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 Ubani¹, Francis Agwom², Oluwatoyin Ruth Morenikeji¹, Shehu Nathan³, Pam Luka⁴, Arinze Umera¹, Usal Uma¹, Simeon Omale⁴, Nnaemeka Emmanuel Nnadi, John Chineye Aguiyi¹

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, Boko, 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

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

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68 **2. Results**

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

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

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91 **Table 1.** Comparison of Binding affinities of library to some known ligands and the
92 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

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

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

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102 **TABLE 2** binding affinities of the compounds on the 6vbs and their Interaction with
 103 the binding site

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

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

107 the binding site

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

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

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118 **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.	Lolilide	1.53	1.84	1.69
10.	Shikonin	2.08	2.02	2.05

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120 clog P = octanol/water coefficient

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

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

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

142 **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	+	+

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144 ^aMol. Wt.: Molecular weight

145 ^bTPSA: Total Polar Surface Area

146 ^cNo. HBA: Number of hydrogen bond acceptors

147 ^dNo. HBD: Number of hydrogen bond donors

148 ^eNo. RB: Number of rotatable bonds

149 ^fMean clog P: Mean of calculated log P values

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

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

S/ N	Compound	Hepatotoxic ity	ImmunoToxic ity	Carcinogeni city	Mutangen icity	Cytotoxic y	Possible Toxicity Targets
1.	Scopoludic acid	-	++	-	-	-	AR, AO, PGS
2.	Baicalin	--	--	+	-	--	AO, PGS
3.	Sylibinin	--	++	-	--	--	PGS
4.	Solanidine	--	++	-	--	+	AR, PGS
5.	Naringenin	-	--	-	--	+	AR, PGS
6.	Oleanane	--	--	++	--	--	
7.	Dammaren olic acid	-	-	--	--	--	AR, AO PGS
8.	Quercetin	-	+	--	-	--	AO, AR, PGS
9.	Loliolide	-	+	--	-	--	AO, PGS
10.	Shikonin	-	-	++	-	+	PG

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

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

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

162 **Discussion**

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

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

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

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

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205 **4. Materials and Methods**

206 Plant Compounds with antiviral activities were mined from PubChem data base
207 (<https://pubchem.ncbi.nlm.nih.gov/>). Two proteins including the main protease
208 (6lu7) and the crystal structure of COVID-19 main protease(19) in complex with an
209 inhibitor N3 and the Spike glycoprotein, N-ACETYL-D-GLUCOSAMINE
210 (6vsb10.1126/science.abb2507) were downloaded from the protein database (PDB).
211 The proteins were prepared using Discovery studio (version)(20) and a rigid docking
212 scoring function was carried out using PyRx software(21). The results of the dock
213 poses were visualized using Discovery Studio.

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

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218 **5. Conclusions**

219 From the 22 phyto-compounds that were virtually screened, Scopodulcic acid and
220 Dammarenolic acid showed the best binding energies with the Spike glycoprotein
221 (6vsb) and the M^{pro} (6flu7) respectively. This makes them potential lead compounds
222 for development into candidates against the SARS COV 2. Furthermore, the FDA
223 approved drug silybinin (Legalon) with good binding affinity on the two targets can
224 be evaluated further for possible repurposing against the SARS COV2 virus.

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227 **Conflicts of Interest:** The authors declare no conflict of interest

228 **Reference:**

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

- 234 3. Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veerle DJC. Structure,
235 function, and antigenicity of the SARS-CoV-2 spike glycoprotein. 2020.
- 236 4. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RAJNEJoM.
237 Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia.
238 2012;367(19):1814-20.
- 239 5. Neher RA, Dyrda R, Druelle V, Hodcroft EB, Albert JJSMW. Potential impact of
240 seasonal forcing on a SARS-CoV-2 pandemic. 2020;150(1112).
- 241 6. Anand K, Ziebuhr J, Wadhwani P, Mesters JR, Hilgenfeld RJS. Coronavirus main
242 proteinase (3CLpro) structure: basis for design of anti-SARS drugs.
243 2003;300(5626):1763-7.
- 244 7. Hilgenfeld RJTFj. From SARS to MERS: crystallographic studies on coronaviral
245 proteases enable antiviral drug design. 2014;281(18):4085-96.
- 246 8. Ferenci P, Scherzer TM, Kerschner H, Rutter K, Beinhardt S, Hofer H, et al.
247 Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding
248 to pegylated interferon/ribavirin therapy. 2008;135(5):1561-7.
- 249 9. Chen L, Li J, Luo C, Liu H, Xu W, Chen G, et al. Binding interaction of
250 quercetin-3- β -galactoside and its synthetic derivatives with SARS-CoV 3CLpro:
251 Structure-activity relationship studies reveal salient pharmacophore features.
252 2006;14(24):8295-306.
- 253 10. Ginzberg I, Tokuhisa JG, Veilleux REJPR. Potato steroidal glycoalkaloids:
254 biosynthesis and genetic manipulation. 2009;52(1):1-15.
- 255 11. Friedman M, McDonald GM, Filadelfi-Keszi MJCRIPS. Potato glycoalkaloids:
256 chemistry, analysis, safety, and plant physiology. 1997;16(1):55-132.
- 257 12. Thorne H, Clarke G, Skuce RJAr. The inactivation of herpes simplex virus by some
258 Solanaceae glycoalkaloids. 1985;5(6):335-43.
- 259 13. Banerjee P, Eckert AO, Schrey AK, Preissner RJNar. ProTox-II: a webserver for
260 the prediction of toxicity of chemicals. 2018;46(W1):W257-W63.
- 261 14. Esimone CO, Eck G, Nworu CS, Hoffmann D, Überla K, Proksch PJP.
262 Dammarenolic acid, a secodammarane triterpenoid from *Aglaia* sp. shows potent
263 anti-retroviral activity in vitro. 2010;17(7):540-7.
- 264 15. Esimone C, Eck G, Duong T, Überla K, Proksch P, Grunwald TJDP-AIJoPS.
265 Potential anti-respiratory syncytial virus lead compounds from *Aglaia* species.
266 2008;63(10):768-73.
- 267 16. Liu C-H, Jassey A, Hsu H-Y, Lin L-TJM. Antiviral Activities of Silymarin and
268 Derivatives. 2019;24(8):1552.
- 269 17. Polyak SJ, Ferenci P, Pawlotsky JMJD. Hepatoprotective and antiviral functions of
270 silymarin components in hepatitis C virus infection. 2013;57(3):1262-71.
- 271 18. Wagoner J, Negash A, Kane OJ, Martinez LE, Nahmias Y, Bourne N, et al. Multiple
272 effects of silymarin on the hepatitis C virus lifecycle. 2010;51(6):1912-21.
- 273 19. 10.2210/pdb6LU7/pdb.
- 274 20. Biovia DSJSD. Discovery Studio Modeling Environment Release 2017, Dassault
275 Systemes. 2016.

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

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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 Interaction with Residues	Bond
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 Interaction with Residues	Bond
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	+	+

^aMol. Wt.: Molecular weight

^bTPSA: Total Polar Surface Area

^cNo. HBA: Number of hydrogen bond acceptors

^dNo. HBD: Number of hydrogen bond donors

^eNo. RB: Number of rotatable bonds

^fMean clog P: Mean of calculated log P values

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

S/ N	Compound	Hepatotoxic ity	ImmunoToxic ity	Carcinogeni city	Mutangen icity	Cytoxicit y	Possible Toxicity Targets
1.	Scopodulci c acid	-	++	-	-	-	AR, AO, PGS
2.	Baicalin	--	--	+	-	--	AO, PGS
3.	Sylibinin	--	++	-	--	--	PGS
4.	Solanidine	--	++	-	--	+	AR, PGS
5.	Naringenin	-	--	-	--	+	AR, PGS
6.	Oleanane	--	--	++	--	--	
7.	Dammaren olic acid	-	-	--	--	--	AR, AO PGS
8.	Quercetin	-	+	--	-	--	AO, AR, PGS
9.	Lolilide	-	+	--	-	--	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

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