In-silico screening of potential immune-boosting phytocompounds from several medicinal plants against SARS-CoV-2

Rahul Koli[1], V. S. Mannur[1*], Shankar Gharge[2], Ravichandra N[1]

[1] Department of Pharmaceutical Quality Assurance, KLE University's College of Pharmacy, Nehru Nagar, Belagavi 590010, Karnataka, India.
[2] Department of Pharmaceutical Chemistry, KLE University's College of Pharmacy, Nehru Nagar, Belagavi 590010, Karnataka, India
[*]Correspondence
[1*]Department of Pharmaceutical Quality Assurance, KLE University's College of Pharmacy, Nehru Nagar, Belagavi 590010, Karnataka, India.

Dr. V. S. Mannur: drvsmannur@gmail.com

Abstract

Background: Ayurvedic medicines are the traditional medicinal system of India and they are usually composed of mixture of herbal drugs or the extracts of the active principles of various plants having therapeutic activities. Based on the available literature the following plants *Tinospora cardifolia* (Guduchi), *Piper longum* (Pippali), *Glycyrrhiza glabra* (Licorice) and *Withania somnifera* (Ashwagandha) are used as a preventive measure against various diseases, which acts by boosting the immunity against the severity of infection caused by novel coronavirus (COVID-19). In the present study the selected active constituents from above mentioned plants were used to carry out in-silico studies against covid19. MolSoft and Admet SAR2.0 were used to predict the drug likeness score and pharmacokinetic profile of phytoconstituents and protein-ligand interaction of selected phytocompounds were predicted from AutoDock Vina by PyRx 0.8 and visualization is done by BIOVIA Discovery Studio 2021. Present study concluded that, amongst all the selected phytocompounds, Withanolide D has shown good binding affinity of -8.9kcal/mol with COVID-19 main protease 3CLpro and also Withanolide D has shown good binding affinity of -9.1kcal/mol with SARS-CoV main peptidase 2GTB. The study provides the scientific evidence of this Ayurvedic formulation to combat COVID-19.

Keywords: Molecular docking, Herbal, Withanolide D, COVID-19, Druggability

Introduction

Coronavirus disease 2019 (COVID-19), it is a communicable respiratory disease give rise to SARS corona virus 2 (SARS CoV-2). This infection was first recognized in Wuhan city of China and the WHO was aware in December 2019 and By April 2022, the WHO announced over 492,189,439 confirmed cases in over 200 countries around the globe. Most independents that test positive for COVID-19 undergo mild symptoms with fever, fatigue and dry cough as the most usual symptoms. Although, due to a large number of infected individuals, there have been over 6,159,474 deaths worldwide as of April 4 2022, In India 43,030,925 cases were confirmed by April 2022 and death rate is confirmed at 521,487 [1].

As the result of the wider spreading of the disease, many of the countries have placed limits to traveling and social gatherings, as well as closed schools and nonessential workplaces. The impact of the pandemic affects everyone, ill and healthy, in all aspects of daily livings.

Ayurveda is one of the medicinal traditional systems of India. The ideas behind Ayurveda are preventing nonessential hurting and living a long healthy life. Ayurveda involves the use of natural compounds and the root cause of the disease by restoring balance at the same time create a healthy life style to cure the frequency of imbalance. Herbal medicines have existed around the world wide with long provided history and they were applied in ancient India, Chinese, Greek, Egyptian medicines for various therapies. In Ayurveda mono (single) or polyherbal (multiple herbs) are used for the treatment. The ayurvedic literature 'Sharangdhar Samhita' focused the concept of polyherbalism to achieve higher therapeutic efficacy. The active phytoconstituents of single plants are insufficient to achieve the desirable therapeutic effects when combining the multiple herbs in a particular ratio, it will give a good therapeutic effect and reduce the toxicity profile. Many plant-based medicines have flavonoids, alkaloids, phenols and tannins that exhibit immune-modulatory properties. In the current context of pandemic, a lot is spoken on hygiene, social distancing and food to prevent impact on health. This proposal is an attempt to identify few ayurvedic botanicals utilized in Jwara, Kasa, Shwasaroga, Krimi and Pratishyaya Chikista with corroborated anti-viral and immune-modulatory activities as main or adjuvant therapy for community self-reliance in the wake of COVID-19 pandemic.

Ayurveda extensive knowledge based on preventive care by which each individual can achieve by uplifting and maintain his or her immunity. In Ayurveda immunity comes under 'VYADHIKSAMATWA' In Ayurveda many single drugs or compound formulation were mentioned as Rasayana to boost up immunity. (Bala or Vyadhiksamatwa) [2].

Based on the Ayurvedic and scientific literature, the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy), India issued an advisory where it recommended the use of number of immune-boosting herbal medicinal drugs among that we have chosen most immune-boosting medicinal plants for our study , those are *Tinospora cardifolia* (Guduchi), *Piper longum* (Pippali), *Glycyrrhiza glabra* (Licorice) and *Withania somnifera* (Ashwagandha) for self-care which will develop immunity

against severe infection caused by COVID-19 [3-6]. Hence, in the present study, we proposed to elucidate the probable interaction of the phytoconstituents from individual ingredients to boost the immunity by molecular docking approach to support with scientific shreds of evidence.

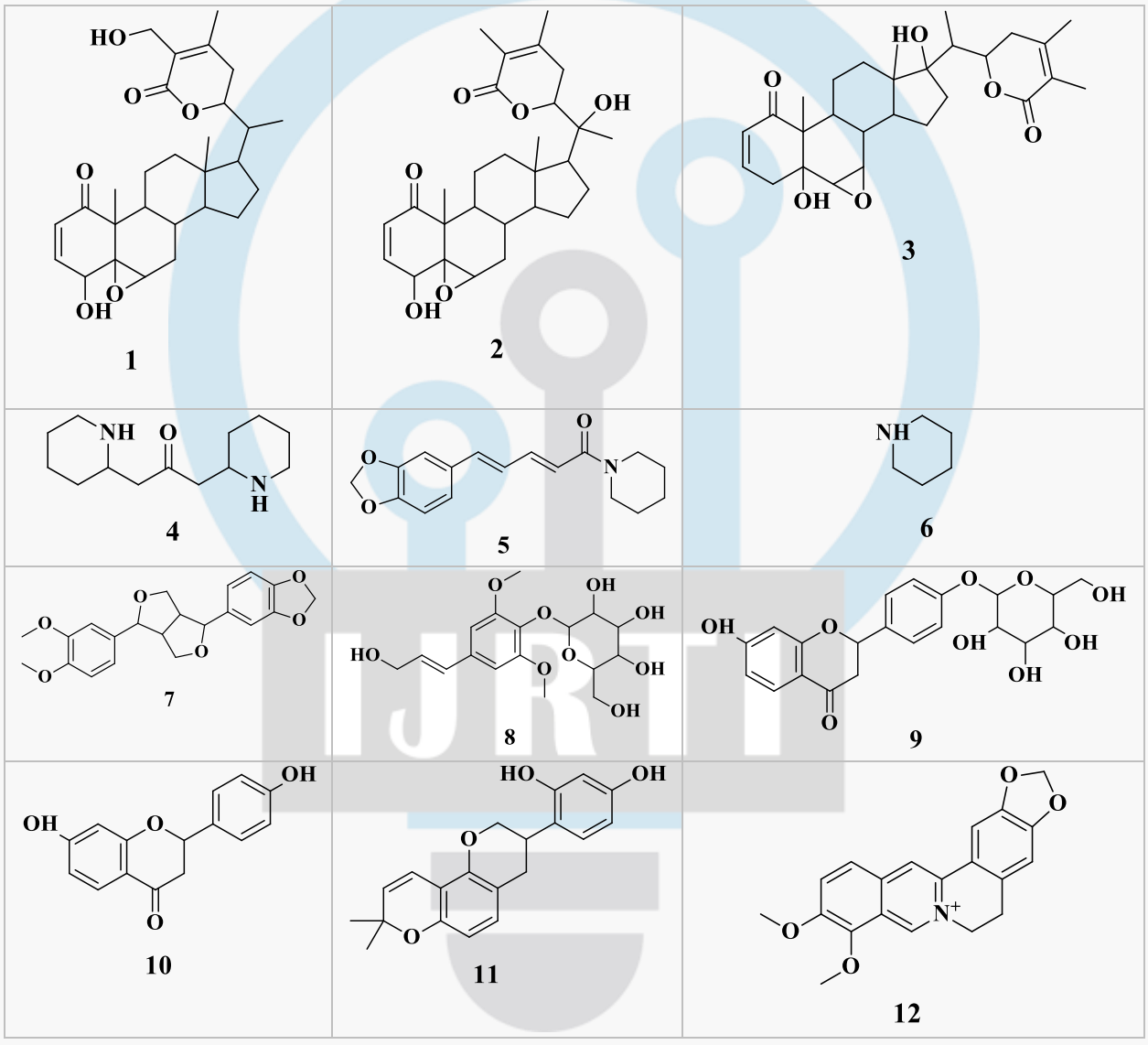
Materials and Methods

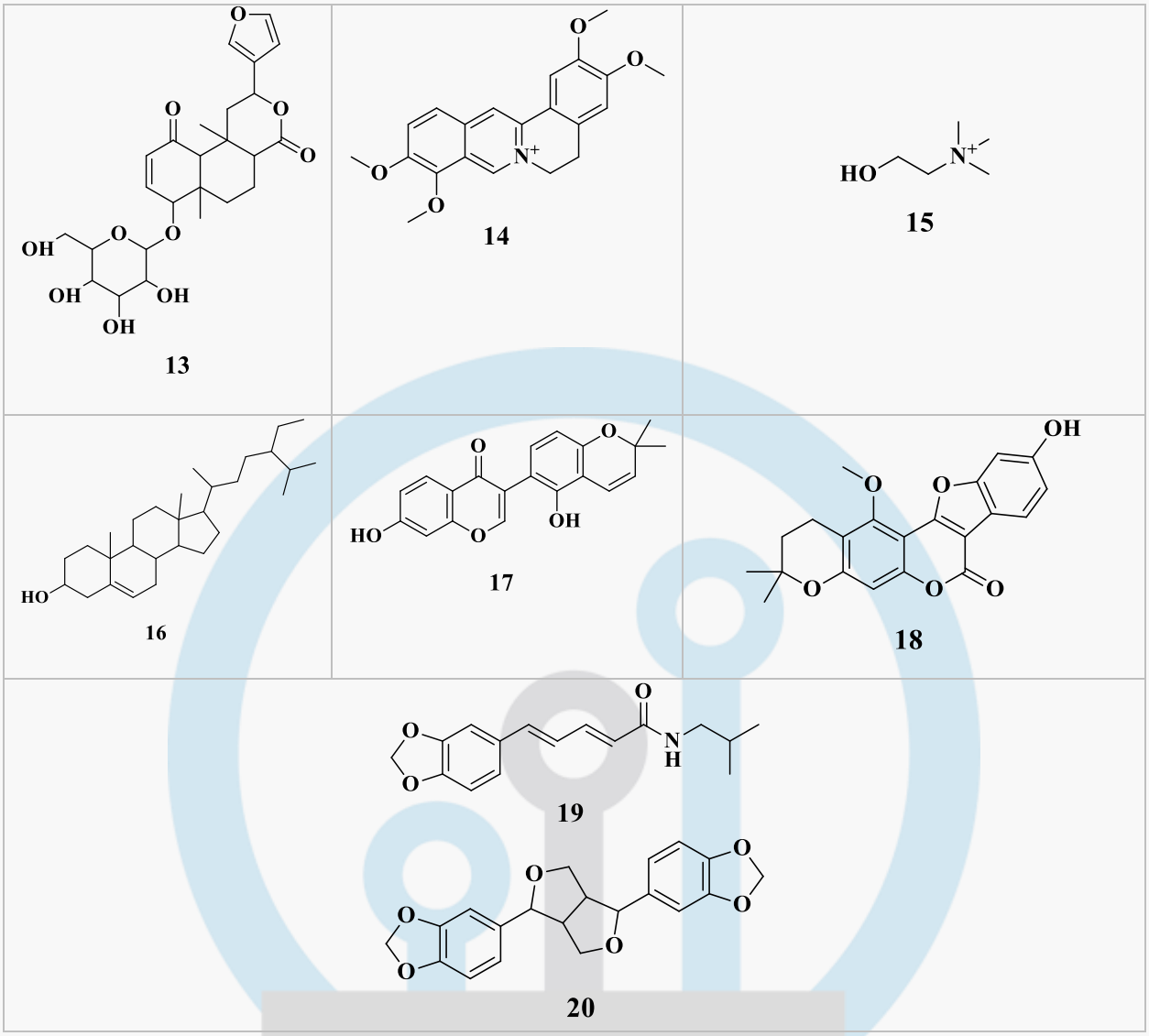
Determination of Druggability and ADMET profile

In present study, Drug likeness score of each phytoconstituents from all the four immune-boosting drugs was calculated based on Lipinski's rule of five using MolSoft (**https://www.molsoft.com/).** Likewise, the probability for pharmacokinetic properties such as Blood Brain Barrier (BBB), P-glycoprotein, plasma protein binding, skin permeability, buffer solubility and Human intestinal absorption along with Toxicology and other important aspects of ADMET was predicted using admetSAR2.0 (http://lmmd.ecust.edu.cn/admetsar2) and the structure of all the phytoconstituents are mentioned in Table 1 [7-11].

Table 1 Structure of Phytoconstituents

Structure of all selected phytocompounds were draw from ChemDraw Ultra 12.0.2





1-Withaferin A, 2-Withanolide D, 3-Withanone, 4-Anaferine, 5-Piperine, 6-Piperidine, 7-Fergesin, 8-Syringin, 9-Liquiritin, 10-Liquiritigenin, 11-Glabridin, 12-berberine, 13-Tinosporaside, 14-Palmatine, 15-Choline, 16-Beta-sitosterol, 17-Glabrone, 18-Isoglycerol, 19-Pieprlonguminine, 20-Asarinin.

Preparation of ligand

The 3D structures of all ligand molecules were retrieved from PubChem chemical database (https://pubchem.ncbi.nlm.nih.gov/) in structural data format has been converted to PDB format using Discovery Studio Visualizer (DSV) 2021.PubChem is a universal database that stores chemical structural information, including their biological activities. Furthermore, we minimized ligand's free energy using the MMFF94 force field. [12]. In the present study, from *Withania somnifera* phytocompounds like Withaferin A, Withanolide D, Withanone, Anaferine, [13] from *Piper longum* phytocompounds like Piperine, Piperidine, Fargesin, Piperlonguminine, Asarinin, [14]. from *Glycyrrhiza glabra* phytocompounds like Liquiritin, Liquiritigenin, Glabridin, Beta-sitosterol, Glabrone, Isoglycyrol [15-16] and from *Tinospora cardifolia* berberine, tinosporaside, palmatine, cholin, Syringin [17-18].

Preparation of target protein

We obtained the 3D x-ray crystallographic structures of both targets COVID-19 main protease 3CLpro (PDB ID: 6LU7) and SARS-CoV main peptidase (PDB ID: 2GTB) from PDB (www.rcsb.org). 6LU7 has two chains, "A and C". Chain A contains SARS-CoV-2 main protease enzyme and chain C is a native ligand of protein (mainly, a peptide designed to inhibit the main protease). 2GTB has three chains. Chain A contains SARS coronavirus main peptidase (3CLpro) and the other two chains are native ligands of the protein. Hence, we used chain A of both proteins for the preparation of the macromolecule. Furthermore, we cleaned the binding pocket by removing water molecules and heteroatoms using the DSV 2021 to eliminate the docking interferences; this makes calculations easier so that ligand can form satisfactory interactions with the protein molecule.

Determination of active sites

Amino acids in the active pocket site of a protein were identified by using the Biovia Discovery Studio 2021 and the determination of the amino acids in the active pocket site was used to analyse docking evaluation results [19].

Ligand-protein docking study

For molecular docking interaction, we used AutoDock Vina by PyRx 0.8. The target protein and ligand PDB files were loaded into PyRx software, and AutoDock Vina preferences were obtained for both ligand and protein in PDBQT format. The grid box was generated to the active site, and the exhaustiveness was set to 100. After completion of docking algorithm, the ligand-protein complexes that have the best conformation and lowest binding affinity were selected and visualized in DSV 2021 for their hydrophobic interactions.

Results and Discussion

Druggability and ADMET profile of bioactive phytoconstituents

MolSoft online server was used to screen the phytoconstituents druggable characteristics Among selected compounds mentioned in Table 2, only Withanolide D showed potent drug-like properties. The drug-likeness score of Withanolide D was found to be 0.85 Furthermore, all the phytocompounds were predicted to get absorbed from intestinal tract among all Withanolide D were predicted to cross BBB and also to have highest oral bioavailability and was also less toxic as compared to other phytoconstituents mentioned in Table 3.

Table 2 Drug-likeness properties of selected drugs and ligands

The server has a strong data base to predict the Druggability of phytocompounds by Lipinski's rule of five.

Sl. No	Phytoconstituents	Molecular Formula	Mol Weight (>500)	HBA (>10)	HBD (>5)	Log P (>5)	Drug likeness Score
1	Withaferin A	$C_{28}H_{38}O_6$	470.6g/mol	6	2	3.26	0.37
2	Withanolide D	$C_{28}H_{38}O_6$	470.6g/mol	6	2	3.56	0.85
3	Withanone	$C_{28}H_{38}O_6$	470.6g/mol	6	2	3.55	0.45
4	Anaferine	$C_{13}H_{24}N_2O$	224.34 g/mol	3	2	0.83	-1.49
5	Piperine	$C_{17}H_{19}N0_3$	285.34 g/mol	3	0	3.47	-0.16
6	Piperidine	$C5H_{11}N$	85.15g/mol	1	1	-0.14	-1.01
7	Fargesin	$C_{21}H_{22}O_6$	370.4g/mol	6	0	3.06	-0.31
8	Syringin	$C_{17}H_{24}O_9$	372.4g/mol	9	5	-0.85	0.05
9	Liquiritin	$C_{21}H_{22}O_9$	418.4g/mol	9	5	0.20	0.33
10	Liquiritigenin	$C_{15}H_{12}O_4$	256.25g/mol	4	2	2.40	0.79
11	Glabridin	$C_{20}H_{20}O_4$	324.4 g/mol	4	2	4.08	0.06
12	Berberine	$C_{20}H_{18}NO_4^+$	336.4g/mol	4	0	4.39	0.77
13	Tinosporaside	$C_{25}H_{32}O_{10}$	492.5g/mol	10	4	0.44	-0.20
14	Palmatine	$C_{21}H_{22}NO_4^+$	352.4g/mol	4	0	3.96	0.69
15	Cholin	$C_5H_{14}NO^+$	104.17g/mol	1	1	-0.42	0.02
16	Beta-sitosterol	$C_{29}H_{50}O$	414.7g/mol	1	1	8.45	0.78
17	Glabrone	$C_{20}H_{16}O_5$	336.3 g/mol	5	2	3.52	0.22
18	Isoglycyrol	$C_{21}H_{18}O_6$	366.4 g/mol	6	1	4.34	-0.29
19	Piperlonguminine	$C_{16}H_{19}NO_3$	273.33 g/mol	3	1	3.76	-0.05
20	Asarinin	$C_{20}H_{18}O_6$	354.4 g/mol	6	0	3.42	-0.91

Table 3 ADMET Profile

The server has a strong data base to predict physicochemical properties like pharmacokinetics, water solubility, lipophilicity, drug likeness, Toxicity and medicinal properties with high correctness of phytoconstituents which shown most binding affinity towards SARS COVID 19.

Parameters		Compounds									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
ABSORPTION	HIA	+	+	+	+	+	+	+	+	+	+
	Caco-2	-	-	+	+	-	+	+	-	+	-
	HOB	-	+	+	-	+	+	-	-	+	-
DISTRIBUTION	BBB	-	+	-	+	+	-	+	-	-	+
	P-glycoprotein (i)	+	+	+	+	-	-	-	-	+	+
	P-glycoprotein (s)	+	+	+	+	-	-	-	-	+	+
	PPB	0.91	0.83	0.94	0.89	0.97	0.82	0.62	0.85	0.8	0.7
METABOLISM	CYP3A4 (s)	-	+	-	-	-	-	+	-	-	-
	CYP2C9 (s)	-	-	-	-	+	-	-	-	-	-
	CYP2D6 (s)	-	-	-	-	-	-	+	-	-	-
	CYP3A4 (i)	-	+	-	-	-	-	+	-	-	-
	CYP2D6 (i)	-	-	-	-	-	-	-	-	-	-
	CYP1A2 (i)	-	+	-	-	+	-	-	-	-	+
EXCREATION	Plasma t1/2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Renal clearance	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TOXICITY	HERG	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
	Hepatotoxicity	-	+	-	-	-	-	+	-	-	-
	AOT	III	III	III	III	II	III	II	IV	IV	III
	Eye corrosion	-	-	+	+	+	+	-	-	+	-
	Carcinogenicity	-	-	-	-	-	-	-	-	-	-
	Ames mutagenesis	-	+	-	-	-	-	-	+	-	-

1-Withaferin A, 2-Withanolide D, 3-Withanone, 4-Anaferine, 5-Piperine, 6-Piperidine, 7-Fergesin, 8-Syringin, 9-Liquiritin, 10-Liquiritigenin.

Human either-a-go-go inhibition: HERG, Plasma protein binding: PPB, Blood Brain Barrier: BBB, Human Intestinal Absorption: HIA, Human Oral Bioavailability: HOB, Acute Oral Toxicity: AOT, (i): Inhibiter, (s): Substrate

		11	12	13	14	15	16	17	18	19	20
ABSORPTION	HIA	+	+	+	+	+	+	+	+	+	+
	Caco-2	-	-	+	+	-	+	+	-	+	-
	HOB	-	-	+	-	+	+	-	-	+	-
DISTRIBUTION	BBB	+	+	-	+	-	-	-	-	+	+
	P-glycoprotein (i)	+	+	+	-	-	-	-	-	-	-
	P-glycoprotein (s)	+	+	+	-	-	-	-	-	-	-
	PPB	0.91	0.83	0.94	0.89	0.97	0.82	0.62	0.85	0.8	0.7
METABOLISM	CYP3A4 (s)	+	+	-	-	-	-	+	-	-	+
	CYP2C9 (s)	+	-	-	-	-	-	+	+	+	-
	CYP2D6 (s)	+	+	-	+	-	-	-	-	-	-
	CYP3A4 (i)	+	+	-	+	-	-	-	-	-	-
	CYP2D6 (i)	+	-	-	-	-	-	-	-	-	+
	CYP1A2 (i)	+	+	-	-	-	-	-	+	+	-
EXCREATION	Plasma t1/2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Renal clearance	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TOXICITY	HERG	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
	Hepatotoxicity	-	+	-	-	-	-	+	-	-	-
	AOT	III	III	III	III	II	III	II	IV	IV	III
	Eye corrosion	-	-	+	+	+	+	-	-	+	-
	Carcinogenicity	-	-	-	-	-	-	-	-	-	-
	Ames mutagenesis	-	+	-	-	-	-	-	+	-	-

11-Glabridin, 12-berberine, 13-Tinosporaside, 14-Palmatine, 15-Choline, 16-Beta-sitosterol, 17-Glabrone, 18-Isoglycerol, 19-Pieprlonguminine, 20-Asarinin.
Human either-a-go-go inhibition: HERG, Plasma protein binding: PPB, Blood Brain Barrier: BBB, Human Intestinal Absorption: HIA, Human Oral Bioavailability: HOB, Acute Oral Toxicity: AOT, (i): Inhibiter, (s): Substrate

Ligand-protein interaction

AutoDock by PyRx 0.8v was used to perform a molecular docking study to identify the possible binding affinity and molecular interactions of phytoconstituents. Among all phytocompounds Withanolide D has showed i.e., -8.9kcal/mol lowest binding affinity with COVID-19 main protease 3CLpro (PDB ID: 6LU7) and same Withanolide D has showed -9.1kcal/mol with SARS-CoV main peptidase (PDB ID: 2GTB) mentioned in Table 4 and the 3D and 2D structure of protein-ligand interaction visualization is done by BIOVIA Discovery Studio 2021 showed in Figure 1.

Table 4 Molecular Docking Score / Binding energy of ligand-protein interaction

Binding score of phytoconstituents to targets Binding affinity with COVID-19 main protease 3CLpro **(PDB ID:6LU7)** and binding affinity with SARS-CoV main peptidase **(PDB ID:2GTB)**

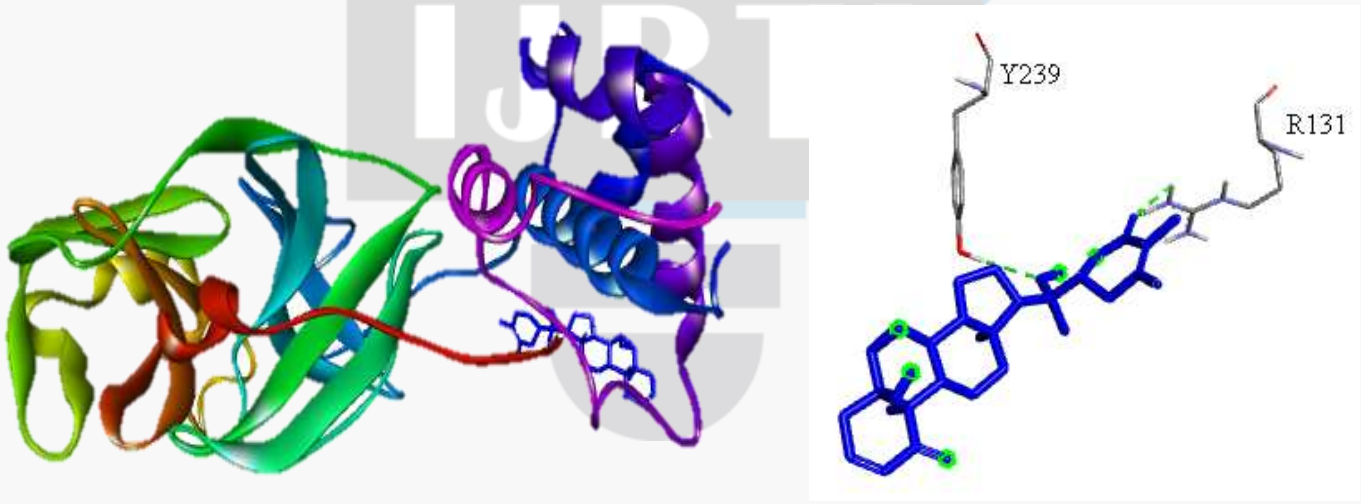
Compounds	PubChem ID	Binding energy (kcal/mol)		Hydrogen bond interactions	
		6LU7	**2GTB**	**Amino acids of 6LU7 involved in the interaction**	**Amino acids of 2GTB involved in the interaction**
Withaferin A	265237	-8.4	-8.7	ARG A:131, THR A:199, ASN A:238, TYR A:239.	LEU A:271, ILE A:286, MET A:276, ARG A:131, THR A:199.
Withanolide D	161671	-8.9	-9.1	TYR A:54, ARG A:40, PHE A:181, ARG A:105,	LEU A:287, ARG A:131, ILE A:286 THR A:199.
Withanone	21679027	-8.5	-8.4	THR A:199	GLY A:195, ASP A:197, ARG A:131, LYS A:137, THR A:199.
Anaferine	443143	-5.3	-5.3	HIS A:41, MET A:49, HIS A:164.	ILE A:106, ILE A:249, PRO A:293.
Piperine	638024	-6.8	-7.0	LEU A:272, ASP A:289, LYS A:137, GLU A:290, LEU A:287.	ILE A:286, TYR A:239, MET A:276, ASN A:277.
Piperidine	8082	-3.4	-3.2	TRP A:218, LEU A:271.	ALA A:173, PHE A:185.
Fargesin	10926754	-7.1	-7.3	THR A:25, GLU A:166, SER A:46, HI5 A:172, CY5 A:145, PHE A:140, HI5 A:163.	GLY A:109, PRO A:252, ILE A:249, VAL A:297, PRO A:293, PHE A:294, LEU A:202.
Syringin	5316860	-6.7	-6.4	ALA A:70, MET A:17, GLY A:120, PRO A:122, GLU A:14	THR A:190
Liquiritin	503737	-7.9	-8.6	THR A:198, ASN A:238, TYR A:237, THR A:199, MET A:276, LEU A:272 LEU A:286.	N/A
Liquiritigenin	114829	-7.7	-7.5	MET A:49, GLU A:166, CY5 A:145, LEU A:141, SER A:144	CY5 A:44
Glabridin	124052	-7.9	-7.6	LEU A:141, SER A:144, GLY A:143, CY5 A:145.	MET A:6, ASP A:295
Berberine	2353	-6.5	-7.8	THR A:199, ALA A:193, ALA A:194.	MET A:276, ASN A:277.

Tinosporaside	14194109	-7.5	-8.3	LEU A:286, ALA A:285, LEU A:272, TYR A:239, THR A:199.	ASP A:289, ARG A:131, LYS A:137, MET A:276.
Palmatine	19009	-6.8	-6.8	VAL A:297, PRO A:293, ILE A:249, HIS A:246, GLN A:110, VAL:202, PHE A:294, PRO A:252.	MET A:276, THR A:199, ILE A:286.
Cholin	305	-3.7	-3.5	CY5 A:145, SER A:144, HIS A:163, ASN A:142, HIS A:164.	N/A
BETA-SITOSTEROL	222284	-7.5	-7.6	ASP A:289.	ARG A:131.
Glabrone	5317652	-7.3	-7.7	LEU A:287, ARG A:131.	LEU A:287, ASP A:289, LYS A:137.
Isoglycyrol	124050	-7.5	-7.4	GLN A:189, HIS A:41, CY5 A:145, MET A:165.	N/A
Piperlonguminine	5320621	-6.1	-6.9	PHE A:294, PRO A:293, VAL A:297.	THR A:111, ILE A:249, ILE A:106, PRO A:293.
Asarinin	11869417	-7.9	8.3	LEU A:272, TYR A:239, LEU A:287, LEU A:286, GLU A:290.	PRO A:293, PHE A:294, ASP A:153, ILE A:249.

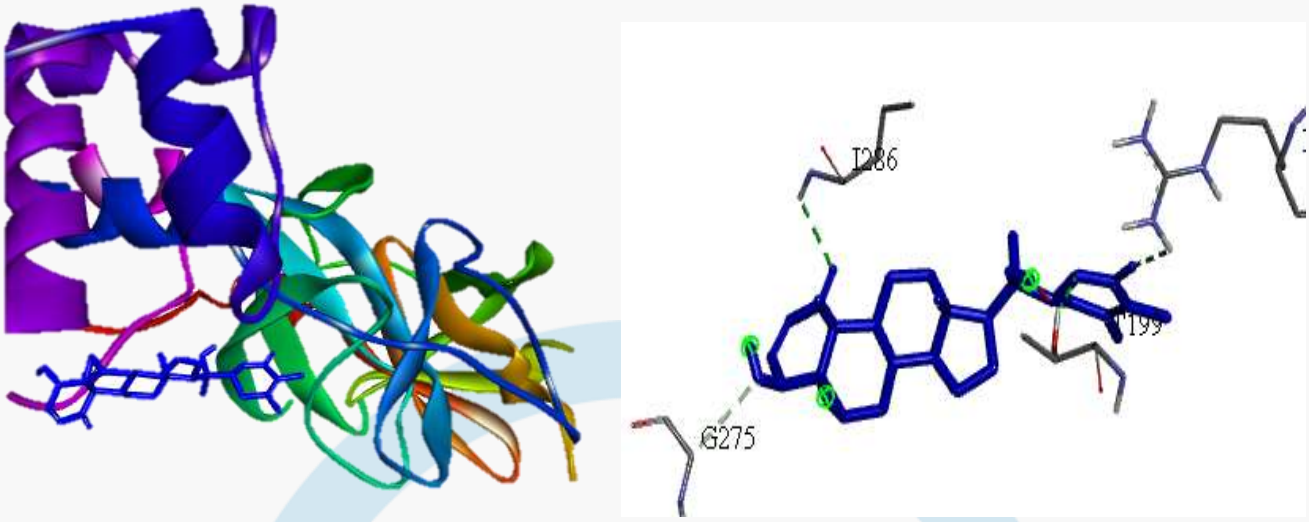
Figure 1: Complex structure of molecular binding affinity

Withanolide D shows lowest Binding affinity with COVID-19 main protease 3CLpro and SARS-CoV main peptidase 2GTB.

Binding affinity with COVID-19 main protease 3CLpro (PDB ID:6LU7)



Binding affinity with SARS-CoV main peptidase (PDB ID:2GTB)



Conclusion

The present study shows that immunomodulatory effect of herbal medicines like *Tinospora cardifolia* (Guduchi), *Piper longum* (Pippali), *Glycyrrhiza glabra* (Licorice) and *Withania somnifera* (Ashwagandha) which could act as prophylactic against COVID-19 and ligand protein interaction predicted that among four immune-modulating herbal medicines the phytocompound Withanolide D has showed -8.9kcal/mol binding affinity with COVID-19 main protease 3CLpro (PDB ID: 6LU7) and same Withanolide D has showed -9.1kcal/mol with SARS-CoV main peptidase (PDB ID: 2GTB).

Acknowledgements

The authors are very thankful to Principal Dr. S. S. Jalalpure and Vice Principal Dr. M. B. Patil for their support and guidance.

Competing interests There is no conflict of interest to claim.

Reference

1. World Health Organization. WHO coronavirus disease (COVID-19) dashboard. (2021). https://covid19.who.in
2. Parasuraman S, Thing GS, Dhanaraj SA. Polyherbal formulation: Concept of ayurveda. Pharmacognosy reviews. 2014 Jul;8(16):73.
3. Khan MB, Rathi B. Tinospora Cordifolia-An immunomodulatory drug in Ayurveda for prevention and treatment of Covid-19. Int. J. Res. Pharm. Sci., 2020, 11 (SPL) (1), 1695-1699
4. Subramaniam K, Subramanian SK, Bhargav S, Parameswari R, Praveena R, Ravikumar R, Yuvaraj E, Kumar VM. Review on potential antiviral and immunomodulatory properties of Piper Longum. InIOP Conference Series: Mater. Sci. Eng. C.2021 (Vol. 1145, (1), p. 012099).
5. Singh V, Singh A. Review on Herbs in Corona. UP state dental journal 2020 issue (1) and (2).
6. Parwe SD, Nisargandha MA, Morey DT. Role of Ashwagandha (Withania Somnifera) as Immunomodulator in Coronavirus in a pandemic. Int. J. Res. Pharm. Sci., 2020, 11 (SPL) (1), 1649-1654.
7. Patil R S, Khatib N A,Patil V S, Suryawanshi S S. Cholonergic acid may be a potent inhibitor of dimeric SARS-CoV-2 main protease 3CLpro: an in silico study. Traditional Medicinal Research. 2020; 1-14.
8. Suryawanshi SS, Jayannache PB, Patil RS, Ms P, Sg A. molecular docking studies on screening and assessment of selected bioflavonoids as potential inhibitors of covid-19 main protease. Asian Journal of Pharmaceutical and Clinical Research. 2020 Aug 31:174-8.
9. Shailendra Sanjay Suryawanshi1, Snehal Maruche, Pruthviraj Pati, MS Palled, Yogesh Pancham.Comparative in-vitro antioxidant activity of fruit extracts of Embelica officinalis Gaertn and drug likeness profile of selected phytoconstituents. International Journal of Botany Studies.2020: 5(6):704-709
10. Ganesh Sampat, Shailendra Sanjay Suryawanshi, Rohan Sawant, Pukar Khanal, M.S.Palled, S.G. Alegaon, Rohini Kavalapure. Molecular docking studies and antibacterial activity of leaves of Tabernamontana divaricate . Journal of Global Trends in Pharmaceutical Sciences. 2020; 11 (2): 7818 – 7824
11. Suryawanshi S S, Patil R S, Jayanache P B, Palled M S, Alegoan S G, Zaranappa. Screening and assessment of selected alkaloids as potential inhibitors of Covid-19 protease enzyme.Journal of Global Trends in Pharmaceutical Science. 2020; 11(2):7711-7718
12. Ganesh Sampat et al., molecular docking studies and antibacterial activity of leaves of tabernamontana divaricata. Journal of Global Trends in Pharmaceutical Sciences. 2020; 11 (2): 7818 – 7824
13. Ziauddin M, Phansalkar N, Patki P, Diwanay S, Patwardhan B. Studies on the immunomodulatory effects of Ashwagandha. Journal of ethnopharmacology. 1996 Feb 1;50(2):69-76.

14. Lakhera S, Devlal K, Ghosh A, Rana M. In silico investigation of phytoconstituents of medicinal herb 'Piper Longum'against SARS-CoV-2 by molecular docking and molecular dynamics analysis. Results in Chemistry. 2021 Jan 1;3:100199.
15. Srivastava V, Yadav A, Sarkar P. Molecular docking and ADMET study of bioactive compounds of Glycyrrhiza glabra against main protease of SARS-CoV2. Materials Today: Proceedings. 2020 Oct 14.
16. Koyuncu İ, Durgun M, Yorulmaz N, Toprak S, Gonel A, Bayraktar N, Caglayan M. Molecular docking demonstration of the liquorice chemical molecules on the protease and ACE2 of COVID-19 virus. Current Enzyme Inhibition. 2021 Jul 1;17(2):98-110.
17. Herowati R, Widodo GP. Molecular Docking studies of chemical constituents of Tinospora cordifolia on glycogen phosphorylase. Procedia Chemistry. 2014 Jan 1; 13:63-8.
18. Krupanidhi S, Abraham Peele K, Venkateswarulu TC, Ayyagari VS, Nazneen Bobby M, John Babu D, Venkata Narayana A, Aishwarya G. Screening of phytochemical compounds of Tinospora cordifolia for their inhibitory activity on SARS-CoV-2: an in-silico study. Journal of Biomolecular Structure and Dynamics. 2021 Sep 2;39(15):5799-803.
19. Xavier GS, Michael S. Molecular docking studies on antiviral drugs for SARS. IJARCSSE 2015; 5:75-79