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IDENTIFICATION OF POTENT BIOACTIVE COMPOUNDS FROM TERMINALIA CHEBULA (RETZ.) TARGETING MULTIPLE RECEPTORS OF SARS-COV-2 THROUGH IN SILICO APPROACH: KING OF AYURVEDA AGAINST COVID-19

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ABSTRACT

Terminalia chebula (Retz.) (*T. chebula*), is a valuable medicinal tree in Asian countries with potential anti-viral properties. It is considered as "King of Medicine" and "Mother of Medicine" due to its exceptional medicinal properties in fighting against various diseases. The bioactive compounds from the *T. chebula* were identified and *in silico* molecular docking was carried out aiming various SARS-CoV-2 targets. The binding energies of the *T. chebula* active compounds towards the active sites of various protein targets of SARS-CoV-2 were represented as MolDock scores and compared with the reference drug scores. Chebulinic Acid, 1,2,3,4,6 penta galloyl β-D-glucose, Chebulagic acid, Terflavin C, Arjunin, Terflavin D, Ellagitanin, Chebulanin, Casuarinin, Punicalin, Corilagin, 1,6 di-O-galloyl-D-glucose, galloyl glucose has shown high binding energies than the reference drugs. Further, *in silico* ADMEK analysis revealed, all the bioactive compounds from *T. chebula* having good bioavailability and no-toxicity except Pyrogallol. We thus hypothesize; various phyto-bioactive compounds of *T. Chebula* may act as a new alternative in the treatment of COVID-19 infection based on the holistic concept of traditional Indian medicine principle.

KEYWORDS: *Terminalia Chebula* (Retz.), COVID-19, SARS-CoV-2, *In silico* docking.

INTRODUCTION

The pandemic COVID-19 caused a huge chaos around the world from the day it was identified in Wuhan (China) in the late December 2019 (Zhu et al. 2020). Global public health is under constant threat of emerging and re-emerging viral infections, particularly those that do not currently have effective vaccines or have the potential treatment strategies (Diamond and Pierson. 2020; Luo and Gao. 2020; Diamond et al. 2019; Bailey et al, 2019; Kaiser and Barrett, 2019; Rossey and Saelens, 2019, Yong et al, 2019). Furthermore, due to increased global travel, trade, and rapid urbanization, increased numbers of viral pathogens are being introduced or reintroduced into areas where they are not normally indigenous (O'Dowd. 2007). This is reflected by the recent emergence of viral outbreaks caused by novel SARS CoV-2. However, the methods of treatment with conventional approach are not satisfied with many side effects and less effective; therefore it is crucial to find an alternate traditional practice to fight against this intractable viral infectious disease (Pandey et al. 2020). Medicinal plants act as a cheap source of unique photo-constituents that are used extensively against various infectious diseases (He et al. 2020). From the time immemorial several medicinal plant preparations were used in the indigenous medicinal systems across the globe and therefore, modern medicines were not able to replace most of them today. Most of the world population depends solely on plant based traditional medicine (Balick and Cox. 2020). This is because their easy availability, less cost with natural origin, higher safety margins and lesser or no side effects (Shubashree et al. 2020).

Terminalia chebula Retz. (*T. chebula*) is a traditional Indian medicinal plant, having multiple pharmacological properties. *T. chebula* is native to India and Pakistan, but also found in other Asian countries. *T. chebula* is a flowering evergreen tree (Family: Combretaceae), referred as "King of Medicine" (Gupata. 2012; Muhammed et al. 2012; Bag et al. 2013) and "Mother of Medicine" (Chandil et al. 2021). It is well known as

'Haritaki' since it carries away all diseases (Rathinamoorthy and Thilagavathi. 2014; Asif et al. 2019). The plant has been used extensively in Indian traditional medicine and Ayush. The plant is rich in Phytosterols, Triterpenoids, Carbohydrate, Glycosides and Phenolic compounds compared to other medicinal plants (Choudary et al. 2020; Hussain. 2021) which are used in the treatment of autoimmune diseases (Mandeville and Cock. 2018), liver toxicity and oxidative stress (Ahmadi-Naji et al. 2017), hepato-protective, neuroprotective (Nigam et al. 2020). The plant extracts were used effectively against various viral diseases such as HIV, HSV and CMV infections (Lee et al, 2011; Jokar. 2016; Basha. 2017; Kesharwai et al 2017, Akhtar 2019). Hence, in the present study, potential phyto chemical compounds from *T. chebula* were docked against various targets of SARS CoV-2 using *in silico* docking approach. Further, the bioavailability and toxicity levels of the potential inhibitor compounds were predicted using *in silico* ADMEK analysis tools.

MATERIALS AND METHODS

Target Selection and Sequence retrieval

Initially, eight Covid-19 targets were selected for the study, which play a major role in the invasion and duplication of the virus. The 3D structures of Spro, Mpro, Npro, PLpro, RdRp, NSP9, MGpro, Nsp15 were obtained from RCSB Protein Data Bank with PDB IDs 6VSB, 6LU7, 6YI3, 6W9C, 6M71, 6W4B and 6VWW respectively and saved in PDB format. Void of the 3D structure of Epro necessitated the construction of the homology model from the protein sequence (YP_009724392.1) using SWISS-MODEL adopting SARS-CoV envelope protein as a template and structural reliability was checked using Rampage Ramachandran Plot Assessment web servers. Two human targets were selected from the literature study, i.e. ACE2 (PDB ID: 1R42) the major functional receptor of the virus and GRP78 (PDB ID: 5E84) major chaperone of unfolded protein response. 3D structures were being obtained from RCSB Protein Data Bank in PDB format. The reference drugs, Hydroxychloroquine, Nelfinavir and Favipiravir were obtained from PubChem. Removal of the water molecules, cofactors and ligands from the targets were done prior to docking.

Ligand preparation

Various bioactive compounds of *T. chebula* were identified and their structures were obtained from PubChem and saved in SDF format for docking studies. The list of the compounds and their PubChem IDs were given in the Table 1. The ligand molecules were prepared for docking studies using Marvin tools.

Table 1: List of phytochemicals from *T. chebula* and reference drugs with Pubchem ID.

S. No.	Name of the Phytochemical compound	PubChem ID
1	Pyrogallol	1057
2	Hydroxychloroquine	3652
3	Vanillic acid	8468
4	Corilagin	73568
5	Maslinic acid	73659
6	Galloyl glucose	124021
7	Chebulagic acid	442674
8	Ferulic acid	445858
9	Ellagitanin	
10	p- Coumaric	1549106
11	2-alpha hydroxyursolic acid	6918774
12	Arjunglucoside	14658050
13	1,6-di-O-gallyol-D-glucose	91227631
14	Terflavin	101587737
15	Chebulinic acid	72284
16	Casurinin	157395
17	1,2,3,4,6-penta galloyl β-D-glucose	374874
18	Punicalin	5388496
19	Chebulanin	75034370
20	Terflavin	101589227
21	Gallic acid	370
22	Nelfinavir	64143
23	Chebulic acid	71308174
24	Favipiravir	492405

Molecular docking

Docking studies were performed using Molegro Virtual Docker Software (MVD, 2010.4.0.0). Initially, each target protein was imported individually and the cavities with large surface area were detected using default parameters. Active sites of the targets were obtained from the literature search and checked for their presence in the cavities detected previously. Grid size was set to

each target individually. Thereafter ligands were imported and set to be docked using default parameters. Ligand evaluation was carried out through internal ES, internal H-bond, and Sp2-Sp2 Torsions during the setup. Energy minimization was performed after docking using the MolDock scoring function by the algorithm. After docking the top-best ranked poses were obtained by enabling the energy threshold. The results were analyzed and discussed.

Estimation of bioavailability and toxicity prediction of phyto-bioactive compounds of *T. chebula*

Estimation of bioavailability and bio-toxicity of the phyto-bioactive compounds was carried out using ALOGPS 2.1 and Pro Tox II web servers. Molecular lipophilicity (Log P) and aqueous solubility (Log S) determine the pharmaco-kinetic properties of the compounds. These values were obtained from ALOGPS 2.1 non java interface. The active compounds of the docking studies were estimated for their bio toxicity using a Pro Tox II webserver. LD50 value of the compounds was classified into various classes according to the Globally Harmonized System of classification (GHS). The compounds were submitted to the web server in SMILES format.

RESULTS

Molecular docking

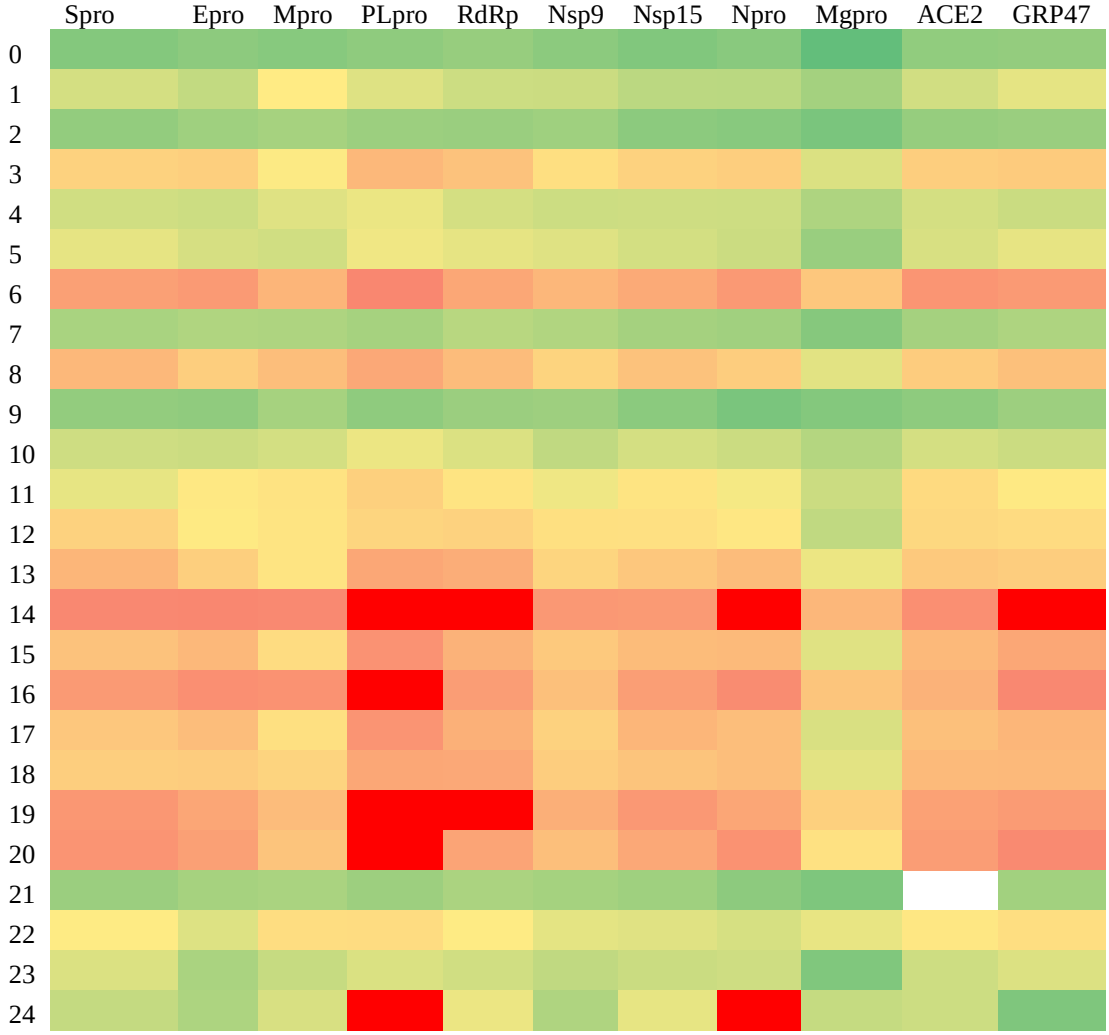
At Spro target, Chebulinic acid (-258.449), Arjunin (-245.294), Terflavin C (-242.252), 1,2,3,4,6 penta galloyl β-D-glucose (-238.165), Chebulagic acid (-231.546), Terflavin D (-206.283), Ellagitannin (-203.717) have shown highest binding affinities (Graph 1). They formed Hydrogen bonds with Asp (568, 574, 586), Gln (853, 949,957) Thr (572, 573, 588, 827), Ser (45, 46), Ile (569, 587), Lys (854, 557), Asn (960, 953, 955), Leu (828, 959), His 1058, Pro 589, Phe 855, Ala 956, and Val 952. The results revealed Asp 568, Gln 853, Thr 572 and Asp 574 as the major binding hotspots of Spro. Chebulinic acid (-260.327 and -258.176) 1,2,3,4,6 penta galloyl β-D-glucose (-250.756 and -247.672) were the high affinity binding molecules towards Epro and Mpro respectively. The hydrogen bonds were observed with Arg 61, Thr (30, 35), Asn (64, 15), Phe (20, 23, 26), Ile 46, Ala (22, 32, 36), Cys 43, Leu (18, 28, 34), Val (24, 25, 29, 47) and Tyr 57. The results revealed that Thr 30, Arg 61, Cys 43, Asn 64 and Phe 23 as the major binding hotspots at Epro. The formation of hydrogen bonds occurred with many residues including Ser (144, 46), Cys (44, 144, 145), Glu 166, Gly 143, Val 186, His (41, 163, 164, 172), Arg 188, Asn 142, Thr (24, 25, 26, 45, 190), Gln (189, 192), Leu (141, 167), Asp (187, 189), Met 49, Pro 168, Phe 140 and Tyr 54. Ser144, Cys145, Glu166, Gly143, His163, 164 and Asn142 were identified as the major binding hotspots of Mpro.

The highest binding efficiencies towards PLpro were 1,2,3,4,6 penta-galloyl β-D-glucose, Chebulinic acid, Arjunin, Terflavin C with Mol Dock score of -294.986, -284.12, -280.775 respectively. The hydrogen bond formation was seen with Gly 160, Leu 162, Val 159, Asp (108, 109), Glu (160,161), His 89, Asn (108, 109, 156), Thr158, Gln 269, and Ser 85 amino acids by the phytochemical compounds of *T. chebula*. The major hotspots for efficient binding of the target and successful inhibition were found to be Gly 160, Leu 162, Thr 158, Glu 161 and Asn 109 for PLpro. Towards RdRp, Nsp9, Npro and MGpro targets, Chebulinic acid showed the best binding efficiency (-288.847, -240.356, -116.902 and -204.778, respectively). The hydrogen bond formation was seen with His 133, Tyr (129, 619), Ser (709, 772, 784, 795, 814), Asn (135, 138, 705, 738, 781), Asp (135, 140, 164, 161, 618, 711, 760, 761), Lys (47, 621, 780, 783, 798), Thr (141, 710), Leu1 42, Ala (130, 702, 706, 762, 771), Glu (136, 167, 796, 811), Val 776, Phe 134 and Gly 774 of RdRp with the docked compounds. The major hotspots for efficient binding of the target and successful inhibition were found to be His 133, Tyr 129, Ser 784, Asn 781, Ser 709 and Lys 47. The hydrogen bond formation was seen with Cys (47, 74), Asn (97, 197), Ser6, Arg (100, 112), Asp79, Thr110, Ala (108, 109), Val (8, 111), Leu (104, 113) and Gln114 at Nsp9. Most of the H-bond interactions are found with Arg 112, Val 111, Leu 113 and Ser 6. The H-bond interactions were formed with Tyr (46, 69, 71), Arg (48, 52, 67, 109), Thr (9, 51, 75), Asn (7, 8), Leu5, Glu (22, 78, 134), Ala (74, 79, 116), Ser11, Pro77 and Phe13 at Npro. The major hotspots for efficient binding of the target and successful inhibition were found to be Tyr (46, 71), Arg 48, Thr 9, and Asn 8. Most of the H-bond interactions are found with Trp 75, Asn 74 and Gly (78, 79) of MGpro.

The highest binding energy was confined to Terflavin C (-240.546) at Nsp15 protein. The H-bond interactions were formed with Asn (5, 53), Ser (2, 104, 242, 244, 294), Glu (4, 22, 57, 234, 261,340), Leu (3, 246, 346), Met (1, 105), Ala 232, Lys (61, 110, 290), Asp (107, 220, 240), Cys 103, Gly (21, 101, 230, 239, 248, 254), Phe (16,241), Val (102, 339), Gln (20, 245), His (235, 250, 338), Pro 334, Trp 333 and Tyr (238, 243, 343). At ACE2 protein target Chebulinic acid and Chebulagic acid were the top hits that bind with high affinity towards the target by forming hydrogen bond interactions with Asp (350, 382), Asn (394, 330), Ala (99, 348, 387), Arg 393, Tyr 385, Ser (43, 44, 47), Lys (26, 353, 562), Leu 391, Glu (37, 375, 402), Phe 390, Pro (346, 389), Trp 69, His (378, 401), Gly (326, 354). The major hotspots for efficient binding of the target are Asp 350, Lys 562 and Arg 393. At GRP74 target, Chebulininc acid followed by 1,2,3,4,6 penta galloyl β-D-glucose have shown high binding affinities towards the target. The H-bond interactions were formed with Arg (101, 506, 528), Gln (182, 526), Glu (143, 463, 498, 533), Asn (104, 177, 524, 527), Asp (105, 178, 186, 500, 525), Ile (504, 522), Leu (474, 475, 505, 529), Thr (102, 124, 189, 469, 477), Tyr 462, Val 507, His 473, Ala79 and Gly 100. The major hotspots for efficient binding of the target are Asn 524, Asn 104, Arg 528, Gln 526, Leu 529 and Ile 522.

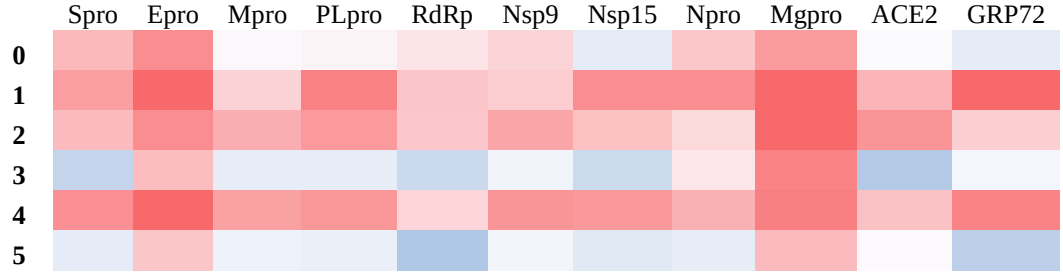
The binding energies of all the compounds from *T. chebula* at various target proteins were shown in the form of heat map (Graph 1). Higher the binding affinity towards the target brighter the color, lesser the affinity for the target, lighter the color intensity. The hydrogen bond energies were shown in Graph 2 for the different compounds at various SARS Cov-2 targets.

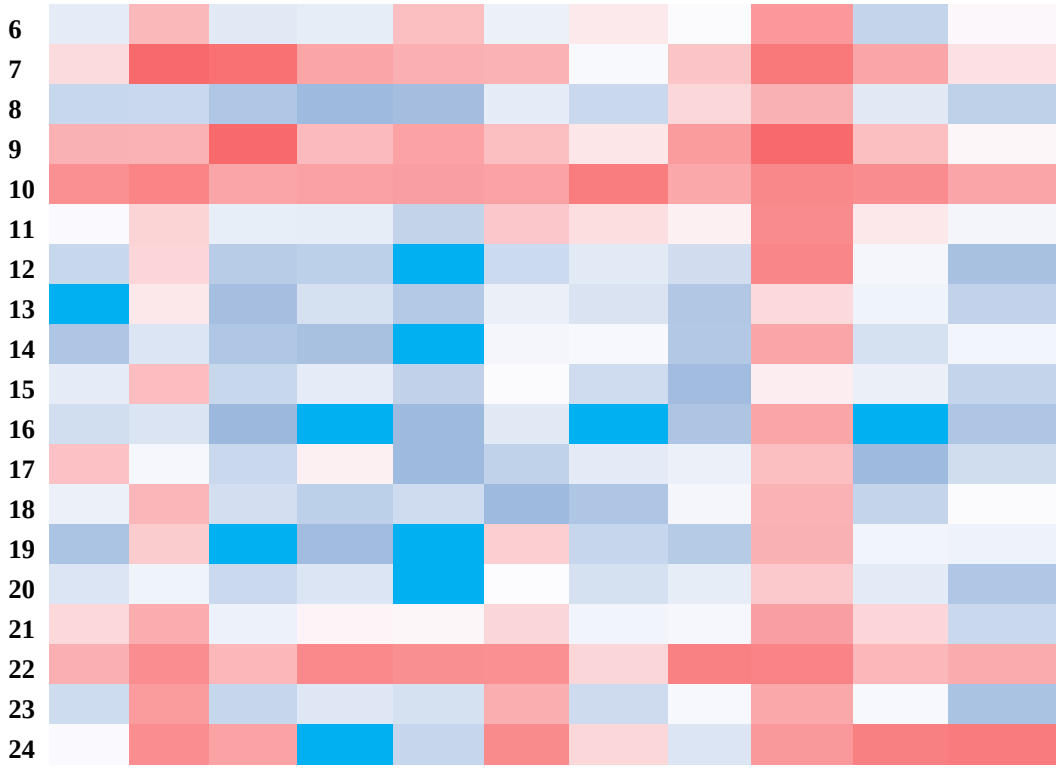
Graph 1: Binding energies of *T. chebula* active compounds and reference drugs towards the active sites of protein targets of SARS-CoV-2 The MolDock scores represent the binding energies/affinities of the compounds towards the active sites of the targets. Lower the MolDock score higher the binding efficiency/affinity. Red color represents higher binding energies, Green color represents lower binding energies.



0-Pyrogallol, 1-Hydroxychloroquine, 2-Vanillic acid, 3-Corilagin, 4-Maslinic acid, 5-Galloyl glucose, 6-Chebulagic acid, 7-Ferulic acid, 8-Ellagitannin, 9-p-Coumaric, 10-2 α hydroxyursolic acid, 11-Arjunglucoside, 12-1,6 di-O-galloyl-D-glucose, 13-Terflavin D, 14-Chebulinic acid, 15-Casuarinin, 16-1,2,3,4,6 penta galloyl β-D-glucose, 17-Punicalin, 18-Chebulanin, 19-Terflavin C, 20-Arjunin, 21-Gallic acid, 22-Nelfinavir, 23-Chebulic acid, 24-Favipiravir

Graph 2: Hydrogen bonding energies of various compounds at different SARS CoV-2targets. Red color indicates lower binding enery whereas Blue color indicates higher binding energy.





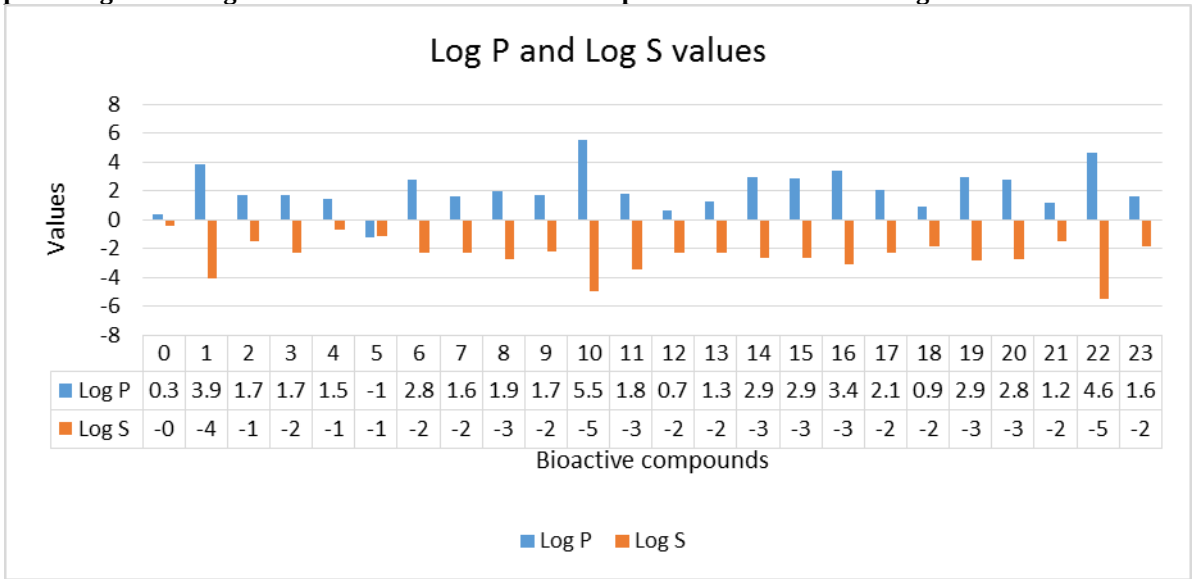
0-Pyrogallol, 1-Hydroxychloroquine, 2-Vanillic acid, 3-Corilagin, 4-Maslinic acid, 5-Galloyl glucose, 6-Chebulagic acid, 7-Ferulic acid, 8-Ellagitannin, 9-p-Coumaric, 10-2 α hydroxyursolic acid, 11-Arjunglucoside, 12-1,6 di-O-galloyl-D-glucose, 13-Terflavin D, 14-Chebulinic acid, 15-Casuarinin, 16-1,2,3,4,6 penta galloyl β-D-glucose, 17-Punicalin, 18-Chebulanin, 19-Terflavin C, 20-Arjunin, 21-Gallic acid, 22-Nelfinavir, 23-Chebulic acid, 24-favipiravir

The bioactive compounds that showed higher target binding efficiency compared to Nelfinavir at all the targets include Chebulinic Acid, 1,2,3,4,6 penta galloyl β-D-glucose, Chebulagic acid, Terflavin C, Arjunin, Terflavin D. Ellagitanin, Chebulanin, Casuarinin showed higher target binding efficiency than Nelfinavir at all targets except MGpro. Punicalin, Corilagin, 1,6 di-O-galloyl-D-glucose showed lowest binding energy than nelfinavir at all targets except MGpro and Mpro. Arjunglucoside has shown high inhibiting property than Nelfinavir at targets PLpro, Npro, Epro, RdRp, Nsp9, Nsp15 and higher than Hydroxychloroquine but lower than Nelfinavir at Mpro, Spro and MGpro. It has to be noted that the compounds that was shown exception at MGpro, Mpro and Spro has highest target binding efficiency than Hydroxychloroquine. The compounds galloyl glucose was found to have highest binding efficiency than hydroxychloroquine at all targets except Mpro, MGpro. 2 α hydroxyursolic acid and maslinic acid were found to have lowest binding energy than hydroxychloroquine but not significant at targets Mpro and Spro. Chebulic acid was found to have highest target binding efficiency than hydroxychloroquine at only RdRp, Spro and Npro targets but was not significant at the other targets. The bioactive compounds that showed least binding efficiency at all targets include vanillic acid, ferulic acid and p-Coumaric, gallic acid. Hence they are not significant.

Log P and Log S Values

The molecular lipophilicity and aqueous solubility are quantified as log P and log S values that determine the pharmacokinetic properties of the compounds. The log P and log S values of all the bioactive compounds are below 5 and -4 respectively as per the Lipinski rule of five indicating good absorption properties of the bioactive compounds in both lipophilic and hydrophilic environments except for 2 alpha hydroxyl ursolic acid whose Log P and Log S values are 5.5 and -5 respectively. The Log P value of Galloyl glucose is less than 0 and therefore can be considered as neurotransmitter Graph 3.

Graph 3: Log P and Log S Values of *T. chebula* active compounds and reference drugs.

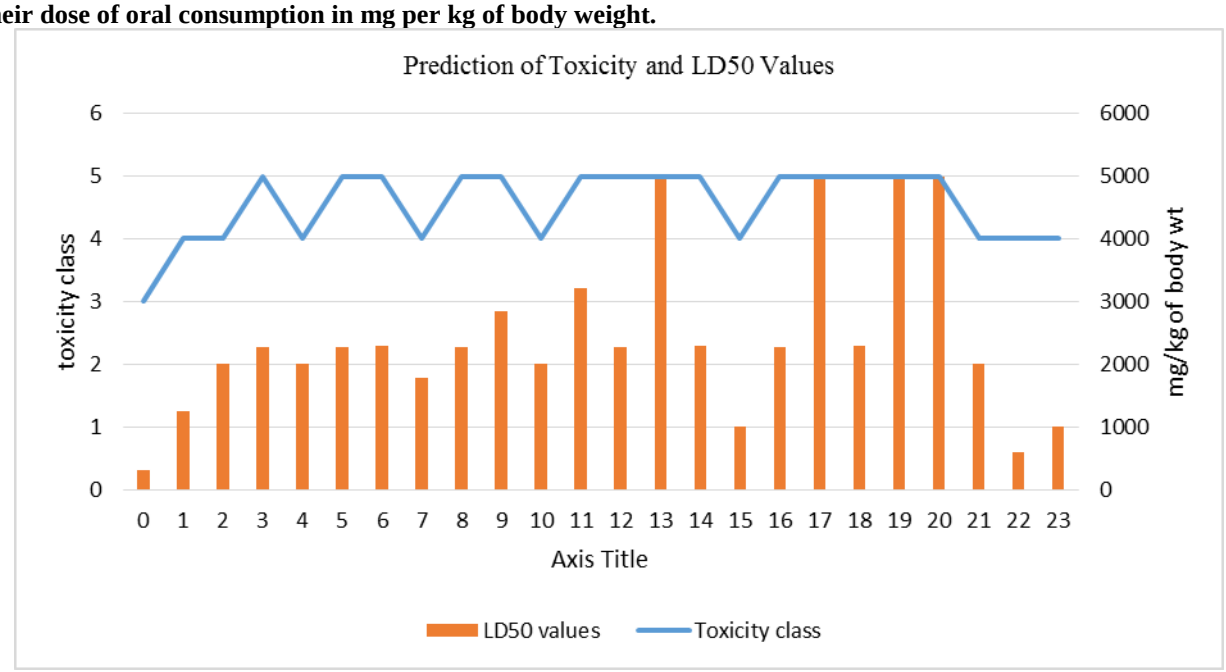


0-Pyrogallol, 1-Hydroxychloroquine, 2-Vanillic acid, 3-Corilagin, 4-Maslinic acid, 5-Galloyl glucose, 6-Chebulagic acid, 7-Ferulic acid, 8-Ellagitannin, 9-p-Coumaric, 10-2 α hydroxyursolic acid, 11-Arjunglucoside, 12-1,6 di-O-galloyl-D-glucose, 13-Terflavin D, 14-Chebulinic acid, 15-Casuarinin, 16-1,2,3,4,6 penta galloyl β-D-glucose, 17-Punicalin, 18-Chebulanin, 19-Terflavin C, 20-Arjunin, 21-Gallic acid, 22-Nelfinavir, .23-Chebulic acid

Toxicity and LD50 values

The LD50 value is lethal dose required (usually per body weight) to kill 50% of the test population. In silico toxicity and LD50 predictions showed that all the bioactive compounds fall under classes 4-5 which indicates that these phyto-active compounds may not affect the individuals upon oral consumption except Pyrogallol. Pyrogallol is the only compound having less LD50 value of 300mg per kg body weight which comes under the class 3 of oral toxicity (Graph 4).

Graph 4: Toxicity and LD50 values of *T. chebula* active compounds which determine their toxicity class as per their dose of oral consumption in mg per kg of body weight.



0-Pyrogallol, 1-Hydroxychloroquine, 2-Vanillic acid, 3-Corilagin, 4-Maslinic acid, 5-Galloyl glucose, 6-Chebulagic acid, 7-Ferulic acid, 8-Ellagitannin, 9-p-Coumaric, 10-2 α hydroxyursolic acid, 11-Arjunglucoside, 12-1,6 di-O-galloyl-D-glucose, 13-Terflavin D, 14-Chebulinic acid, 15-Casuarinin, 16-1,2,3,4,6 penta galloyl β-D-glucose, 17-Punicalin, 18-

Chebulanin, 19-Terflavin C, 20-Arjunin, 21-Gallic acid, 22-Nelfinavir, .23-Chebulic acid.

DISCUSSION

For a successful infection a virus must initially gain entry into the host cell and utilize host machinery for its survival and replication to produce a large number of copies for further infection. The targets chosen for this study are among these chains of events of the virus invasion. Inhibiting these targets through phytochemicals present in *T.chebula* is the major criteria of the present study. After the virus contact with the host it tries to gain entry into the host cells for a successful infection. Spro of virus is involved in the entry of the virus through binding to the host cell receptor ACE2. Epro helps in altering the membrane permeability of host cells through its ion channel activity leading to the membrane fusion of the virus (Jin et al, 2020). ACE2 and GRP47 being the host cell receptor for viral entry plays an important role in the successful invasion of the virus. Blocking these targets ceases viral ability to infect (Vkovski et al. 2020). As observed from our result the bioactive compounds (Chebulinic Acid, 1,2,3,4,6 penta galloyl β-D-glucose, Chebulagic acid, Terflavin C, Arjunin, Terflavin D, Ellagitanin, Chebulanin, Casuarinin, Punicalin, Corilagin, 1,6 di-O-galloyl-D-glucose, galloyl glucose) of *T. chebula* inhibited all the 4 targets. Therefore the viral entry cannot be gained either by the host receptors or by viral proteins. Various *in silico* studies (Tang 2020; Ou 2020, Belouzand 2012, Showeman & Fielding) have shown the inhibition of these targets with phytochemicals.

The immediate step after gaining entry into the host cells is the viral replication and the proteins involved are Nsp9 and Nsp12 (RdRp). Nsp9 along with other essential proteins are involved in the replicative cycle through the formation of viral replicative complex (Sutton et al. 2004). Nsp12 binds with other Nsps to bring about replication and transcription of the viral genome. Nsp15 is involved in the processing of mRNA of the virus like methylation, capping and PolyA addition. Blocking these targets ceases the viral ability to replicate (Snijder et al. 2016; Raj et al. 2021). The ability of *T.chebula* compounds (Chebulinic Acid, 1,2,3,4,6 penta galloyl β-D-glucose, Chebulagic acid, Terflavin C, Arjunin, Terflavin D, Ellagitanin, Chebulanin, Casuarinin, Punicalin, Corilagin, 1,6 di-O-galloyl-D-glucose, Arjunglucoside, galloyl glucose) to block Nsp9 and Nsp12 (RdRp) was observed from our *in silico* docking. Therefore, even if the virus manages to gain entry, the replication can be blocked by above compounds to stop the further progression of the virus. The genome of the virus encodes 16 Nsp's which play a major role in providing machinery required for viral replication, transcription and RNA processing. PLpro along with the Mpro are involved in the cleavage of the polyproteins releasing functional polypeptides (Nsp's) and therefore have a role in the multiplication of the virus. Non availability of these proteins ceases the viral ability to multiply due to lack of replication machinery (Vkovski et al. 2020). From our results of *in silico* docking studies it was observed that the *T.chebula* compounds (Chebulinic Acid, 1,2,3,4,6 penta galloyl β-D-glucose, Chebulagic acid, Terflavin C, Arjunin, Terflavin D, Ellagitanin, Chebulanin, Casuarinin, Arjunglucoside) are able to block these targets. Therefore multiplication of virus can be halted. The most important part for successful invasion of virus is the production of efficient progenies that are capable of infecting new healthy host cells. The assembly of viruses through interactions among the proteins and maintenance of viral intracellular homeostasis is achieved by MGpro whereas the morphogenesis and virion assembly is carriedout by Epro. The formation and maintenance of viral RNP complex along with the assembly of viral genomes and its structural proteins present in the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) to form mature virions is brought by the Npro. Simultaneously altering the host cell proliferation, metabolism and cell cycle by inhibiting cytokinins and CDK4 respectively is also done by Npro. Targeting and blocking these proteins results in immature and inefficient progenies of lower viral titer (Schoeman and Fielding. 2020). From our results of *in silico* docking studies it was observed that the *T.chebula* compounds (Chebulinic Acid, 1,2,3,4,6 penta galloyl β-D-glucose, Chebulagic acid, Terflavin C, Arjunin, Terflavin D, Ellagitanin, Chebulanin, Casuarinin, Arjunglucoside) are able to block these targets. Therefore virion assembly can be inhibited.

So far the efficiency of *T.chebula* compounds in inhibiting different stages of viral life cycle is observed. In order to show their inhibition properties the bioactive compounds has to cross several membranes to reach their target sites. Bioavailability and permeability play crucial role in this context which was measured by log P and log S. Our *in silico* predictions showed good solubility and absorption properties of all the compounds except for pyrogallol. Most of the phytochemicals tend to have bio toxicity. From our study all the compounds fall under class 4 and 5 which indicates their non-toxicity except for pyrogallol. Hence *T.chebula* can be used as a potential phytomedicine in the treatment and management of COVID-19.

CONCLUSION

In this study, *in silico* docking studies was performed to know the efficiency of bioactive compounds of *T.chebula* in inhibition/ blocking of the various targets (Spro, Epro, Mpro, PLpro, RdRp, Nsp 9, Nsp 15, Npro, MGpro, ACE2 and GRP47) at different stages of the invasion of the virus. The results showed most of the phytochemicals from *T. chebula* were effective in inhibiting the targets. It was also found that all the compounds from *T.chebula* has high bioavailability, lipophilicity and less or no toxicity through *in silico* ADMEK analysis. We thus hypothesize that various phyto-bioactive compounds of *T. Chebula* may act as a

new alternative in the treatment of COVID-19 infection based on the holistic concept of traditional Indian medicine principle. Further, in *vitro* studies are needed to find out their drug likeliness and efficacy for drug design.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection was performed by MDS. Data analysis was performed by MDS, CSK, DAF and MS. The first draft of the manuscript was written by MDS and CSK and all the authors commented on previous versions of the manuscript. Final manuscript was reviewed, edited and corrected by KSN. Funding acquisition, Resources and Supervision was carried out by KSN and MS. All authors read and approved the final manuscript.

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Ethical approve

The present study did not use any animal models or cell cultures; hence there is no need of ethical approval for the study.

Conflict of interest

The authors declare that they have no conflict of interest.

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