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In-Silico Screening of Phytochemicals in Febrifuges Used in Siddha Medicine for SARS-CoV-2 RNA Dependent RNA polymerase Inhibitory Activity

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Abstract **Original Research Article**

The contagious disease COVID-19 is a recently out-broken pandemic situation which threatens human kind all over the world. While considering the mortality and severity of this disease, the author attempted to identify the possible inhibition of RNA-dependent RNA polymerase (RdRP) or RNA replicase which catalyzes the replication of RNA from an RNA template by certain bioactive components. So certain herbs which are used as febrifuges in Siddha medicine were analyzed through molecular docking studies. The compounds Betulinicacid, Amaranthin, Betacyanin, Cadambine, 14 –deoxy Andrographolide, lupeol, Neoandrographolide, Tubulosin and Isovitexin have binding energy comparable to Remdesivir.

Keywords: COVID-19, RNA replication, Siddha medicine, Febrifuges and Molecular docking.

INTRODUCTION

SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus-2) initially designated as 2019 novel corona virus (2019nCoV) has been the reason for the severe lethal viral illness declared as Pandemic by World Health organization on March 12, 2020. Coronavirus is a member of a large virus family, the coronaviridae and subfamily orthocoronavirinae which usually causes respiratory illness to humans and animals. The newly emerged novel coronavirus (SARS-CoV-2) is a positive sense single stranded RNA virus and has trimeric spike glycoprotein (S), membrane capsid protein (M), small membrane protein, viral nucleoprotein (N) and an RNA dependent RNA polymerase (RdRp), which are essential for virus replication [1]. Siddha is a form of native medicine practiced in Tamil Nadu. Siddha Pharmacopoeia uses various herbal preparations for treating diseases. Some of the herbs commonly used to treat fevers comes under the category of febtrifuges [2]. Among them, few herbs have been used for treating viral fevers which is owed to the presence of phytochemicals which may have viricidal properties. In this study, we have done In-Silico screening by docking structures of phytochemicals found in febtrifuges against RNA dependent RNA polymerase protein of coronavirus (SARS-CoV-2).

MATERIALS AND METHODS:

Literature search was done for individual plants to identify their constituent phytochemicals.230 Phytochemical ligands were identified from 20 plants. The structure of these phytochemicals were drawn using canonical smiles obtained from Pubchem site using chemsketch software [3] and stored as mol files which were later converted to pdb format using Argus lab software. The structure of the RNA dependent RNA polymerase of coronavirus (SARS-CoV-2) 6m71 was downloaded as pdb file from RCSB PDB site [4, 5]. The structure of protein was loaded to CAST-p website (job id-5ed37a8f24749) and active sites were identified [6]. The protein structure was subjected to removal of water molecules and addition of hydrogen atoms. The target molecule and the ligands were loaded in the

PyRx virtual screening software which uses Autodock Vina for docking [7, 8]. The protein molecule and the ligands were subjected to energy minimisation and were converted to pdbqt format. Grid was created with x-121.778, y-123.473,z-127.006 as centre and with dimensions in Angstroms x-75,y-84,z-106. Docking of the ligands were done using Autodock vina with exhaustiveness of 8.The out put pdbqt files were opened in PyRx and the individual ligand poses were separately saved in pdb format. The protein molecule and out put ligand poses were loaded in PyMOL and their hydrogen bond interaction of ligands with Amino Acid residues were studied [9].

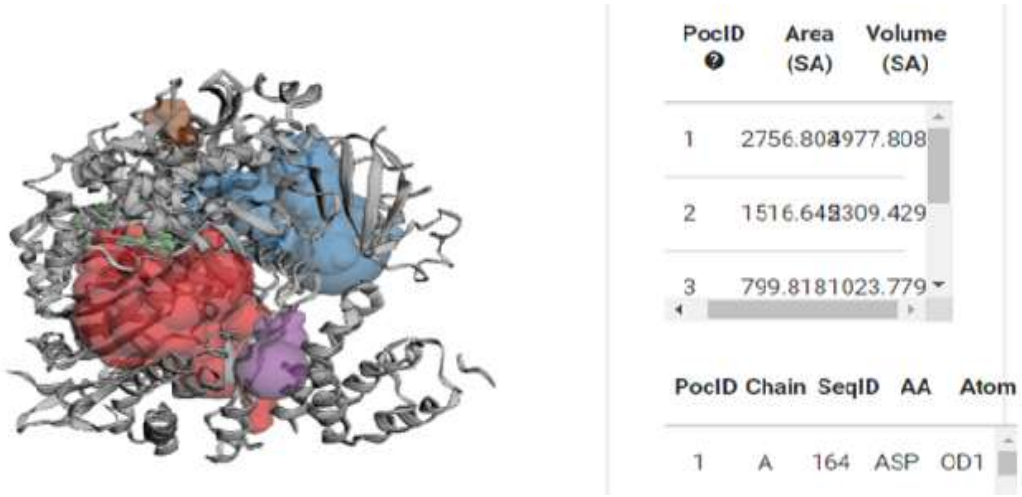
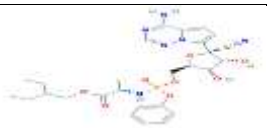
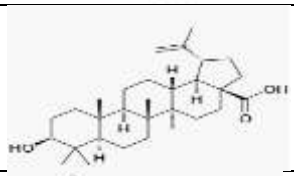
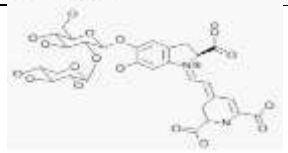
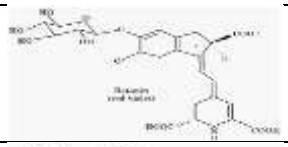
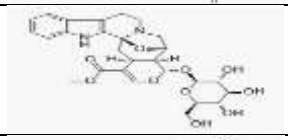
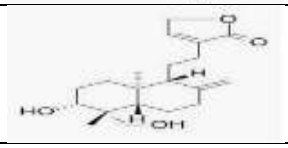
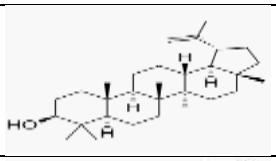
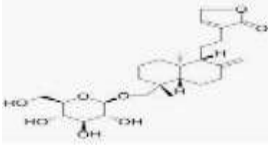
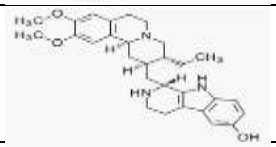
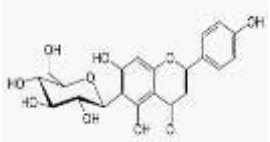
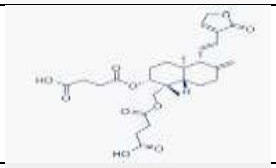
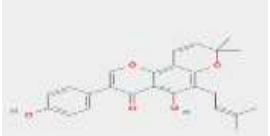
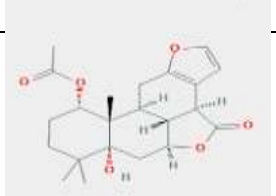
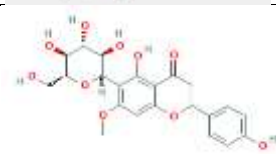
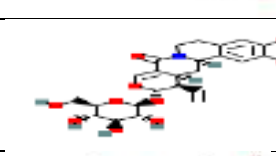
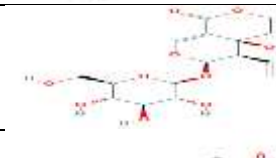
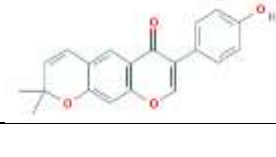


Fig-1: Active sites CASTp

RESULTS AND DISCUSSION

Table-1: Phytochemical structures of febrifuges

Ligands	Binding Affinity	Structure	Source	Hydrogen Bonds
Remdesivir	-9.0		Synthetic	Thr123,Asp126, Ala34,His133
Betulinic acid	-10.2		Alangium salvifolium	Asp208,Thr206, Asn209,Asn39
Amaranthin	-9.7		Amaranthus blitum	Thr710,LYS714, Tyr32,Lys47, Tyr129,Ser784, Thr141
Betacyanin	-9.6		Amaranthus blitum	Thr120, Lys121,Arg33, Asp218,Asp208, Thr206,Asn209, Tyr217
Cadambine	-9.6		Anthecephalus cadamba	Asn781,Ser784, Tyr129,His133, Ser709
14-Deoxy andrographolide	-9.6		Andrographis paniculata	Asn781,His133, Ser784,Ser709, Lys47,Thr710, Asp711

Lupeol	-9.5		Crateva naruvala	Asn209,Asp218
Neo andrographolide	-9.3		Andrographis paniculata	Arg349,Asn628
Tubulosine	-9.3		Alangium salvifolium	Lys508,Asn100, Thr124
Isovitexin	-9.1		Crateva naruvala	Gln773,Gly774, Ser709,Thr710, Asn781,Lys47, Thr141,
Dehydroandrographolide	-8.8		Andrographis paniculata	Asn628,Phe321
Osajin	-8.8		Erythrina variegata	Asp208,Asn209
Caesalmin-B	-8.5		Caesalpinia bonducella	Arg349,Asn628
Swertisin	-8.4		Erythrina variegata	Gly774,His133, Asn138,Thr141
Alangiside	-8.4		Alangium salvifolium	Glu350,Arg349, Asn628,Asn459, Thr319
Erysenegalensin	-8.1		Erythrina variegata	Arg733,Thr206, Asn209
Swertiamarin	-7.8		Erythrina variegata	Lys47,Ser709, Asn781,Phe134
Erythrinin-A	-7.4		Erythrina variegata	Asp760,TRP800

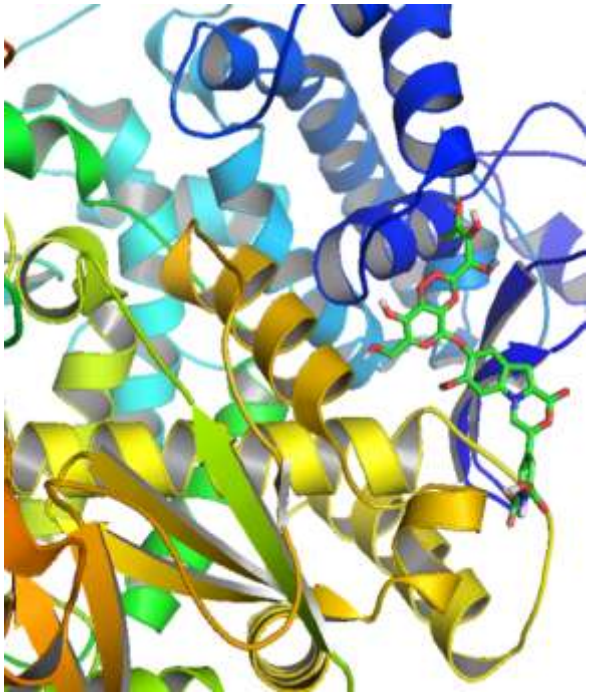


Fig-2: Amaranthin in RdRp

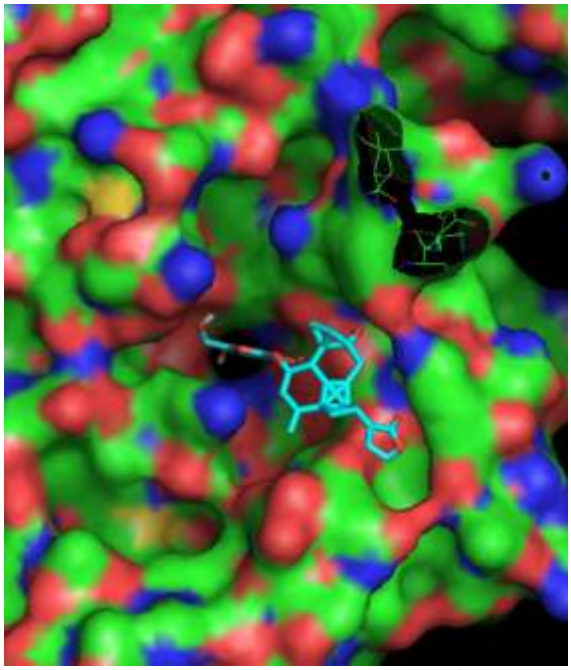


Fig-3: 14-Deoxyandrographolide in RdRp Surface view

Phytochemicals Betulinic acid, Amaranthin, Betacyanin, Cadambine, 14 –deoxy Androgapholide, lupeol, Neoandrographolide, Tubulosin and Isovitexin have binding energy comparable to Remdesivir. 14-Deoxyandrographolide and swertisin show maximum binding energy and form hydrogen bond to His133 similar to Remdesivir. Betulinic acid, Betacyanin, Lupeol, Osajin and Erysenegalensin form hydrogen bonds to aminoacids Thr120, Lys121, Thr206, Asp208, Asn209, Tyr217, Asp218 which form Pocket 3 CAST-P active site. Cadambine, Neoandrographolide, Dehydroandrographolide, Alangiside at their maximum binding energy form hydrogen bonds to aminoacids Arg349, Asn628, Phe321, Glu350,Asn459, Thr319 which form Pocket 2 CAST-P active site.

Jin-Ching Lee have shown that Andrographolide is against hepatitis C virus by up-regulating haeme oxygenase-1 via the p38 MAPK/Nrf2 pathway in human hepatoma cells [10]. Corona virus belongs to the same group of RNA viruses as Hepatitis C Virus and contain RdRp which is similar in structure. So there was a potential antiviral activity exhibited by *Andrographis paniculata* extract as many of its phytochemicals dock to RdRp.

Ying Jun Chang *et al*., has shown that Betacyanins from *Amaranthus dubius* posses antiviral activity against Dengue virus Type2 [11]. Hence some of the phytochemicals in febtrifuges may exert direct viricidal activities and have potency to treat Corona virus illness by inhibiting RdRp.

CONCLUSION

Phytochemicals in plants used as febtrifuges shown good binding affinity to RdRp comparable to Remdesivir. Some of the febrifuges used in Siddha medicine may contain phytochemicals with activity against RdRp and may have been useful in treating fever due to their direct antiviral properties rather than anti-inflammatory activity. So, it can be strongly suggested that the above discussed febrifuges mentioned in Siddha Pharmacopoeia can be used in treating COVID 19 and further the efficacy of those active components should be tested through in vitro method before being recommended as a drug.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P. A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*. 2020 Jan 24; 382:727-733.
2. Murugesa Mudaliar. Siddha Materia Medica, (Guna Padam) Department of Indian Medicine and Homeopathy. 2013; 904.
3. ACD/ChemSketch version 12.01, Advanced Chemistry Development, Inc., Toronto, On, Canada, www.acdlabs.com, 2009.
4. Gao Y, Yan L, Huang Y, Liu F, Zhao Y, Cao L, Wang T, Sun Q, Ming Z, Zhang L, Ge J. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. Science. 2020 May 15;368(6492):779-82.
5. Rose PW, Prlić A, Altunkaya A, Bi C, Bradley AR, Christie CH, Costanzo LD, Duarte JM, Dutta S, Feng Z, Green RK. The RCSB protein data bank: integrative view of protein, gene and 3D structural information. *Nucleic acids research*. 2016 Oct 27:gkw1000.
6. Tian W, Chen C, Lei X, Zhao J, Liang J. CASTp 3.0: computed atlas of surface topography of

proteins. *Nucleic acids research.* 2018 Jul 2;46(W1):W363-7.
7. Huey R, Morris GM, Olson AJ, Goodsell DS. A semiempirical free energy force field with charge- based desolvation. *Journal of computational chemistry*. 2007 Apr 30;28(6):1145-52.
8. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of computational chemistry. 2010 Jan 30;31(2):455-61.
9. DeLano WL. Pymol: An open-source molecular graphics tool. *CCP4 Newsletter on protein crystallography*. 2002 Mar;40(1):82-92.
10. Lee JC, Tseng CK, Young KC, Sun HY, Wang SW, Chen WC, Lin CK, Wu YH. Andrographolide exerts anti- hepatitis C virus activity by up-regulating haeme oxygenase- 1 via the p38 MAPK/N rf2 pathway in human hepatoma cells. *British journal of pharmacology*. 2014 Jan;171(1):237-52.
11. Chang YJ, Pong LY, Hassan SS, Choo WS. Antiviral activity of betacyanins from red pitahaya (Hylocereus polyrhizus) and red spinach (Amaranthus dubius) against dengue virus type 2 (GenBank accession no. MH488959). *Access Microbiology*. 2020 Jan 1;2(1):e000073.