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Insilico Studies on the Phytoconstituents of *Musa Paradisiaca* for Sars Cov-2 Main Protease Inhibitory Activity

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ABSTRACT

The aim of the present study is to determine whether the phytoconstituents of Musa paradisiacal possess anti-viral activity for COVID-19. Molecular docking studies were done using Autodock software. Also selected phytoconstituents of Musa paradisiacal were explored for pharmacokinetics, toxicity studies using pkCSM. Lipinski rule of 5 and drug likeness score were studied using molinspiration software. All selected phytoconstituents of Musa paradisiaca showed negative binding energy against SARSCoV2 Main protease, among them the constituent hydroxyanigoruf one showed similar binding energy (-10.61 Kcal/mole) to that of standard nelfinavir (-10.6 Kcal/mole). The constituents leucocyanidin, quercetin, sitoindoside-I and hydroxyanigorufone complies with Lipinski rule of 5 which indicates they possess good bioavailability.

INTRODUCTION

Corona virus disease 2019 is a respiratory infection caused by Severe Acute Respiratory Syndrome Coronavirus (SARSCoV2) which was originated in Wuhan city China [1], [2]. SARSCoV2 spreads COVID-19 through mucus membrane of upper respiratory tract followed by lower, this in turn manifests the other cells resulting in cytokine storm and more immune responses [3], [4]. The incubation period of COVID-19 is generally 1-14 days in some cases it is 3-7 days. The common clinical manifestation includes runny nose, fever, sore throat, diarrhoea, vomiting and shortness of breath. Also in some case it is asymptomatic [5], [6]. For diagnosis of this disease, a swab of nasopharynx as sample and Reverse transcription polymerase chain reaction is considered to be a standard method [7], [8].

Main protease (M^{PRO}) also known as 3CL protease plays a major role in assembly of replication transcription of virus by maturing the functional polypeptides. Hence, this serves as the target tool in development of effective therapeutic drug against novel corona virus [3], [9]. Successfully Liu et al 2020 has crystallised COVID-19 Main protease M^{PRO} which helps to carry out the in silico studies [7], [10], [11].

In traditional system of medicine, medicinal plants are used frequently in treating different diseases across world in different areas. Plant resources play key role in development of new lead molecule due to presence of various classes of secondary metabolites. *Musa paradisiaca*, a herbaceous plant is rich source of secondary metabolites such as flavonoids, acyl steryl glycoside, triterpenes etc [12]. It is the need of the hour to explore the medicinal plants in the management of COVID-19. Hence, this research workaims to explore the phytoconstituents of *Musa paradisiacal* for in silico anti-viral activity against Main protease of COVID-19.

MATERIALS AND METHODS

a) Molecular Docking

Nelfinavir comes under the class protease inhibitors which are used in the treatment of HIV infection. Considering its inhibitory activity on SARSCoV2, in this research work nelfinavir is used as standard. Molecular docking was carried out using autodock 4.2 for selected phytoconstituents of *Musa paradisiaca*against SARS CoV2 main protease.

Protein was downloaded from protein data bank (PDB ID 7CB7) and active sites were found from PDB sum. The PDB format of phytoconstituents of *Musa paradisiaca*were downloaded from Pubchem.

Table: 1 Phytoconstituents of *Musa paradisiaca*

PARTS	PHYTOCONSTITUENTS	COMPOUND CODE
Unripe pulp	Leucocyanidin	T1
	Quercetin	T2
Fruit	Sitoindoside-I	T3
	Hydroxyanigorufone	T4
	Rel-(3s,4aR, 10bR)-5 hydroxy-3-(4-hydroxyphenyl-9-methoxy-4a, 5,6, 10b-tetrahydro-3H-naphthol-[2,1-b] pyran	T5
	1,2-dihydro-1,2,3-trihydroxy-9-[4 methyphenylphenalene]	T6
Flower	Syringin	T7
	6s-9R-Roseoside	T8

b) Lipinski rule of 5

Pfizer's rule of five or Lipinski's rule of five is used to evaluate the drug likeness or bioavailability of chemical compound. Drug likenessscore in turn determines whether the chemical compound is fit to be drug or not. Here, the Lipinski rule of five and drug likeness score were studied using molinspiration software.

c) Prediction of Pharmacokinetic Properties

Pharmacokinetic deals with study of ADME properties of drug (i.e.) Absorption, Distribution, Metabolism and Excretion. The ADME properties of selected phytoconstituents of *Musa paradisiaca*were studied using pkCSM an online tool.

d) Toxicity Study

Toxicity study deals with the investigation of short or long term toxic effect of chemical compound/drug on animals. The toxicity study of phytoconstituents of *Musa paradisiaca*were performed using pkCSM, an online tool.

RESULTS

a) Molecular Docking

Molecular docking for selected phytoconstituents of *Musa paradisiaca*were studied using Autodock software and the table 2 represent the docking parameters of docked constituents. Figure1 (a-g) represents theAutodock view of interaction between ligand (constituents) and main protease.

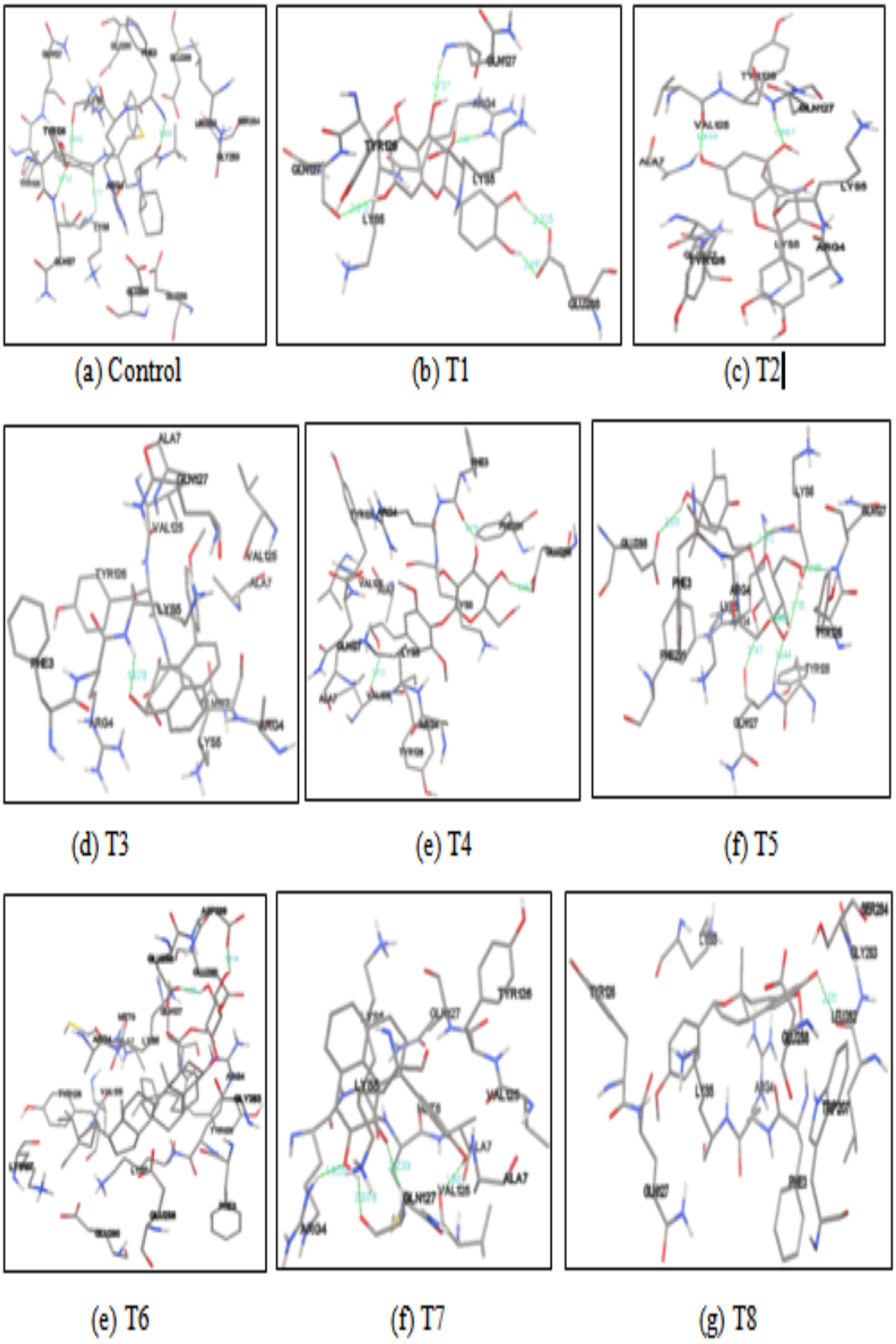

Figure 1: (a) – (g) represents the Autodock view of interaction of phytoconstituentsof *Musa paradisiaca* and main protease.

Table: 2 Interaction of Constituents with Amino Acids at the Active Site of the Protein Main Protease

S.No.	Compound Code	Binding energy (kcal/mole)	Inhibition constant	No. of Hydrogen bonds formed	Amino acids involved in hydrogen bond	Distance between donor and acceptor
1	Control	-10.6	17.0nM	4	B:LYS5	2.042
					B:GLN127	1.752
					A:LYS5	2.113
					A:PHE3	1.986
2	T1	-7.84	1.8uM	5	B:GLU228	2.011
					B:GLU228	2.205
					A:ARG	1.8
					A:GLN127	1.737
					B:GLN127	2.212
3	T2	-8.13	1.1uM	2	B:VAL125	1.909
					B:GLN127	1.867
4	T3	-5.64	73.38uM	2	B:ASP289	1.814
					B:GLU288	1.76
5	T4	-10.61	16.68nM	4	A:ARG	1.905
					B:GLN127	2.078
					B:GLN127	2.239
					B:VAL125	1.987
6	T5	-8.94	280.13nM	1	A:LEU282	2.511
7	T6	-9.54	101.04nM	1	A:LYS5	1.878
8	T7	-6.65	13.3uM	3	A:VAL125	1.913
					A:GLU288	1.992
					A:PHE3	1.711
9	T8	-8.24	904.55nM	6	B:LYS5	2.145
					A:LYS	2.118
					A:GLN127	2.01
					B:GLU288	2.011
					A:LYS5	1.966
					B:GLN127	2.147

b) Lipinski rule of 5

The selected phytoconstituents of *Musa paradisiaca*were subjected to mol inspiration and Lipinski rule of five and drug likeness score for the phytoconstituents were given in table 3 and table 4 respectively.

Table: 3 Lipinski rule of five properties for the phytoconstituents of *Musa paradisiaca*

Compound Code	Log P	Molecular weight (g)	No. of Hydrogen bond acceptor	No. of Hydrogen bond donor
T1	0.38	306.27	6	7
T2	0.71	304.25	7	5
T3	10.03	801.25	7	3

T4	4.25	288.30	3	2
T5	3.72	338.40	4	1
T6	2.45	322.36	4	3
T7	-0.66	372.37	9	5
T8	-0.42	372.41	8	5

Table: 4 Drug likeness score for Phytoconstituents of *Musa paradisiaca*

Compound Code	GPCR	Ion channel	Nuclear receptor	Protease inhibitor	Enzyme inhibitor	Kinase inhibitor
T1	0.25	0.13	0.42	0.08	0.36	-0.10
T2	0.09	0.03	0.29	0.05	0.29	-0.04
T3	-1.66	-2.79	-2.26	-1.16	-1.83	-2.74
T4	-0.04	-0.07	0.16	-0.18	0.21	0.23
T5	0.39	0.02	0.31	-0..05	0.23	-0.08
T6	0.28	0.13	0.33	0.16	0.21	0.08
T7	0.11	0.09	0.09	-0.04	0.38	-0.08
T8	0.29	0.25	0.25	0.27	0.70	-0.36

c) Prediction of Pharmacokinetic properties

Table 5 represents the pharmacokinetic properties of phytoconstituents of *Musa paradisiaca*using pkCSM, an online tool.

Table: 5 Pharmacokinetic Properties of Phytoconstituents of *Musa paradisiaca*

Compound code	Absorption						Distribution			Metabolism						Excretion	
	Water solubility (logmol/L)	$CaCo_2$(log Papp in 10^{-6}cm/s)	Intestinal absorption (% Absorbed)	P-glycoprotein substrate	P-glycoprotein I inhibitor	P-glycoprotein II inhibitor	VDSS (human) (log L/Kg)	Fraction unbound (human)(Fu)	BBB permeability (log BB)	CYP2D6 Substrate	CYP3AA Substrate	CYPIA2 Inhibitor	CYP2C19 Inhibitor	CYP2D6 Inhibitor	CYP344 Inhibitor	Total clearance (logml/min/Kg)	Renal OCT2 Substrate
T1	-3.127	-0.456	65.493	yes	no	no	0.356	0.16	-1.281	no	no	no	no	no	no	0.154	no
T2	-3.742	-0.287	59.896	yes	no	no	0.288	0.14	-1.214	no	no	no	no	no	yes	0.063	no
T3	-3.404	0.366	85.523	yes	yes	yes	-2.036	0.155	-1.427	no	yes	no	no	no	no	0.88	no
T4	-4.878	1.283	91.809	yes	no	yes	-0.082	0.073	0.15	no	yes	yes	yes	no	yes	0.059	no
T5	-4.445	1.58	95.769	no	yes	no	0.452	0.105	-0.159	no	no	yes	yes	no	yes	0.152	no
T6	-3.451	1.042	97.45	yes	no	no	-1.053	0	-0.936	no	yes	yes	yes	no	yes	0.081	no
T7	-3.131	-0.007	42.349	yes	no	no	0.048	0.408	-1.349	no	no	no	no	no	no	0.232	no
T8	-1.371	-0.363	32.811	yes	no	no	-0.105	0.59	-1.28	no	no	no	no	no	no	1.625	no

d) Toxicity Study

Table 6 represent the toxicity studies of phytoconstituents of *Musa paradisiaca*using pkCSM, an online tool.

Table 6: Toxicity studies of phytoconstituents of *Musa paradisiaca*

Compound code	Toxicity Studies							
	AMES Toxicity	**Max tolerance dose/ human (logmg/kg /day)**	**hERGI inhibitor**	**hERG II inhibitor**	**Oral Rat Acute toxicity (LD50) (mol/k)**	**Oral Rat chronic toxicity (LOAEL)(log mg/kg bw/day)**	**Hepatotoxicity**	**Minnow toxicity (logmM)**
T1	yes	0.765	no	no	2.221	2.932	no	2.154
T2	yes	0.747	no	no	2.3	2.005	no	2.014
T3	no	0.041	no	no	2.548	2.673	no	-6.454
T4	yes	0.482	no	yes	2.114	1.8	no	0.157
T5	no	0.564	no	yes	2.403	1.93	no	-0.245
T6	yes	0.596	no	yes	2.289	1..291	no	-0.521
T7	no	0.399	no	no	3.046	4.321	no	4.103
T8	no	0.848	no	no	2.764	3.517	no	4.897

CONCLUSION

Docking studies for the selected phytoconstituents of *Musa paradisiacal* were carried out using autodock 4.2 to determine the inhibitory activity against SARSCoV2 main protease. Phytoconstituents of *Musa paradisiacal* (T1-T8) showed negative binding energy which indicates that, they have inhibitory activity on main protease. Among them compound T4 showed similar binding energy (-10.61Kcal/mole) to that of standard nelfinavir (-10.6 Kcal/mole). Hence, *Musa paradisiacal* possess antiviral activity against the SARSCoV-2.

Lipinski rule of five and drug likeness score of phytoconstituents of *Musa paradisiacal* were studied using mol inspiration software and the constituents leucocyanidin, quercetin, sitoindoside-I, hydroxyanigorufone,Rel-(3s,4aR, 10bR)-5 hydroxy-3-(4-hydroxyphenyl-9-methoxy-4a, 5,6, 10b-tetrahydro-3H-naphthol-[2,1-b] pyran and 1,2-dihydro-1,2,3-trihydroxy-9-[4 methyphenylphenalene] complies with Lipinski rule of five which indicates that they have good bioavailability. Pharmacokinetic properties of phytoconstituents of *Musa paradisiacal* were studied using pkCSM and constituents comply with the standard value.

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