalcones against essential proteins of SARS-CoV-2. Eur J Pharmacol. 886: 173448,

Balmeh N, Samira M, Niloofar M anjd Anasik K. (2020) Predicted therapeutic targets for COVID-19 disease by inhibiting SARS-CoV-2 and its related receptors Informatics Med Unlocked 20: 100407,

Berretta AA, Marcelo ADS, José MCC and David DJ. (2020) Propolis and its potential against SARS-CoV-2 infection mechanisms and COVID-19 disease: Running title: Propolis against SARS-CoV-2 infection and COVID-19. Biomed Pharmacother. 131: 110622.

Chidambaram SK, Daoud A, Saud A, Surendrakumar R and Idhayadhulla A. (2020) In silico molecular docking: Evaluation of coumarin based derivatives against SARS-CoV-2. J Infection Public Hlth. 13(11): 1671-1677.

Dwarka D, Clement A, John JM, Mahmoud ES and Himansu B. (2020) Identification of potential SARS-CoV-2 inhibitors from South African medicinal plant extracts using molecular modelling approaches. South African J Botany 133: 273-284.

Dwight LM, Ariane S, Ulrike S, Stefan L and Cord N. (2020) Candidate drugs against SARS-CoV-2 and COVID-19. Pharmacol Res. 157: 104859.

Gurung AB, Mohammad AA, Joongku L, Mohammad AF and Khalid MAA. (2020) Unravelling lead antiviral phytochemicals for the inhibition of SARS-CoV-2

Mpro enzyme through in silico approach. Life Sci. 255: 117831.

Gurung AB, Mohammad AA, Joongku L, Mohammad AF and Khalid MAA. (2020) Structure-based virtual screening of phytochemicals and repurposing of FDA approved antiviral drugs unravels lead molecules as potential inhibitors of coronavirus 3C-like protease enzyme. J King Saud Univ - Science 32(6): 2845-2853.

Jayalakshmi V, Albin J,k Willayat YW, Suguru PR, Kishore KJ, Reddy HP and Kandimalla R. (2020) SARS-CoV-2 pathophysiology and assessment of coronaviruses in CNS diseases with a focus on therapeutic targets. Biochim Biophys Acta (BBA) Molec Basis f Disease 1866(10): 165889.

Kanchanok K, Yong P, Kamol S and Prachya K. (2020) Molecular modelling investigation for drugs and nutraceuticals against protease of SARS-CoV-2. J Molec Graphics Modelling 101: 107717.

Khare P, Sahu U, Pandey SC and Samant M. (2020) Current approaches for target-specific drug discovery using natural compounds against SARS-CoV-2 infection. Virus Res. 290: 198169.

Kumar N, Mishra B, Adeel M, Mohammad A and Shahid MM. (2020) Integrative network biology framework elucidates molecular mechanisms of SARS-CoV-2 pathogenesis. iScience 23(9): 101526.

Kuppuswamy K, Subramaniam S and Balasubramanian R. (2020) 1,2,4 triazolo(1,5-a) pyrimidin-7-ones as novel SARS-CoV-2 Main protease inhibitors: In silico screening and molecular dynamics simulation of potential COVID-19 drug candidates. Biophys Chem. 267: 106478.

Kushwaha PP, Singh AK, Prajapati SK, Shuaib M, Gupta S and Kumar S. (2021) Phytochemicals present in Indian ginseng possess potential to inhibit SARS-CoV-2 virulence: A molecular docking and MD simulation study. Microb Pathogen. 157: 104954.

Li C, Lin W and Linzhu R. (2020) Antiviral mechanisms of candidate chemical medicines and traditional Chinese medicines for SARS-CoV-2 infection. Virus Res. 286: 198073.

Mahmoud AA, Ibrahim AHM, Taha AA, Hussien EAA, Tarik BA, Hesham MR, Seedi EI, Pare PW, Efferth T and Hegazy MEF. (2020) In silico drug discovery of major metabolites from spices as SARS-CoV-2 main protease inhibitors. Computers Biol Med. 126: 104046.

Mubarak AA, Ali A, Alhumaidi BA, Manal AA and Safar M A. (2020) Structure-based virtual screening and molecular dynamics of phytochemicals derived from Saudi medicinal plants to identify potential COVID-19 therapeutics. Arabian J Chem. 13(9): 7224-7234.

Muhseen ZT, Alaa RH, Halah MHAH, Muhammad TQ and Guanglin L. (2020) Promising terpenes as SARS-CoV-2 spike receptor-binding domain (RBD) attachment inhibitors to the human ACE2 receptor: Integrated computational approach. J Molec Liquids 320: 114493.

Nag A, Paul S, Banerjee R and Kundu R. (2021) In silico study of some selective phytochemicals against a hypothetical SARS-CoV-2 spike RBD using molecular docking tools. Computers Biol Med. 137: 104818.

Omotayo OO, Joseph MA, Folasade MA, Alfredo JS, Olatomide AF, Charles OA and Gildardo R. (2021) Computational screening of phytochemicals from three medicinal plants as inhibitors of transmembrane protease serine 2 implicated in SARS-CoV-2 infection. Phytomed Plus 1(4): 100135.

Padmini R, Maheshwari VU, Saravanan P, Lee KW, Razia M, Mona S, Alwahibi B, Ravindran, Elshikh MS, Kim YO, Kim H and Kim HJ. (2020) Identification of novel bioactive molecules from garlic bulbs: A special effort to determine the anticancer potential against lung cancer with targeted drugs. Saudi J Biol Sci. 27(12): 3274-3289.

Salvatore VG, Edoardo N, Nunzio I, Antonio S, Francesco C, Claudia M, Maria SM, Giuseppe R and Antonella S. (2021) Interaction of selected terpenoids with two SARS-CoV-2 key therapeutic targets: An in silico study through molecular docking and dynamics simulations. Computers Biol Med. 134: 104538.

Sarkar D. (2021) Molecular docking study to Identify potent fungal metabolites as inhibitors against SARS-CoV-2 main protease enzyme. Int J Pharm Bio Sci. 12(2): 78-85.

Sarkar D. (2022) In-silico research to screen various phytochemicals as potential therapeutics against beta glucan synthase enzyme from black fungus endangering Covid Patients in India. Inter J Zool Invest. 8(1): 320-337.

Seema AK, Nagarajan SK, Veena R, Velusamy P, Periyar SS and Thirumurthy M. (2020) Computational evaluation of major components from plant essential oils as potent inhibitors of SARS-CoV-2 spike protein. J Molec Struct. 1221: 128823.

Sharma N, Mehanathan M, Prasad A and Prasad M. (2020) Genomics approaches to synthesize plant-based biomolecules for therapeutic applications to combat SARS-CoV-2. Genomics 112(6): 4322-4331.

Venkateshan M, Muthu M, Suresh J and Kumar RR. (2020) Azafluorene derivatives as inhibitors of SARS CoV-2 RdRp: Synthesis, physicochemical, quantum chemical, modeling and molecular docking analysis, J Molec Struct. 1220: 128741.

Víctor JCR, Rebeca IM, Jose MPP, Concepción R and

Lucia MR. (2020) SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev. 54: 62-75.

Wathore R, Gupta A, Bherwani H and Labhasetwar N. (2020) Understanding air and water borne transmission and survival of coronavirus: Insights and way forward for SARS-CoV-2. Sci Total Environ. 749: 141486.

Zhang Y, Liu X, Ruan J, Zhuang X, Zhang X and Li Z. Phytochemicals of garlic: Promising candidates for cancer therapy. Biomed Pharmacother. 123: 109730.