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Determining Andrographolide potential against COVID 19 and Compare it among Active pharmaceutical Agent utilized for antiviral activity against COVID 19 using ADME properties and Molecular docking

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SARS-Co V-2 is now synonymously used as a terror for human health. It has deadly impacted whole world due to lack of vaccine and target oriented therapy .World scientific communities and researchers are searching treatment to get rid of it by applying holistic effort. Major guideline which is used as a first line of treatment is Antimalarial drug like Hydroxychloroquine or Anti HIV drugs like Lopinavir/ritonavir or combination of them. In this work an attempt was made to analyze the physiochemical ,ADME properties of these drugs used in the treatment of COVID 19 and after comparing the significant properties use it for molecular docking study along with phytoconstituent Andrographolide. This phytoconstituent has been reported possess antiviral activity against COVID 19. The best Active pharmaceutical agent chose after analyzing different physiochemical and ADME properties was Hydroxychloroquine due to its molecular weight ,Log P value ,Oral bioavailability and Solubility .Most of the Physicochemical and ADME properties of Andrographolide was similar to Hydroxychloroquine and this caused to perform comparative Molecular docking study of both Hydroxychloroquine and Andrographolide. The result of the Molecular Docking revealed that Andrographolide may be used in the treatment of COVID 19 virus after clinical studies since it has much similarity with Hydroxychloroquine and it's a plant based component which is more safe due to its less oral toxicity compared to Hydroxychloroquine and less protein drug binding property.

Keywords: Hydroxychloroquine, Lopinavir, Ritonavir, Andrographolid, Covid 19

I. Introduction

World health organization has proposed three Active pharmaceutical agents Lopinavir, Ritonavir and Hydroxychloroquine for the treatment of Covid 19.[1] Lopinavir/ritonavir used as sixth drug in the HIV-1 protease inhibitor (PI) class and approved by the US Food and Drug Administration. Chandwani, A et al.(2008)]The suitable adult dose of lopinavir/ritonavir is 400 mg/100 mg twice a day (Hashem, MA. et al.2020) Hydroxychloroquine is also being used in the treatment which Inhibits infection of cells by SARS-CoV-2 in vitro and it is also approved for malaria prophylaxis and autoimmune disease (Liu J et al.2020). It supposed to acts by changes the pH of endosomes and prevents viral entry, it also hinder the transport and post-entry events of Virus (Singh, A.K et al.2020).

In some researches it was also predicted that Andrographolide which is a major bioactive phytoconstituent found in parts of *Andrographis paniculata*, family acanthaceae has been reported to have a wide range of biological activities, such as anti-HIV, anti-inflammatory, hepatoprotective, antiplatelet aggregation, antiallergic, CHIKV infection and could effectively interact with targets of SARS-CoV-2. Therefore Andrographolide and its derivative may be used in treatment of SARS-CoV-2 infections (Canrong, W et al.2020) (Wintachai, P 2015) Molecular docking is the process of how two or more molecular structures fit peculiarly and perfectly

together. The efficiency of a protein (enzyme) to interact with small molecules and form a supramolecular complex exhibits a major role of in the protein dynamics (Thanasekaran, J et al . 2013) These properties of andrographolide form the foundation for the magnanimous use of this wonder compound to restrain virus replication along with virus-induced pathogenesis (KhannaV et al . 2013).

II. Research Objectives

This research examines the properties of Andrographolide which make it a suitable and perfect ligand to perform molecular docking study with the COVID 19 Virus protein. That is why an attempt was made to do computational molecular docking study using phytoconstituent of Andrographis paniculata, Andrographolide with COVID 19 viral protein 6LU7, Resolution: 2.16 Å

Viral protein SARS-CoV-2 main protease was taken from PDB database PDB Id 6LU7 and to compare the potential of Andrographolide comparative docking study also performed with Hydroxychloroquine. [10]

The databank and database available online like Protein Data Banks ,ZINC ,Indian Medicinal Plant for phytoconstituents, Different software like Marvin Sketch, Pymol, Chimera, Swissdock, Swiss Target Prediction and ADMETSAR Tools Biopharmaceutical tools, discovery studio format converting software were referred to.

III. Research Methodology

The research followed a thoroughly developed research methodology. The research was performed in a planned manner. Initially drug molecule active against COVID 19 were selected approved by World health organization then they all were subjected for ADMET sar studies. Different Biopharmaceutical properties were analyzed like better permeability, activity, route of drug administration, solubility. Comparative analysis of these molecules were done based on their drug likeliness properties. The selected phytoconstituents was also analyzed by ADMET sar studies and then it was compared with the best drug molecule previously selected and subjected for docking study. Then different Computational based molecular docking property were calculated and proved phytoconstituent on the basis of result obtained.

Fig 1. Andrographis paniculata [16]

IV. Research Analysis

ADMET Sar study of Active pharmaceutical Ingredients acting against COVID19 (Smellie A et al . 1995)

This was performed by subjecting the smile notation of all the molecules for calculation of ADMET Sar . It was observed by analyzing the calculated properties of Hydroxychloroquine that its molecular weight is 335.88 which is less as compare to other two anti HIV drug Lopinavir and Ritonavir, If we compare Log P value which is the true indicator of nature of Active Pharmaceutical Ingredient revealed that Hydroxychloroquine is bit hydrophobic but Lopinavir is bit more hydrophobic than Hydroxychloroquine as indicted by Log P value 3.78 for Hydroxychloroquine and 4.33 for Lopinavir . Ritonavir is even more hydrophobic exhibited Log P 5.91 .It was also observed that property of transferring Blood brain Barrier and CaCo-2 permeability was equally exhibited by Hydroxychloroquine and Lopinavir. Eye corrosion and Eye irritation were missing in all the active pharmaceutical agent , Hydroxychloroquine is the only active pharmaceutical agent revealed oral bioavailability as compared to anti HIV drug Andrographolide and hydroxychloroquine. ADME SAR studies also showed least hydrogen donor and acceptor of Hydroxychloroquine as compared to Lopinavir and Ritonavir

Discussion – One more interpretation and result can be concluded out of less molecular weight of Hydroxychloroquine and that is its bioavailability is more due to its permeability characteristic generally it is consider that lower is molecular weight of the active

pharmaceutical ingredient better is its permeability with the membrane that might be the reason of its major use in the treatment. Similar property was exhibited by Andrographolide due its molecular weight which is less than 350 as shown in table -1

Andrographolide and hydroxychloroquine they both are less hydrophobic as compared to Lopinavir and Ritonavir shown by Log P Value .Both exhibited permeability for caco-2 and blood brain barrier ,They both showed no eye irritation and corrosion .If we compare acute oral toxicity then It was found to be lease among all the drug candidate that may be Lopinavir , Ritonavir or Hydroxychloroquine .Plasma protein binding tendency of Andrographolide and hydroxychloroquine are less as compared to Lopinavir and Ritonavir. Water solubility of Andrographolide was also more.

Target prediction study - Target prediction study of Andrographolide revealed its interaction with 15 human body proteins with the probability of 0.2 to 0.6. Same result was exhibited by the Andrographolide it showed interaction with 15 protein with little bit more probability which was0.7 to 0.9. Though Lopinavir showed target efficiency with 100 human body targets with the probability of

0.05 to 0.03 which was comparatively less as compared to Andrographolide and hydroxychloroquine .Ritonavir revealed better target binding with cytochrome P 450 , kappa Opoid receptor ,Neurokinin and thromboxane a synthase with the probability of 1 but for rest of the 20 target it was constant. 0.020. Here also if we compare between Hydroxychloroquine and lopinavir then Hydroxychloroquine is better for the comparative study with Andrographolide(Raikwar N et al . 2020)

Molecular docking -The pocket of the protein had volume of 112 , surface 260.88 and the value of R factor is 0.202.The amino acid descriptor of the pocket were # ALA1,# ARG1,# ASN1,# ASP1,# CYS0.# GLN0,# GLU0,# GLY1,# HIS0,# ILE0,# LEU0,# LYS1,# MET0,# PHE0,# PRO0,# SER0,# THR3,# TRP0 & # TY . Molecular docking revealed that out of 256 Covid 19 virus protein and Andrographolide ligand the best complex revealed fullfitness was 10.56 and out of 256 Covid 19 virus protein and Hydroxychloroquine ligand the best complex revealed 18.83 fullfitness, Delta G that is energy of best complex was -7.40 Kcal-mol for Andrographolide ligand with Covid 19 virus protein and -8.09 Kcal-mol for Hydroxychloroquine ligand with Covid 19 virus protein(Jin, Z et al 2020) Though distance between the atom calculated was 1.780 Å for Andrographolide with virus protein which was least as compared to Hydroxychloroquine which was 16.87 Å Even the angle was also less -174.39° for Andrographolide ligand with Covid 19 virus as compared to Hydroxychloroquine which was -8.44°. From the result of docking it can be concluded that Andrographolide can be used to treat Covid 19 since it also showed least distance, comparatively less angle and almost same ADMETSar properties like Hydroxychloroquine. (Mishra A et al . 2020)

V. Conclusion

It has been observed that whole world is utilizing active pharmaceutical agent Hydroxychloroquine for the treatment of COVID 19 virus .In this work we selected three potent drug which is given by World health organization to treat COVID 19 affected patient. As per some recent publications it was predicted that Andrographolide may have potential against Covid 19 Virus .In this work all the ADMETSar properties was calculated and analyzed for Lopinavir Ritonavir and Hydroxychloroquine which revealed Hydroxychloroquine as least molecular weight ,good log P value better Bioavailability and comparatively less protein binding. Hydroxychloroquine revealed better ADMET properties thus it was selected for molecular Docking study and comparative study with Andrographolide. The result of Molecular docking revealed that Andrographolide can be used to treat Covid 19 virus since it also showed least distance, comparatively less angle and almost same ADMETSar properties like Hydroxychloroquine.

VI. Scope for Further Research

The scope of this work is that once the after clinical studies are performed these phytoconstituents can be used in the treatment of COVID 19 and many more such studies would be performed by using new and different phytoconstituents .

VII. Conflict of Interest

We hereby declare no conflict of interests related to the submission of my / our paper "Determining Andrographolide potential against COVID 19 and Compare it among Active pharmaceutical Agent utilized for antiviral activity against COVID 19 using ADME properties and Molecular docking" to International Journal of Research in Innovative Multidisciplinary Studies.

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IX. References

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X. Annexures

Table 1. General Properties estimated using Structure activity relationship of Active pharmaceutical agents

S.no	Properties	Hydroxychloroquine	Andrographolide	Lopinavir	Ritonavir
1	Molecular Weight	335.88	350.46	628.81	720.96
2	AlogP	3.78	1.96	4.33	5.91
3	H-Bond Acceptor	4	5	5	9
4	H-Bond Donor	2	3	4	4
5	Rotatable Bonds	9	3	15	17
6	Blood Brain Barrier	+	+	+	-
7	Caco-2	+	+	+	-
8	Eye corrosion	-	-	-	-
9	Eye irritation	-	-	-	-
11	Human oral bioavailability	+	-	-	-
12	Acute Oral Toxicity (Probability)	2.36	2.03	3.19	2.28
13	Plasma protein binding (Probability)	0.72	0.59	1.19	1.13
14	Subcellular localization (Probability)	Lysosomes	Mitochondria	Mitochondria	Lysosomes
15	Water solubility (Probability)	-3.56	-2.85	-3.41	-3.22

+ve and –ve sign indicates presence and absence of that property

Fig 2. Target prediction of a Andrographolide , b Hydroxychloroquine, c Ritonavir and d Lopinavir .

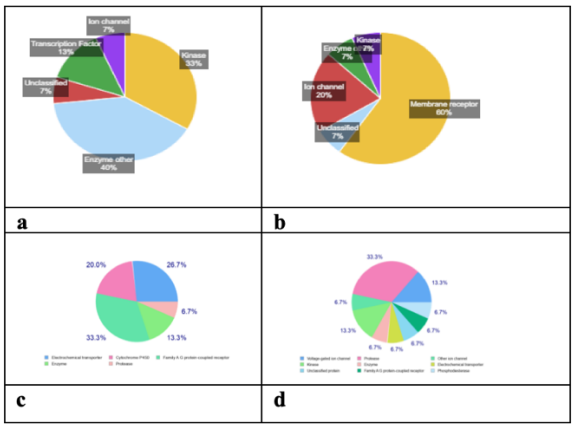
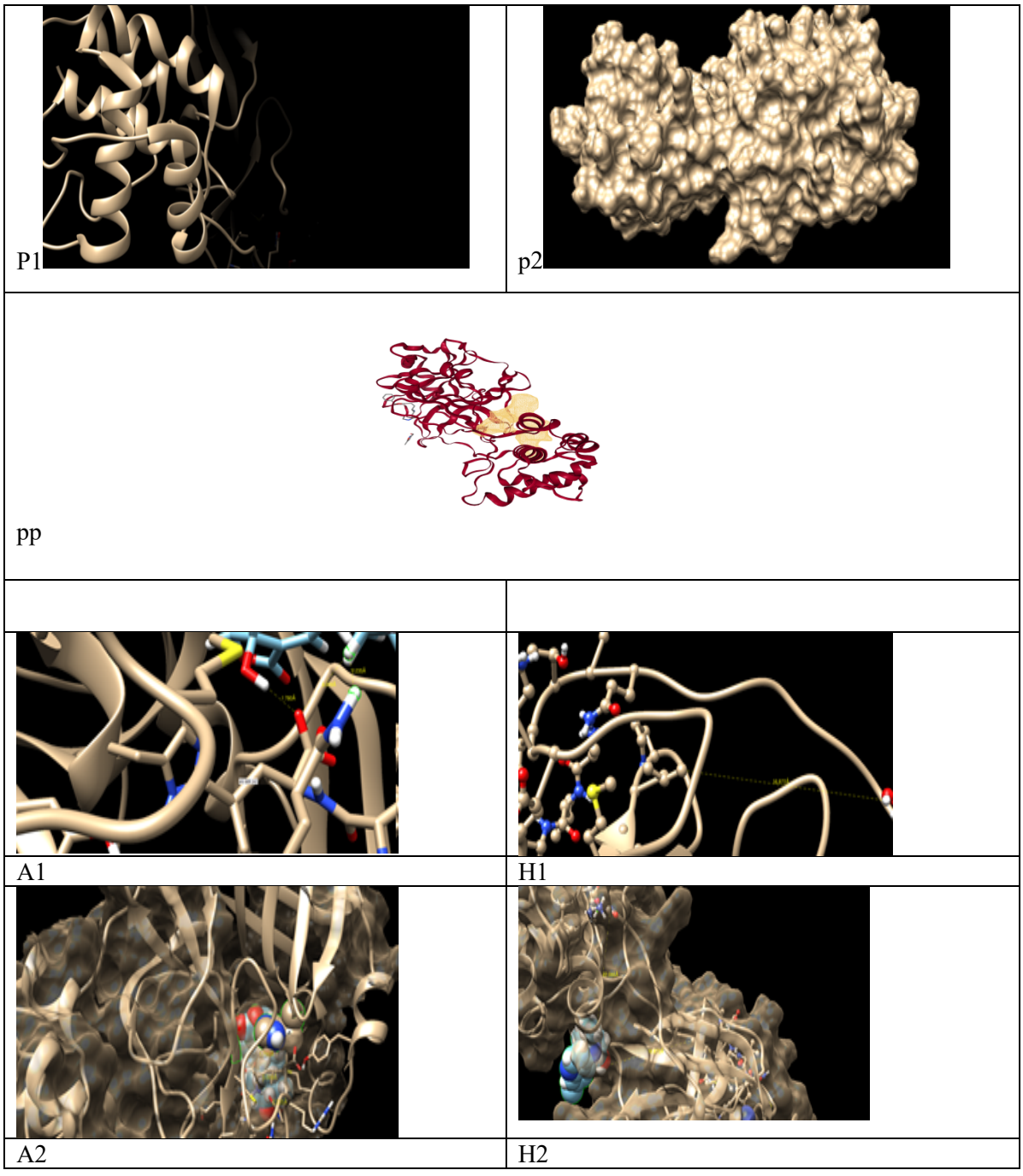


Fig 3 . Pictorial representation



Note: P1 shows software sketch of Pure covid viral protein P2 shows surface of covid Viral protein ,A1 Shows distance of Andrographlide atom. And covid viral protein ,A2 shows sphere ligand Andrographolide in to the cavity of Covid virus protein ,H1 shows distance of Hydroxychloroquine, atom. and Covid viral protein , A2 shows sphere Hydroxychloroquine ligand in to the cavity of Covid virus protein, PP is the protein structure with pocket.

Table 2. Molecular Docking properties of Andrographolide and Hydroxychloroquine

S.no	Parameters	Andrographolide	Hydroxychloroquine
1	Energy $Kcal^{-mol}$	10.5694	18.838
2	SimpleFitness	10.5694	18.838
3	FullFitness	-1220.9	-1235.15
4	DeltaG $Kcal^{-mol}$	-7.40	-8.09
5	Cluster	3	26
6	ClusterRank	0	1
7	Distance	1.780 Å	16.87 Å
8	Angle	-174.39°	-8.44°