MOLECULAR DOCKING ANALYSIS OF SOME PHYTOCHEMICALS ON TWO SARS-COV-2 TARGETS

POTENTIAL LEAD COMPOUNDS AGAINST TWO TARGET SITES OF SARS-COV-2 OBTAINED FROM PLANTS

Amaka Ubani[1], Francis Agwom[2], oluwatoyin RuthMorenikeji[1] Shehu Nathan[3], Pam Luka[4], Arinze Umera[1], Usal Uma[1]r, Simeon Omale[4], Nnaemeka Emmanuel Nnadi, John Chineye Aguiyi[1]

1. African Centre of Excellence in Phytomedicine research and Development, University of Jos, Jos, Plateau State, Nigeria
2. Department of pharmaceutical & Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Jos, Nigeria
3. Biotechnology Centre, National Veterinary Research Institute, Vom. Nigeria
4. Department of Pharmacology, Faculty of Pharmaceutical Sciences, University of Jos, Jos, Plateau State
5. Department of Microbiology, Faculty of Natural and Applied Sciences, Plateau State University, Bokkos, Nigeria

* Correspondence: eennadi@gmail.com; Tel.: (+2348068124819)

Abstract:

COV spike (S) glycoprotein and M^{pro} are two key targets that have been identified for vaccines and drug development against the COVID-19 disease. Virtual screening of some compounds of plants origin that have shown antiviral activities were carried out on the two targets, 6lu7 and 6vsb by docking with the PyRx software. The binding affinities were compared with other compounds and drugs already identified as potential ligands for 6lu7 and 6vsb as well as Chloroquine and hydroxychloroquine. The docked compounds with best binding affinities were also filtered for drug likeness using the SwissADME and PROTOX platforms on the basis of Physicochemical properties and toxicity respectively. The docking results revealed that scopodulcic acid and dammarenolic acid had the best binding affinity on the s-glycoprotein and M^{pro} protein targets respectively. Silybinin also demonstrated a good binding affinity to both protein targets making it a potential candidate for further evaluation as repurposed candidate for SARS COV2 with likelihood of having a multitarget activity.

Keywords: *Covid-19, s-glycorotein, Mpro, Virtual screening*

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), family *Coronaviridae*, genus *Betacoronavirus*, is spreading widely in China, causing coronavirus disease 2019 (COVID-19)(1). Since 2003, three Coronaviruses have been associated with pneumonia, the first was severe acute respiratory syndrome coronavirus (SARS-CoV)(2) which affected 8,098 people causing 774 deaths between 2002 and 2003(3), the second was Middle-East respiratory syndrome coronavirus (MERS-CoV)(4) which affected 27 countries and infecting a total of 2,494 individuals and claiming 858 lives(4). SARS-CoV-2 is a human pathogen which has been declared a global pandemic by the World Health Organisation (5). SARS-CoV and SARS-CoV-2 are closely related and originated in bats, who most likely serve as reservoir host for these two viruses (4). To date, no therapeutics or vaccines are approved against any human-infecting coronaviruses(4).

The entry into the host cell by the Coronaviruses is usually mediated by spike (S) glycoprotein (4). This glycoprotein interacts with the angiotensin-converting enzyme 2 (ACE2) enabling the virus penetration into the host. The main protease (M^{pro} also known as $3CL^{pro}$) is one of the best characterized drug targets among coronaviruses (6). The protease enzyme is essential for processing the polyproteins that are translated from the viral RNA(7). For this study, these two drug targets were selected for SARS-CoV-2 using plant based compounds screened against them.

Therefore, potent inhibitors of these two targets will be able to interfere with the SARS COV-2 replication process and thus serves as potential drugs for the management of the COVID-19. Hence, this work is aimed at identifying other

potential lead compounds of plant origin that can serve as candidates for testing against the SARS COV2 virus.

.

.

2. Results

A library of 22 compounds of plant origin known to have antiviral activity were obtained from Pubchem data base. Though the compounds are chemically diverse they consist of largely flavonoids and terpenes. Some compounds from the citrus family made were found among the library, though they could not make it among the top six selected compounds for each target demonstrated some good binding affinities.

Most of the compounds has showed similar binding affinities to the selected protein targets (6lu7 and 6vsb) compared to the training sets of known ligands to the selected targets. (See table 1)

Table 1. Comparison of Binding affinities of library to some known ligands and the co-crystalised ligand

Protein target	Co crystalized ligand	Ligands(drugs) used in treatment	Phytochemicals
6LU7		Remesivir -7.1	Dammarenolic acid -7.2
		Favipiravir -5.3	Quercetin -7.1
		Chloroquine -5.2	Solanidine -7.0
			Silymarin -6.9
			Silvestrol -6.7
			Shikonin -6.6
6VSB		Remesivir -7.3	Scopadulcic acid -9.6
		Favipiravir -5.3	Baicalin -9.4
		Chloroquine -5.2	Legalon -9.2
			Solanidine -9.1
			Naringenin -9.0
			Oleanane -9.0
			Silymarin -8.6

However, the top six compounds with most favourable binding affinity were selected for each of the targets.

The outcome of the binding affinities of the selected compounds on the 6lu7 and 6vbs targets are presented in **Table 2 and Table 3** respectively.

TABLE 2 binding affinities of the compounds on the 6vsb and their Interaction with the binding site

S/N	Ligands	Binding Affinity (Kcal/Mol)	Hydrogen Bond Interaction	Hydrophobic Bond Interaction with Residues

			with Residues	
1.	Scopadulcic Acid	-9.6	GLN B: 913	TYR C:904, GLY B:1093, VAL B:911, ARG B: 1107, ASN B:907, THR B:912, ASN B:1119, GLN B:1113, GLY B: 910, GLN B:1106, GLU B:1092, PHE A:1121, ARG A:1091
2.	Baicalin	-9.4	ARG B:1039, ARG A:1039, ARG C:1039, ALA B:1020, ASN C:1023	ALA C:1026, LEU B:1024, GLN C:784, SER C:1030, ASP B:1041, LEU C:1024, THR C:1027, PHE B:1042, PHE C:1042, PHE A:1042, THR B:1027, SER B:1021, GLU C:780.
3.	Sylibinin	-9.2	GLU A:954, ARG B:765	GLU A:1017, ARG A:1014, ALA B:766, LYS B:776, LYS A:947, LEU A:948, PRO A:728, VAL A:951, ILE A:1018, ALA B:766, GLN A:957, GLN B:762, GLN A:1010, ILE A:1013, LEU B:1012, ARG B:1019, GLU B:773.
4.	Solanidine	-9.1		TYR A:369, TYR C:489, ARG C:454, PRO C:491, TYR C:421, ASN C:460, LEU C:461
5.	Naringenin	-9.0	GLU C:1092, ARG C:1107, ASN C:1108, GLY C:910, ILE C:909	ASN C:907, THR C:912, GLN C:1113, ARG B:1091, GLU B:1092, GLY C:1093, GLN C:1106, TYR A:904
6.	Oleanane	-9		LEU A:1141, ASP C:1118, LEU C:1141, PRO A:1140, ASP A:1118, THR A:1117, THR B:1116, ASP B:1118, PRO B:1140, GLU B:1144, ASP A:1139, GLU A:1144

TABLE 3 binding affinities of the compounds on the 6LU7 and their Interaction with the binding site

S/N	Ligands	Binding Affinity (Kcal/Mol)	Hydrogen Bond Interaction	Hydrophobic Bond Interaction with Residues

			with Residues	
1.	Dammarenolic acid	-7.2	THR A: 111, GLN A: 110, GLN A: 107	VAL A:104, ARG A: 105, ILE A: 106, THR A: 292, PHE A: 112, GLN A: 127, ASP A: 295, ASN A: 152, PHE A: 294, PHE A: 294, PHE A: 8, ASP A: 153, SER A: 158, ILE A: 152
2.	Quercetin	-7.1	------	-----
3.	Solanidine	-7.0	-------	VAL A: 104, LYS A: 102, SER A: 158, ASP A: 153, ILE A: 152, ASN A: 151, ASN A: 151, PHE A: 8, ARG A: 105, GLN A: 107, ILE A: 106
4.	Silybinin	-6.8	ARG A: 105, ASP A: 176	ASN A: 180, GLU A: 178, PHE A: 103, VAL A: 104, SER A: 158, ASN A: 151, THR A: 111, GLN A: 110, ILE A: 106, GLN A: 107
5.	Loliolide	-6.7	------	------
6.	Shikonin	-6.6	THR A: 111, SER A: 158	PHE A: 294, PHE A: 8, GLN A: 110, ILE A: 106, ASN A: 151, PHE A: 112, LYS A: 102, ASP A: 153, VAL A: 104

The binding affinities of the top six compounds on the 6vsb target are comparable to each other that is they all lie within a close range of 9 to 9.6 kcal/mol indicating that they might likely have equal or comparable potential as lead compounds for the 6vsb spike glycoprotein.

Table 4. Comparison of the calculated cLog P values for the selected compounds

S/N	Compound	SwisADME cLog P	Molinspiration cLog p	Mean calculated cLog P
1.	Scopodulcic acid	4.57	5.01	4.79

2.	Baicalin	0.22	0.55	0.77
3.	Sylibinin	1.59	1.47	3.06
4.	Solanidine	5.01	5.93	5.47
5.	Naringenin	1.84	2.12	1.98
6.	Oleanane	8.57	8.86	8.72
7.	Dammarenolic acid	6.74	8.08	7.41
8.	Quercetin	1.23	1.68	1.46
9.	Loliolide	1.53	1.84	1.69
10.	Shikonin	2.08	2.02	2.05

clog P = octanol/water coffecient

One of the compounds sylibinin (8)is an FDA approved drug, which showed up as active on both MPro and spike glycoprotein will make a good candidate of repurposing. Finding Quercetin as a potential inhibitor of the Mpro Protein (6flu7) of the SARS COV2 corresponds with an earlier report(9)

Looking at the the cLog P of the compounds, there was no correlation observed between the lipophilicity and the interaction with the receptors. However, for the compounds acting on 6lu7 (S/N 3,4,7,8,9 and 10 in Table 4), interaction with the receptor is correlated with low lipophilicity with the exception of solanidine and Dammarenolic acid that are have high cLogP values. Though both compounds also use their polar functional groups in interacting with the receptor. Bacailin and Naringenin showed good hydrogen bond interaction with the 6vsb receptor due to their polarity.

Filtering the compounds for drug likeness on the basis of Linpinski's and/or Veber's rule showed that all the compounds have drug like properties except baicalin which failed the two filtering scales applied (Table 5). This implies that baicalin is not worth considering further without any structural modification.

Table 5. Drug likeness

S/N	Compound	Mol. Wt[a](g/mol)	TPSA[b]	HBA[c]	HBD[d]	RB[e]	cLogP[f]	Lipinski filter	Veber filter
1.	Scopodulcic acid	438.56	80.67	5	1	4	4.79	+	+
2.	Baicalin	446.36	187.12	11	6	4	0.77	-	-
3.	Sylibinin	482.44	155.14	10	5	4	3.06	+	-
4.	Solanidine	397.64	23.47	2	1	0	5.47	+	-
5.	Naringenin	272.25	86.99	5	3	1	1.98	+	+
6.	Oleanane	412.75	0.00	0	0	0	8.72	+	+
7.	Dammarenolic acid	458.72	57.53	3	2	1	7.41	+	+
8.	Quercetin	302.24	131.36	7	5	1	1.46	+	+
9.	Loliolide	196.24	46.53	3	1	0	1.69	+	+
10.	Shikonin	288.3	94.83	5	3	3	2.05	+	+

[a]Mol. Wt.: Molecular weight
[b]TPSA: Total Polar Surface Area
[c]No. HBA: Number of hydrogen bond acceptors
[d]No. HBD: Number of hydrogen bond donors
[e]No. RB: Number of rotatable bonds
[f]Mean clog P: Mean of calculated log P values

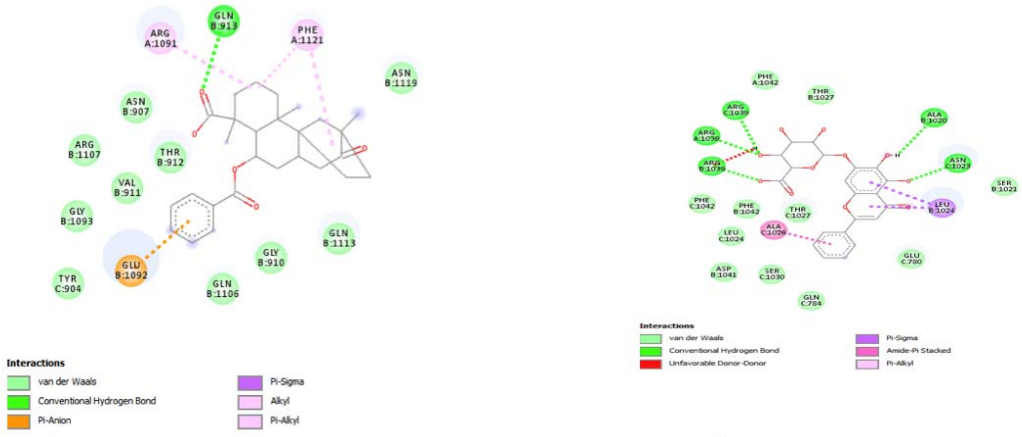


Figure 1. Best Binding pose and Interaction of (a) Scopodulcic acid and (b) Baicalin on the 6vsb protein.

Table 6. Predicted Toxicity Profile of the compounds using PROTOX II

S/N	Compound	Hepatotoxicity	ImmunoToxicity	Carcinogenicity	Mutagenicity	Cytoxicity	Possible Toxicity Targets
1.	Scopodulcic acid	-	++	-	-	-	AR, AO, PGS
2.	Baicalin	--	--	+	-	--	AO, PGS
3.	Sylibinin	--	++	-	--	--	PGS
4.	Solanidine	--	++	-	--	+	AR, PGS
5.	Naringenin	-	--	-	--	+	AR, PGS
6.	Oleanane	--	--	++	--	--	
7.	Dammarenolic acid	-	-	--	--	--	AR, AO PGS
8.	Quercetin	-	+	--	-	--	AO, AR, PGS
9.	Loliolide	-	+	--	-	--	AO, PGS
10.	Shikonin	-	-	++	-	+	PG

Key: -- inactive, - less inactive, + Active and ++ More active

AR = Androgen Receptor, AO = Amine Oxidase A & PGS=Prostaglandin G/H Synthase 1

The predicted toxicity profile of the selected compounds shows that all the compounds are likely to be relatively safe. Which makes them good potential candidates for anti-infectives because the chances of achieving selective toxicity is high. Baicalin is most likely the safest.

Discussion

Two compounds among the top six selected for each target, solanidine and sylibinin were observed to have good binding affinity on both the 6vsb and the 6flu7. This make them potential multitarget acting inhibitors on the SARS-COV2. Solanidine is a Steroidal glycoalkaloids found in potatoes(10), although toxic to humans and animals, Solanidine has been reported to be effective against herpes viruses (HSV), herpes genitalis and herpes zoster(11) Its acivity against HSV is atttibuted to the presence of a sugar moiety(12). In silico method of drug screening using PROTOX II, showed that Solanidine is cytotoxic and immunotoxic. Prototox II is a cost and time conservative approach of testing and determining the toxicity of a compound to be considered a drug of choice(13). It incorporates molecular similarity, pharmacophores, fragment propensities and machine-learning models for the prediction of various toxicity endpoints; such as acute toxicity, hepatotoxicity, cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, adverse outcomes pathways (Tox21) and toxicity targets(13)

A safe drug must not be toxic to its host target. Based on the Protox II evaluation of Toxicity, Dammarenolic acid emerges as the compound of choice with the least toxicity. Dammarenolic acid have been reported as effective antiviral agents Dammarenolic acid potently inhibited the in vitro replication of other retroviruses,

including Simian immunodeficiency virus and Murine leukemic virus in vector-based antiviral screening studies and has been proposed as a potential lead compound in the development of anti-retrovirals. (14) The compound is cytotoxic and demonstrate potential against respiratory syncytial virus(15). We therefore propose that the evaluation of Dammarenolic acid will hold the key to COVID19 drug considering its drugability and low toxicity.

This study proposes a potential re-purposing of silybinin for the management of COVID19 diseases. Silybinin(Silymarin) possesses potent antiviral activities against numerous viruses, particularly hepatitis C virus (HCV)(16, 17) It has been reported to have activities against a wide range of viral groups including flaviviruses (hepatitis C virus and dengue virus), togaviruses (Chikungunya virus and Mayaro virus), influenza virus, human immunodeficiency virus, and hepatitis B virus(16). Silymarin inhibits HCV in both *in vitro* and *in vivo* by inhibiting HCV entry, RNA synthesis, viral protein expression and infectious virus production; in addition it also acts by blocking of the virus cell-to-cell spread(18). As an FDA approved drug for the management of Hepatitis disease. In silico analysis of this drugs in this study has shown that it has acitivity against SAR COV 2 S-glycoprotein and proteas(M^{pro}) targets making it a drug to be considered with multi-target ability in the management of this disease.

4. Materials and Methods

Plant Compounds with antiviral activities were mined from PubChem data base (https://pubchem.ncbi.nlm.nih.gov/). Two proteins including the main protease (6lu7) and the crystal structure of COVID-19 main protease(19) in complex with an inhibitor N3 and the Spike glycoprotein, N-ACETYL-D-GLUCOSAMINE (6vsb10.1126/science.abb2507) were downloaded from the protein database (PDB). The proteins were prepared using Discovery studio (version)(20) and a rigid docking scoring function was carried out using PyRx software(21). The results of the dock poses were visualized using Discovery Studio.

The Physicochemical properties and druggability of selected compounds were predicted using SwissADME(22) and Molinspiration(23) platforms and their predicted toxicity profile also compared using the PROTOX platform(24)

5. Conclusions

From the 22 phyto-compounds that were virtually screened, Scopodulcic acid and Dammarenolic acid showed the best binding energies with the Spike glycoprotein (6vsb) and the M^{pro} (6flu7) respectively. This makes them potential lead compounds for development into candidates against the SARS COV 2. Furthermore, the FDA approved drug silybinin (Legalon) with good binding affinity on the two targets can be evaluated further for possible repurposing against the SARS COV2 virus.

Funding: This research received no external funding

Conflicts of Interest: The authors declare no conflict of interest

Reference:

1. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. 2020:1-4.
2. Drosten C, Günther S, Preiser W, Van Der Werf S, Brodt H-R, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. 2003;348(20):1967-76.

3. Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler DJC. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. 2020.
4. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RAJNEJoM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. 2012;367(19):1814-20.
5. Neher RA, Dyrdak R, Druelle V, Hodcroft EB, Albert JJSMW. Potential impact of seasonal forcing on a SARS-CoV-2 pandemic. 2020;150(1112).
6. Anand K, Ziebuhr J, Wadhwani P, Mesters JR, Hilgenfeld RJS. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. 2003;300(5626):1763-7.
7. Hilgenfeld RJTFj. From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. 2014;281(18):4085-96.
8. Ferenci P, Scherzer TM, Kerschner H, Rutter K, Beinhardt S, Hofer H, et al. Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to pegylated interferon/ribavirin therapy. 2008;135(5):1561-7.
9. Chen L, Li J, Luo C, Liu H, Xu W, Chen G, et al. Binding interaction of quercetin-3-β-galactoside and its synthetic derivatives with SARS-CoV 3CLpro: Structure–activity relationship studies reveal salient pharmacophore features. 2006;14(24):8295-306.
10. Ginzberg I, Tokuhisa JG, Veilleux REJPR. Potato steroidal glycoalkaloids: biosynthesis and genetic manipulation. 2009;52(1):1-15.
11. Friedman M, McDonald GM, Filadelfi-Keszi MJCRiPS. Potato glycoalkaloids: chemistry, analysis, safety, and plant physiology. 1997;16(1):55-132.
12. Thorne H, Clarke G, Skuce RJAr. The inactivation of herpes simplex virus by some Solanaceae glycoalkaloids. 1985;5(6):335-43.
13. Banerjee P, Eckert AO, Schrey AK, Preissner RJNar. ProTox-II: a webserver for the prediction of toxicity of chemicals. 2018;46(W1):W257-W63.
14. Esimone CO, Eck G, Nworu CS, Hoffmann D, Überla K, Proksch PJP. Dammarenolic acid, a secodammarane triterpenoid from Aglaia sp. shows potent anti-retroviral activity in vitro. 2010;17(7):540-7.
15. Esimone C, Eck G, Duong T, Überla K, Proksch P, Grunwald TJDP-AIJoPS. Potential anti-respiratory syncytial virus lead compounds from Aglaia species. 2008;63(10):768-73.
16. Liu C-H, Jassey A, Hsu H-Y, Lin L-TJM. Antiviral Activities of Silymarin and Derivatives. 2019;24(8):1552.
17. Polyak SJ, Ferenci P, Pawlotsky JMJH. Hepatoprotective and antiviral functions of silymarin components in hepatitis C virus infection. 2013;57(3):1262-71.
18. Wagoner J, Negash A, Kane OJ, Martinez LE, Nahmias Y, Bourne N, et al. Multiple effects of silymarin on the hepatitis C virus lifecycle. 2010;51(6):1912-21.
19. 10.2210/pdb6LU7/pdb.
20. Biovia DSJSD. Discovery Studio Modeling Environment Release 2017, Dassault Systemes. 2016.

21. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Chemical biology: Springer; 2015. p. 243-50.
22. Daina A, Michielin O, Zoete VJSr. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. 2017;7:42717.
23. Jarrahpour A, Motamedifar M, Zarei M, Youssoufi M, Mimouni M, Chohan Z, et al. Petra, osiris, and molinspiration together as a guide in drug design: predictions and correlation structure/antibacterial activity relationships of new N-Sulfonyl monocyclic β-lactams. 2010;185(2):491-7.
24. Drwal MN, Banerjee P, Dunkel M, Wettig MR, Preissner RJNar. ProTox: a web server for the in silico prediction of rodent oral toxicity. 2014;42(W1):W53-W8.

Table 1. Comparison of Binding affinities of library to some known ligands and the co-crystalised ligand

Protein target	**Co crystalized ligand**	**Ligands(drugs) used in treatment**	**Phytochemicals**
6LU7		Remesivir -7.1	Dammarenolic acid -7.2
		Favipiravir -5.3	Quercetin -7.1
		Chloroquine -5.2	Solanidine -7.0
			Silymarin -6.9
			Silvestrol -6.7
			Shikonin -6.6
6VSB		Remesivir -7.3	Scopadulcic acid -9.6
		Favipiravir -5.3	Baicalin -9.4
		Chloroquine -5.2	Legalon -9.2
			Solanidine -9.1
			Naringenin -9.0
			Oleanane -9.0
			Silymarin -8.6

TABLE 2 binding affinities of the compounds on the 6vsb and their Interaction with the binding site

S/N	Ligands	Binding Affinity (Kcal/Mol)	Hydrogen Bond Interaction with Residues	Hydrophobic Bond Interaction with Residues
1.	Scopadulcic Acid	-9.6	GLN B: 913	TYR C:904, GLY B:1093, VAL B:911, ARG B: 1107, ASN B:907, THR B:912, ASN B:1119, GLN B:1113, GLY B: 910, GLN B:1106, GLU B:1092, PHE A:1121, ARG A:1091
2.	Baicalin	-9.4	ARG B:1039, ARG A:1039, ARG C:1039, ALA B:1020, ASN C:1023	ALA C:1026, LEU B:1024, GLN C:784, SER C:1030, ASP B:1041, LEU C:1024, THR C:1027, PHE B:1042, PHE C:1042, PHE A:1042, THR B:1027, SER B:1021, GLU C:780.
3.	Sylibinin	-9.2	GLU A:954, ARG B:765	GLU A:1017, ARG A:1014, ALA B:766, LYS B:776, LYS A:947, LEU A:948, PRO A:728, VAL A:951, ILE A:1018, ALA B:766, GLN A:957, GLN B:762, GLN A:1010, ILE A:1013, LEU B:1012, ARG B:1019, GLU B:773.
4.	Solanidine	-9.1		TYR A:369, TYR C:489, ARG C:454, PRO C:491, TYR C:421, ASN C:460, LEU C:461
5.	Naringenin	-9.0	GLU C:1092, ARG C:1107, ASN C:1108, GLY C:910, ILE C:909	ASN C:907, THR C:912, GLN C:1113, ARG B:1091, GLU B:1092, GLY C:1093, GLN C:1106, TYR A:904
6.	Oleanane	-9		LEU A:1141, ASP C:1118, LEU C:1141, PRO A:1140, ASP A:1118, THR A:1117, THR B:1116, ASP B:1118, PRO B:1140, GLU B:1144, ASP A:1139, GLU A:1144

TABLE 3 binding affinities of the compounds on the 6LU7 and their Interaction with the binding site

S/N	Ligands	Binding Affinity (Kcal/Mol)	Hydrogen Bond Interaction with Residues	Hydrophobic Bond Interaction with Residues
1.	Dammarenolic acid	-7.2	THR A: 111, GLN A: 110, GLN A: 107	VAL A:104, ARG A: 105, ILE A: 106, THR A: 292, PHE A: 112, GLN A: 127, ASP A: 295, ASN A: 152, PHE A: 294, PHE A: 294, PHE A: 8, ASP A: 153, SER A: 158, ILE A: 152
2.	Quercetin	-7.1	------	-----
3.	Solanidine	-7.0	-------	VAL A: 104, LYS A: 102, SER A: 158, ASP A: 153, ILE A: 152, ASN A: 151, ASN A: 151, PHE A: 8, ARG A: 105, GLN A: 107, ILE A: 106
4.	Silybinin	-6.8	ARG A: 105, ASP A: 176	ASN A: 180, GLU A: 178, PHE A: 103, VAL A: 104, SER A: 158, ASN A: 151, THR A: 111, GLN A: 110, ILE A: 106, GLN A: 107
5.	Loliolide	-6.7	------	------
6.	Shikonin	-6.6	THR A: 111, SER A: 158	PHE A: 294, PHE A: 8, GLN A: 110, ILE A: 106, ASN A: 151, PHE A: 112, LYS A: 102, ASP A: 153, VAL A: 104

Table 4. Comparison of the calculated cLog P values for the selected compounds

S/N	Compound	SwisADME cLog P	Molinspiration cLog p	Mean calculated cLog P
1.	Scopodulcic acid	4.57	5.01	4.79
2.	Baicalin	0.22	0.55	0.77
3.	Sylibinin	1.59	1.47	3.06
4.	Solanidine	5.01	5.93	5.47
5.	Naringenin	1.84	2.12	1.98
6.	Oleanane	8.57	8.86	8.72
7.	Dammarenolic acid	6.74	8.08	7.41
8.	Quercetin	1.23	1.68	1.46
9.	Loliolide	1.53	1.84	1.69
10.	Shikonin	2.08	2.02	2.05

clog P = octanol/water coffecient

Table 5. Drug likeness

S/N	Compound	Mol. Wt[a](g/mol)	TPSA[b]	HBA[c]	HBD[d]	RB[e]	cLogP[f]	Lipinski filter	Veber filter
1.	Scopodulcic acid	438.56	80.67	5	1	4	4.79	+	+
2.	Baicalin	446.36	187.12	11	6	4	0.77	-	-
3.	Sylibinin	482.44	155.14	10	5	4	3.06	+	-
4.	Solanidine	397.64	23.47	2	1	0	5.47	+	-
5.	Naringenin	272.25	86.99	5	3	1	1.98	+	+
6.	Oleanane	412.75	0.00	0	0	0	8.72	+	+
7.	Dammarenolic acid	458.72	57.53	3	2	1	7.41	+	+
8.	Quercetin	302.24	131.36	7	5	1	1.46	+	+
9.	Loliolide	196.24	46.53	3	1	0	1.69	+	+
10.	Shikonin	288.3	94.83	5	3	3	2.05	+	+

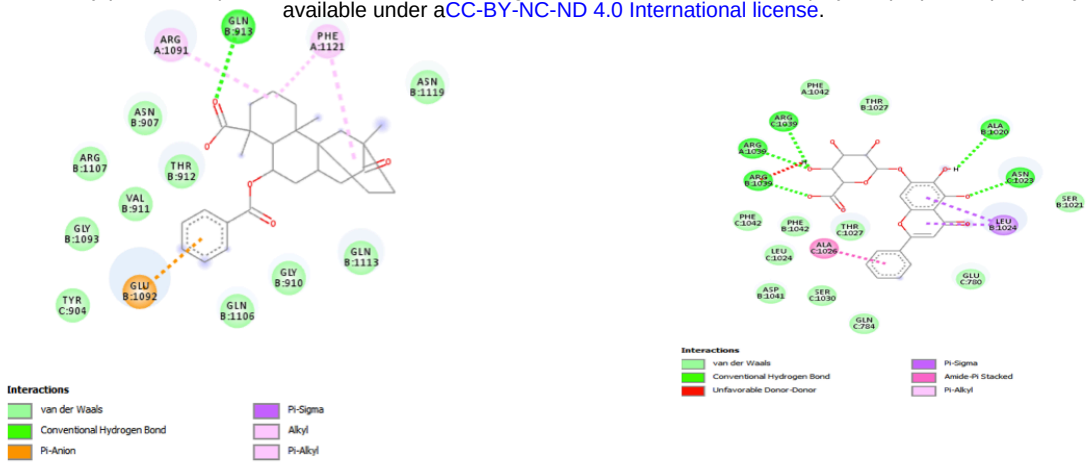
[a]Mol. Wt.: Molecular weight
[b]TPSA: Total Polar Surface Area
[c]No. HBA: Number of hydrogen bond acceptors
[d]No. HBD: Number of hydrogen bond donors
[e]No. RB: Number of rotatable bonds
[f]Mean clog P: Mean of calculated log P values

Table 6. Predicted Toxicity Profile of the compounds using PROTOX II

S/N	**Compound**	Hepatotoxicity	ImmunoToxicity	Carcinogenicity	Mutangenicity	Cytoxicity	Possible Toxicity Targets
1.	Scopodulic acid	-	++	-	-	-	AR, AO, PGS
2.	Baicalin	--	--	+	-	--	AO, PGS
3.	Sylibinin	--	++	-	--	--	PGS
4.	Solanidine	--	++	-	--	+	AR, PGS
5.	Naringenin	-	--	-	--	+	AR, PGS
6.	Oleanane	--	--	++	--	--	
7.	Dammarenolic acid	-	-	--	--	--	AR, AO PGS
8.	Quercetin	-	+	--	-	--	AO, AR, PGS
9.	Loliolide	-	+	--	-	--	AO, PGS
10.	Shikonin	-	-	++	-	+	PG

Key: -- inactive, - less inactive, + Active and ++ More active

AR = Androgen Receptor, AO = Amine Oxidase A & PGS=Prostaglandin G/H Synthase



A B

Figure 1. Best Binding pose and Interaction of (a) Scopodulcic acid and (b) Baicalin on the 6vsb protein.