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Original article

Inhibition of SARS-CoV2 viral infection with natural antiviral plants constituents: An in-silico approach



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ABSTRACT

Background and Objective: In 2019, a novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) was declared pandemic. Advancement in computational technology has provided rapid and cost-effective techniques to test the efficacy of newer therapeutic agents. This study evaluated some of the potent phytochemicals obtained from AYUSH (Ayurveda, Yoga, Naturopathy, Unani, Siddha, Sowa-Rigpa, and Homeopathy)-listed medicinal plants against SARS-CoV-2 proteins using computational techniques.

Materials and methods: The potential SARS-CoV-2 protein targets were utilized to study the ligand–protein binding characteristics. The bioactive agents were obtained from ashwagandha, liquorice, amla, neem, tinospora, pepper, and stevia. Ivermectin was utilized as a reference agent to compare its efficacy with phytochemicals.

Results: The computational analysis suggested that all the bioactive components from the selected plants possessed negative docking scores (ranging from –6.24 to –10.53). The phytoconstituents were well absorbed, distributed in the body except for the CNS, metabolized by liver enzymes, well cleared from the body, and well tolerated. The data suggest that AYUSH-recommended plants demonstrated therapeutic efficacy against SARS CoV-2 virus infection with significantly reduced toxicity.

Conclusion: The phytoconstituents were found to hinder the early stages of infection, such as absorption and penetration, while ivermectin prevented the passage of genetic material from the cytoplasm to the nucleus. Additional research involving living tissues and clinical trials are suggested to corroborate the computational findings.

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1. Introduction

Pandemics are one of the major reasons for devastating human health, including infections caused by viruses, bacteria, and fungi. A virus is a submicron parasite that resides in the host cell. The viruses either contain RNA or DNA but not both (Domingo, 2020).

The pandemic began to spread coronaviruses from the Coronaviridae family in the early twenty-first century (Davidson, 2021; Wang et al., 2020; Jeffrey and Kenneth, 2005). Coronavirus contains an RNA genome in its capsid, which contains spike proteins that are the main cause for the binding of the virus to host cells (Boopathi et al., 2021). A coronavirus variant named severe acute

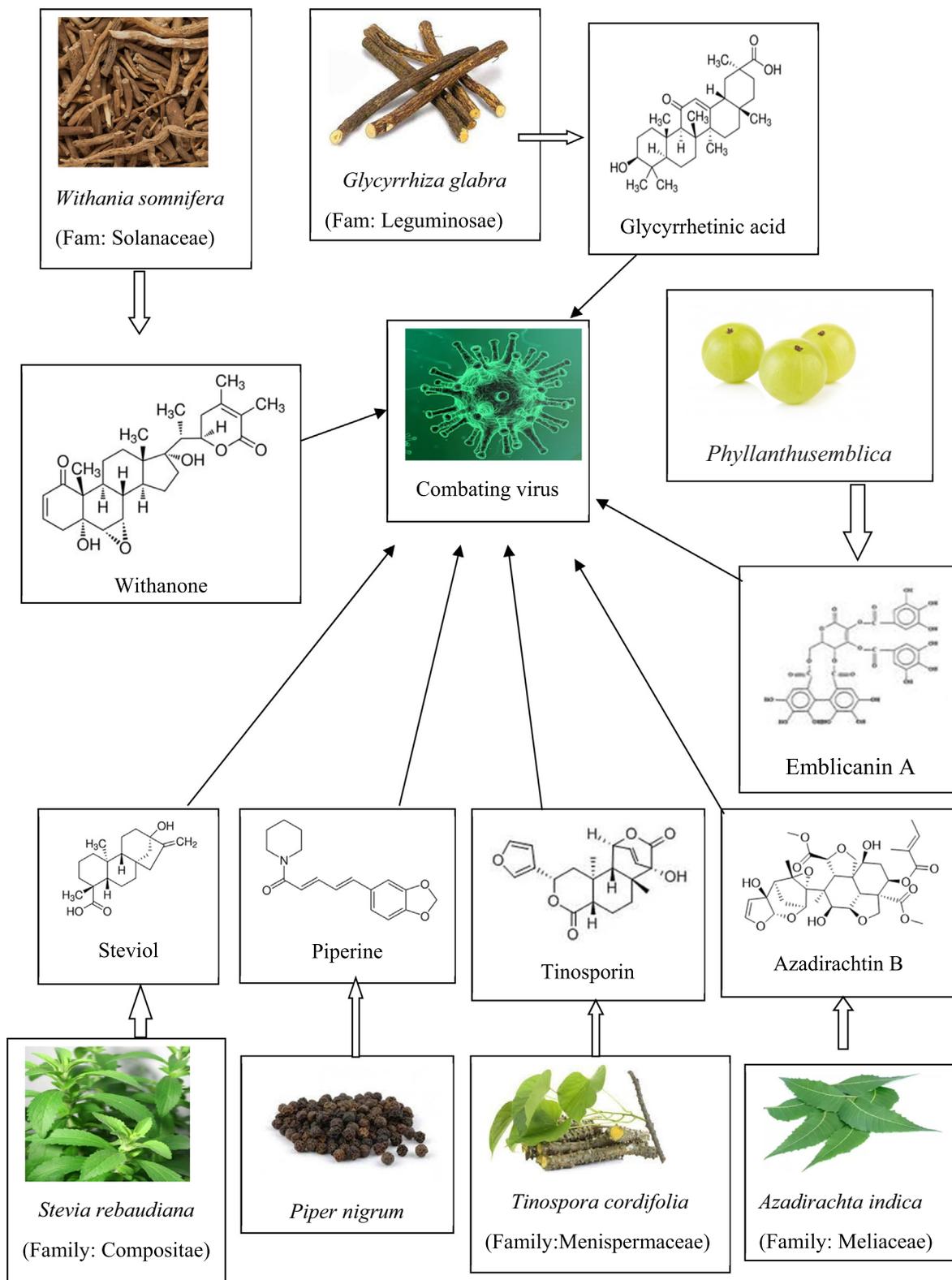
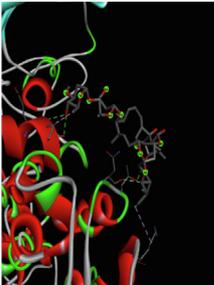
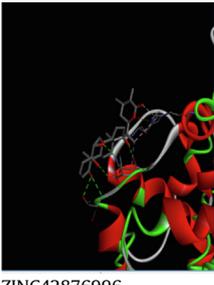
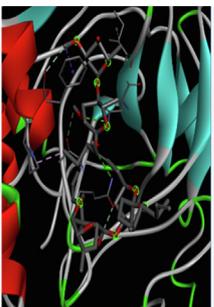
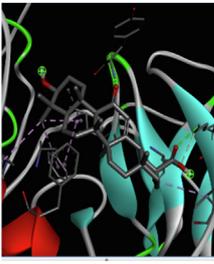
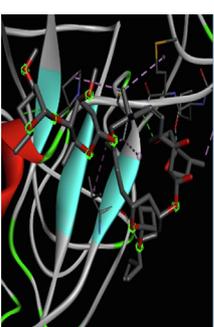


Fig. 1. The phytochemical constituents with biological source used for the computational study.

Table 1
Phytochemical ligands' biological source, 3D, 2D structure with ZINC ID, and docking score.

Phytochemicals/ Repurposed drugs	Biological Source	3d and 2D structure with ZINC ID	Docking Score (Kcal/mol)
PBD ID:6LZG Ivermectin (Standard)	<i>Streptomyces avermitilis</i>		-4.67
Withanone (Compound A)	Ashwagandha (<i>Withania somnifera</i>)	ZINC238808778 	-7.67
PDB ID:4TWW Ivermectin (Standard)	<i>Streptomyces avermitilis</i>	ZINC42876996 	-7.39
Glycyrrhethinic acid (Compound B)	Liquorice (<i>Glycyrrhiza glabra</i>)	ZINC238808778 	-7.55
PDB ID:7AEH Ivermectin (Standard)	<i>Streptomyces avermitilis</i>	ZINC19203128 	-7.28

(continued on next page)

respiratory syndrome (SARS) was discovered in humans in 2002. Later in 2012, a mutated variant of influenza that also had similarities with coronavirus was identified as MERS-CoV in Saudi Arabia (Shereen et al., 2020). In 2019, the coronavirus came with a much superior mutant, namely Severe Acute Respiratory Syndrome Corona virus-2 (SARS-CoV-2). SARS-CoV-2 was also identified as Corona virus-induced disease 2019 (COVID-19), which started earliest in Wuhan, China, in November. The mutation in spike proteins on the surface of SARS-CoV-2 has a greater affinity to bind with angiotensin-converting enzyme II (ACE-II) than SARS-CoV. The spike proteins are present as a trimer in mature viruses, which helps in the entry of the virus into the cell (Xie et al., 2020). The S1 of SARS-CoV-2 RBD recognizes most of the sites in ACE-2, as it is only present in a lying-down position that helps in enhanced binding to ACE-2 (Shang et al., 2020). On entering the cell, the proteases activate the virus and infect the cell. The discovery of medicines and vaccines began as the virus spread, but only a few of them showed a positive response in treating the virus. As the virus became resistant to the drugs, several mutated forms such as alpha, beta, gamma, delta, and omicron evolved.

Recently, many scientific studies have revealed anti-viral activity with some specific natural plants, especially against the COVID virus (Ahmad et al., 2022; Das, 2022; Gezici and Sekeroglu, 2020). Natural plants demonstrated a positive effect on COVID control through physiochemical actions such as anti-mutagenic, antiviral, antioxidant, and anti-inflammatory properties. Herbal plants have low toxic substances that help with high intake and minor side effects (Umar et al., 2021). In daily life, a human consumes a lot of plant material in the form of food, through which immunity is easily acquired for various diseases, including COVID (Borse et al., 2021). The Indian Ministry of Ayurveda, Yoga, Naturopathy, Unani, Siddha, Sowa-Rigpa, and Homoeopathy (AYUSH) has recommended several important medicinal plants that have a significant impact in combating viral infections, particularly SARS-CoV-2. The selected plants are *Withania somnifera*, *Glycyrrhiza glabra*, *Phyllanthus emblica*, *Azadirachta indica*, *Tinospora cordifolia*, *Piper nigrum* and *Stevia rebaudiana*. All the listed plants contain potent bioactive compounds that have versatile therapeutic as well as medicinal properties. A literature survey revealed that withanone in *Withania somnifera* belongs to the Solanaceae family, shows

potent antiviral activity (Kumar et al., 2022). Further, glycyrrhetic acid from *Glycyrrhiza glabra* (F: Leguminosae) reported its potent antiviral activity (Huan et al., 2021) and emollicanin A from amla fruit (F: Phyllanthaceae) showed highly potent antiviral effects (Kar et al., 2022). Additionally, azadirachtin B from neem tree (F: Meliaceae) showed remarkable effects in combating viral infection (Baidya et al., 2021), and tinosporin from *Tinospora cordifolia* (F: Menispermaceae) demonstrated both antiviral agent and immunomodulatory properties (Khan and Rathi, 2020). Piperine from *Piper nigrum* (Family: Piperaceae) has recently been shown to have potent antiviral activity in addition to strong immunomodulatory potential (Nag and Chowdhury, 2020). Finally, steviol from *Stevia rebaudiana* (F: Asteraceae) shown to have potent antiviral activity (Peteliuk et al., 2021).

Therefore, it was our interest to determine the anti-COVID-19 capabilities of those plants and their bioactive constituents, which have been demonstrated to possess antiviral effects in different studies and listed in the medicinal plant list of the AYUSH department. The goal of this study was to compare the anti-COVID potential of the above-mentioned plants and their major bioactive constituents to standard Ivermectin using an in-silico method.

2. Materials and methods

2.1. Selection of target and ligand

In the study, 7 potential targets of SARS CoV-2 were selected. 3D structural models of 6LZG (ACE2, SpS1 pro), 4TWW (3CL pro), 7AEH (3CL pro, Nsp5), 5S2T (Nsp3 pro), 7KZA (HCAB, LCAB), 7KVL (M pro), and 6 W63 (3CL pro) were acquired from the RCSB PDB (protein data bank) in PDB format. Prior to docking, energy minimization was performed by using MOE 2018 (molecular operating environment), water and ligand molecules were also removed before minimization. Ivermectin was used as a standard drug (Popp et al., 2021). Ligands were selected from literature studies based on antiviral properties. The chemical constituents in Ashwagandha (*Withanone*) (Dhanjal et al., 2021), Licorice (*Glycyrrhetic acid*) (Maddah et al., 2021), Amla (*Emblicanin A*) (Murugesan et al., 2021), Neem (*Azadirachtin B*) (Adegbola et al., 2021), *Tinospora* (*Tinosporin*) (Saha and Gosh, 2013), Black pepper

Table 2
ADMET properties of the phytochemical ligands.

ADMET properties	Ivermectin	Ligand						
		A	B	C	D	E	F	G
ABSORPTION								
Water solubility	-4.33	-3.91	-4.222	-2.892	-3.47	-3.917	-3.464	-2.907
Caco2 permeability	0.577	0.982	1.053	-0.711	0.987	1.219	1.596	1.347
Intestinal absorption (human)	79.159	96.061	100	66.526	86.595	98.005	94.444	98.759
P-glycoprotein substrate	Yes	Yes	Yes	Yes	Yes	No	Yes	No
DISTRIBUTION								
VDss (human)	0.64	0.46	-1.004	0.002	0.875	0.243	0.158	-0.942
CNS permeability	-3.416	-2.818	-1.017	-6.199	-3.094	-2.923	-1.879	-0.134
METABOLISM								
CYP3A4 substrate	Yes	Yes	Yes	No	No	Yes	Yes	Yes
CYP2C19 inhibitor	No	No	No	No	No	No	Yes	No
CYP2C9 inhibitor	No	No	No	Yes	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No	No	No
EXCRETION								
Total Clearance	0.533	0.381	-0.114	0.641	0.263	0.689	0.232	0.507
Renal OCT2 substrate	No	Yes	No	Yes	No	No	Yes	No
TOXICITY								
AMES toxicity	No	No	No	No	No	No	No	No
Max. tolerated dose (human)	-1.288	-0.569	0.741	0.438	-0.446	-0.314	-0.38	-0.141
hERG II inhibitor	No	No	No	Yes	Yes	No	No	No
Oral Rat Acute Toxicity (LD50)	3.706	2.806	3.824	2.481	3.339	2.819	2.811	1.954
Hepatotoxicity	Yes	No	No	No	No	No	Yes	Yes

Note: Ligand A – Withanone, ligand B – Glycyrrhetic acid, ligand C – Emblicanin A, ligand D – Azadirachtin B, ligand E – Tinosporin, ligand F – Piperine and ligand G – Steviol.

(Piperine) (Lee et al., 2020), and Stevia (Steviol) (Das 2022) was used as a ligand that were effective against viral infections (Fig. 1). The structures of ligands were obtained from the ZINC15 database in SDF format. The online structure file generator tool from the national cancer institute is used to convert SDF format to PDB format. The biological sources, 2D structure, and ligand ID along with the docking score are mentioned in Table 1.

2.2. Docking studies

The docking studies were conducted using AutoDock 4.2. Docking is used to predicting the binding interaction between protein and ligand, which gives specific activity. The binding interaction defines the basic biochemical processes based on the behaviour of the ligand at the site of a protein. At the end of docking studies, a docking score is obtained which determines the binding affinity of the target and ligand. The more negative is the docking score, the better the binding affinity and the greater the positive docking score, the weaker the binding activity. Discovery Studio 2021 was used for the visualization of the interaction between ligand and target. The obtained docking scores are compared with the docking score of standard ivermectin on the target.

2.3. ADMET studies

ADMET studies were performed by using pkCSM which depicted the values of parameters for different ligands, which were further compared with the standard Ivermectin.

3. Results

3.1. Molecular docking analysis

In the present study, 7 medicinal plants were selected, and a chemical constituent from each plant with antiviral properties was docked with SARS-CoV-2 proteins. Ivermectin was used as a reference drug and docked with all the proteins used in this study, as it was approved by the FDA for treating COVID-19. 6LZG was docked with ligand A (withanone), 4TWW was docked with ligand B (glycyrrhetic acid), 7AEH was docked with ligand C (emblicannin A), 5S2T was docked with ligand D (azadirachtin B), 7KZA was docked with ligand E (tinospurin), 7KVL was docked with ligand F (piperine), and 6 W63 was docked with ligand G (steviol), and each of these proteins was docked with ivermectin, respectively. The binding energies of the phytochemicals and the control drug are depicted in Table 1. The docking scores for the different proteins were found to be 6LZG (Ivermectin = -4.67, Withanone = -7.67), 4TWW (Ivermectin = -7.39, Glycyrrhetic acid = -7.55), 7AEH (Ivermectin = -7.28, Emblicannin A = -10.53), 5S2T (Ivermectin = -6.08, Azadirachtin B = -9.94), 7KZA (Ivermectin = -6.26, Tinospurin = -7.13), 7KVL (Ivermectin = -6.02, Piperine = -6.24), and 6 W63 (Ivermectin = -6.2, Steviol = -6.7).

Table 3
Molecular properties of phytochemical ligands.

Molecular properties	Ivermectin	Ligands						
		A	B	C	D	E	F	G
Molecular weight	875.1	470.6	470.6	782.5	662.6	358.3	285.3	318.4
Log P	5.60	3.49	6.41	1.36	-0.09	2.53	2.99	4.155
Rotatable bonds	8	2	1	4	5	1	3	1
Acceptor	14	6	3	22	14	6	3	2
Donors	3	2	2	12	3	1	0	2

Note: Ligand A – Withanone, ligand B – Glycyrrhetic acid, ligand C – Emblicannin A, ligand D – Azadirachtin B, ligand E – Tinospurin, ligand F – Piperine and ligand G – Steviol.

3.2. ADMET studies

For the development and discovery of new drugs, absorption, distribution, metabolism, elimination, and toxicity play a significant role. The SMILES format of ligands was used to predict their properties. The study evaluated water solubility, intestinal absorption, CNS permeability, LD50, hepatotoxicity, etc., which are depicted in Table 2. All tested phytochemical ligands scored negative values for the water solubility characteristics, and the highest (-4.22) was found to be for ligand B (Glycyrrhetic acid). The Caco2 permeability was found to be positive for all ligands except ligand C (Emblicannin A). The intestinal absorption was found to be 100 % for ligand B (Glycyrrhetic acid) and the lowest was observed with ligand C (Emblicannin A). All ligands showed p-glycoprotein substrate activity except ligand E (Tinospurin) and ligand G (Steviol). The highest VDss value (0.875) was observed for ligand D (Azadirachtin B) and the lowest (-1.004) was for ligand B (Glycyrrhetic acid).

All ligands except ligand C (Emblicannin A) and ligand D (Azadirachtin B) exhibited CYP3A4 substrate activity. The ligands F (piperine) and C (emblicannin A) inhibited CYP2C19 and CYP2C9, respectively. The highest total clearance (0.689) was found with ligand E (Tinospurin) and the lowest (-0.1114) with ligand B (Glycyrrhetic acid). Renal OCT2 substrate was found with three ligands, such as ligand A (Withanone), ligand C (Emblicannin A) and ligand F (Piperine).

None of the tested ligands exhibited AMES toxicity potential. The maximum tolerated dose was found to be highest (0.741) for ligand B (Glycyrrhetic acid), highest oral rat acute toxicity (LD 50) value was observed with ligand D (Azadirachtin B); and two ligands (Piperine and Steviol) showed hepatotoxicity potential.

The ligands' molecular properties are listed in Table 3. The highest molecular weight was found with ligand C (Emblicannin A). The highest log P value for ligand B (Glycyrrhetic acid), more rotatable bonds in ligand D (Tinospurin), more acceptor ability with ligand C (Emblicannin A), and donor property in ligand C (Emblicannin A).

4. Discussion

According to the literature, herbal medicines have been used since ancient times in the treatment of multiple health hazards, including a vast number of infectious diseases (Siddique et al., 2021). Following the completion of the preclinical and clinical evaluations, several of them are commercially marketed. These components are gaining popularity, being derived from nature, they are devoid of serious adverse effects and have been reported to cure the disease by treating the root cause (Singh et al., 2020). As a result, it is believed that any medicinal plant may serve as a potential source for the treatment of every disease, including viral infections (Aschale et al., 2021).

Diseases caused by infectious microorganisms present difficulties in treatment due to the quick development of resistance.

Besides, the medications might interfere with the host cell's functioning, leading to the appearance of several adverse effects. Viruses made of either RNA or DNA complicate treatment because the organism rapidly modifies its structural components to develop resistance to therapeutic interventions (Davidson, 2021; Qin et al., 2021; Sulimov et al., 2021). Several medicinal plants have been shown to exhibit strong inhibition (*in vitro*) against viral replication, boosting the likelihood of discovering new bioactive plant chemicals (Severson et al., 2008). Based on this research, in the present study, ashwagandha, liquorice, amla, neem, tinospora, pepper, and Stevia were selected as per the AYUSH recommendation. As reported, the bioactive constituents of these selected plants have shown potent antiviral properties in *in vitro* studies. Withanone from Ashwagandha showed *in vitro* antiviral activity by targeting the viral main protease (M^{Pro}) and host transmembrane TMPRSS2 (Balkrishna et al., 2021). Also, emblicanin A from *Phyllanthus emblica* reported the inhibitory activity of herpes simplex virus type-1 (HSV-1) and type-2 (HSV-2) (Chojnacka et al., 2021).

Computer-aided drug design (CADD) is currently one of the most widely used approaches for drug development and discovery (Wang et al., 2018). The research suggests that docking studies can be performed on the phytochemicals of herbal plants. Docking studies were done using Autodock, which helps in depicting the required data. The herbal plants were selected based on their anti-viral properties and other pharmacological activities that were liable for blocking the entry of the coronavirus (SARS-CoV-2) (Fallah et al., 2021).

According to the literature, docking studies are determined by hydrogen bonds, as they play a crucial role in docking. It was found that hydrogen bonds had a direct relationship with the binding energy (docking score). Based on this, the current study was conducted to determine the efficacy of the AYUSH-recommended plants against SARS-CoV-2 viral infection using an *in-silico* docking study. Ivermectin has been approved by the FDA for clinical studies against SARS-CoV-2, which was used as a reference (Caly et al., 2020) for the present study and has shown less binding energy and less hydrogen bonding compared to the ligands such as A, B, C, E, F, and G (Table 1). The test compounds exhibited satisfactory pharmacokinetic properties and low toxicity potential compared to the reference drug (Table 2). The findings are consistent with previous findings that compounds with antiviral properties may be effective against SARS-CoV-2 (Caly et al., 2020).

In our study, a similar result was also recorded where emblicanin A (from *Phyllanthus emblica*) showed a higher binding affinity with a -10.53 (Sharma et al., 2020; Xu et al., 2021), followed by Azadirachtin B (from *Azadirachta indica*) with a binding affinity of 9.94 when compared with the reference Ivermectin. Except for neem, all other herbal plants in the study showed better hydrogen bonding, but azadirachtin B acts as an adjuvant. Compared to all the test compounds, ligand C (emblicanin A) showed the best activity, which is a phytoconstituent of Amla. Interestingly, the Stevia plant also showed potent antiviral action by binding affinity with a value of -6.9 when docked with the steviol group, which was higher than piperine (-6.24) from *Piper nigrum* (piperine), although both piperine and steviol showed hepatotoxic potential (Tables 1 and 2). These findings support previous findings that compounds with high binding affinity for proteins have higher negativity in docking scores (Fallah et al., 2021).

5. Conclusion

In this study, molecular docking and ADMET studies were carried out for phytochemicals from important AYUSH-recommended herbal plants with SARS-CoV-2 proteins. Ivermectin

was used as a controlled drug and was found to have less docking properties as well as hepatotoxic. In comparison, all the phytochemical ligands tested exhibited strong binding characteristics with SARS-CoV-2 proteins, but emblicanin A and azadirachtin B were found to be superior. The data suggest that the phytochemical constituents could be potential agents against SARS-CoV-2. However, more studies are needed to validate the potential of the compounds using both animal and clinical tests.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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