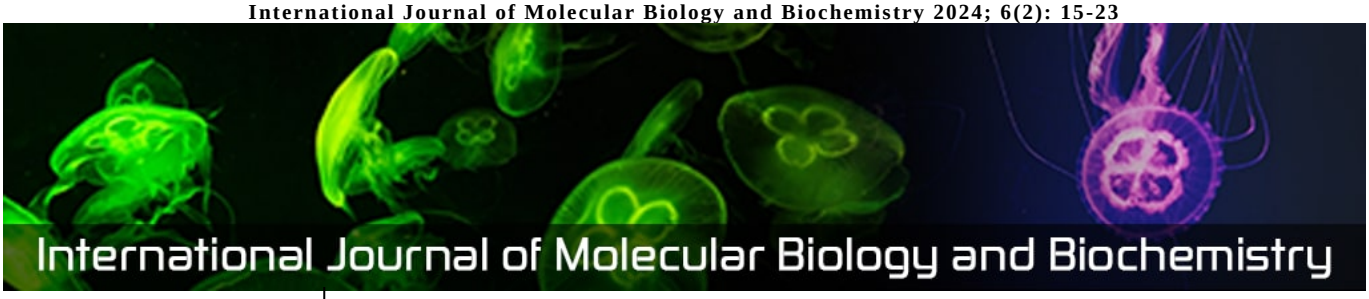

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Essential secondary metabolites of *Azadirachta indica* leaf in search of drug for COVID-19 treatment: *In-silico* ADMET and bioactivity predictions

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Abstract
Introduction: "coronavirus disease 2019" is a pandemic of acute respiratory sickness that was triggered by the highly transmissible and dangerous coronavirus, SARS-CoV-2, which poses risks to both public health and safety. The ADMET and bioactive properties of bioactive metabolites of *A. indica* leaf were predicted in the search for potential drug(s) for treatment and management of COVID-19.
Research Method: The pharmacokinetic properties of 12 secondary metabolites from *A. indica* and 5 FDA approved drugs for treatment of COVID-19 were predicted using SWISSADME and ADMET lab online tools and Molinspiration server for bioactivity prediction.
Results: The bioactive secondary metabolites and the drugs showed good ADMET and bioactivity properties, but ivermectin, azadirachtin A, azadirachtin D, azadirachtin H, azadirachtin F, azadirachtin I and nimbolin, have relatively poor properties. Similarly, most of the compounds have relatively tolerable toxicity level but remdesivir and nimboline. However, compounds from *A. indica* showed better properties in comparison to the FDA approved drug for COVID-19 treatment.
Conclusion: Some of these compounds from *A. indica* leaf have relatively good ADMET and bioactive properties, and hence the need to dock them with human ACE2 in order to evaluate their binding interactions and thus their respective inhibitory constants.

Keywords: ADMET, *A. indica*, COVID-19, secondary metabolites, SARS-CoV-2, bioactivity and pharmacokinetic

Introduction

The acute respiratory disease coronavirus disease 2019 (also known as COVID-19) [1] is a pandemic that presents dangers to both public health and safety. The highly contagious and pathogenic SARS-CoV-2 coronavirus, which first surfaced in late 2019, was the culprit. According to Mehta *et al.* [2], positive-sense single-stranded RNA coronavirus 2 is linked to severe acute respiratory syndrome. Even though it is less deadly than the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV), the rapid spread of this highly contagious sickness has posed the greatest threat to global health in this century [3]. It is the third human coronavirus known to utilize the peptidase, angiotensin converting enzyme 2 (ACE2), to penetrate hosts, after SARS-CoV and MERS-CoV. SARS-CoV-2 and ACE2's interaction is crucial for the development of COVID-19 from an early infection to a severe sickness. Comprehending the cellular origins of SARS-CoV-2 disease may help researchers develop treatments that stop the onset of severe sickness and, as a result, reduce mortality.

Three of the seven known human coronaviruses—SARS-CoV, SARS-CoV-2, and MERS-CoV—are extremely pathogenic, while the other four—HCoV-NL63, HCoV-229E, HCoV-OC43, and HCOV-HKU1—cause "common colds" and are less virulent. The ACE2 is the receptor used by SARS-CoV, SARS-CoV-2, and HCoV-NL63 to enter cells. According to Zhou *et al.* [4], HCoV-229E utilizes CD13 (aminopeptidase N), whereas MERS-CoV binds DPP-4 (dipeptidyl peptidase-4). Given that the reactions do not necessitate the endopeptidase active site, it appears to be a major converging point that all known human coronavirus

receptors are cell surface peptidases. The fact that three coronaviruses have been selected to attack a specific region of ACE2 is noteworthy [4, 5]. Contrarily, the receptor-binding domain of the spike (S) protein is encoded by the coronavirus genome's most variable region. This indicates that several sequences using varied structural strategies converging on the same region of the same protein were created by the diversity of these viruses.

Despite some treatments having exhibited some promise in certain individual subpopulations or for some objectives, antivirals against SARS-CoV-2 and COVID-19 have not yet been proven to be generally effective treatments. SARS-CoV-2 is activated to enter the cell via human proteases acting as entry activators, while ACE2 acts as the receptor for the virus. Therefore, COVID-19 could be treated with medications that block this entry. Therefore, a potential therapeutic strategy is to prevent the S protein from binding to ACE2 by using soluble recombinant hACE2, specific monoclonal antibodies, or fusion inhibitors that target the SARS-CoV-2 S protein [6-8]. Therefore, screening medicinal plants that contain a wide variety of bioactive chemical repositories may be a good first step in identifying possible therapeutic candidates for treating SARS-CoV-2. As a result, this study looked into the *In-silico* pharmacokinetic properties of unique bioactive compounds from *A. indica* leaf.

According to Prashanth and Krishnaiah [9], *Azadirachta indica* Linn is a tropical evergreen tree that is origin to India and as well present in other Southeast Asian countries. Locals call it Neem," and it is a member of the Meliaceae mahogany family. This vital medicinal plant, which has been dubbed the "Tree of the 21st Century" by the UN, has historically been used to treat a number of illnesses. It is known as "Divine Tree," "Life Giving Tree," "Nature's Drugstore," "Village Pharmacy," and "Panacea for All Diseases" in India, according to [10, 11]. In tropical and subtropical climates, including Nigeria, it thrives. According to studies [12, 13], the bitter compounds found in virtually every part of the plant—fruit, seeds, oil, leaves, roots, and bark—have antiviral, anti-retroviral, anti-inflammatory, anti-ulcer, anti-fungal, antibacterial, anti-plasmodial, antiseptic, antipyretic, and anti-diabetic properties. Ascorbic acid, n-hexacosanol, amino acids, 7-desacetyl-7-benzoylazadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, and nimbiol are among the chemical components that can be found in neem leaves [14]. Some of the other primary active components include nimbolin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin [15]. The most important active component, azadirachtin, is also well known for its biological activity and medicinal properties. It is possible to computationally screen the pharmacokinetic characteristics of its bioactive elements in advance to assess their antiviral effectiveness in the treatment of the virulent and globally endemic COVID-19 virus. The reason for this is because the leaves showed enormous biological and therapeutic activities [12, 13, 16]. Recently, it was discovered that the bioactive secondary metabolite azadirachtin-A from *A. indica* may be able to block the main protease of the SARS-CoV-2 virus [17-19]. Therefore, the goal of this study was to estimate the *In-silico* ADMET and bioactivity of key bioactive chemicals from *A. indica* leaf that may have possible inhibitory effects on human ACE2, which is crucial for COVID-19 entrance and invasion into host cells.

Materials and Methods

- **Ligands/Metabolites Selection**
  In the works of [20, 21], unique and essential secondary metabolites (ligands) were identified from the leaf of *A. indica*, and their two-dimensional (2-D) structures were downloaded and retrieved from the PubChem database [22]. PubChem (https://pubchem.ncbi.nlm.nih.gov) has one of the largest databases of publicly available chemical information and has rapidly developed into a key chemical information resource, serving scientific communities in a variety of fields including cheminformatics, chemical biology, medicinal chemistry, and drug discovery [22].
- **The compounds or ligands chosen were**
  Azadirachtin-A, Azadirachtin-D, Azadirachtin-H, Azadirachtin-F, Azadirachtin-I, Desacetylnimbin, Azadiradione, Nimbin, Nimbolin, Nimbolide, Nimbinene, and Azadirone.
  Additionally, a few COVID-19 therapeutic options that have been FDA-approved were highlighted. Remdesivir, Baricitinib, Paritaprevir, Ivermectin, and 2-monolinolenin were equally retrieved from PubChem in order to compare them with the bioactive compounds from *A. indica* leaf.

Drug Likeness Prediction

The ADMET (absorption, distribution, metabolism, excretion, and toxicity) and physicochemical features of the discovered secondary metabolites from neem leaf and the FDA COVID-19 authorized medications were predicted using the SwissADME tool [23] (http://www.swissadme.ch) and the ADMETlab program [24]. The druggability or drug-likeness of these compounds was predicted using Lipinski's rule of five utilizing the SwissADME online tool [23]. This web server determines how closely related a compound is to an oral drug using Lipinski's Rule [25], which validates that attribute for the substance. The physicochemical parameters include solubility (LogP), topological polar surface area (TPSA), molecular weight (MW), number of hydrogen bond acceptors (No.HBA), number of hydrogen bond donors (No.HBD), and volume (Vol).

Bioactivity Prediction

The compounds were subsequently investigated for biological characteristics (bioactivities) using the Molinspiration service (www.molinspiration.com) [26]. The six characteristics anticipated by molinspiration bioactivity included GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor, and enzyme inhibitor.

Results

Table 1 showed the molecular formula and PubChem CID of the ligands investigated. Also, figure 1 showed the 2-D structures of the ligands as obtained from PubChem.

Table 1: Ligands and Their PubChem CID

S/No	Ligands	PubChem CID	Molecular Formula
1	Remdesivir	1.21E+08	$C_{27}H_{39}N_6O_8P$
2	Baricitinib	44205240	$C_{16}H_{17}N_7O_2S$
3	Paritaprevir	45110509	$C_{40}H_{43}N_7O_7S$
4	Ivermectin	6321424	$C_{48}H_{74}O_{14}$
5	2-monolinolenin	11674746	$C_{21}H_{36}O_4$
6	Azadirachtin A	4369359	$C_{35}H_{44}O_{16}$
7	Azadirachtin D	65981	$C_{34}H_{40}O_{14}$
8	Azadirachtin H	16134956	$C_{33}H_{42}O_{14}$
9	Azadirachtin F	1.32E+08	$C_{33}H_{40}O_{14}$
10	Azadirachtin I	5281303	$C_{32}H_{42}O_{12}$
11	Desacetylnimbin	5281654	$C_{28}H_{36}O_4$
12	Azadiradione	5316860	$C_{28}H_{36}O_4$
13	Nimbin	108058	$C_{30}H_{36}O_9$
14	Nimbolin	6443035	$C_{39}H_{46}O_{10}$
15	Nimbolide	12313356	$C_{27}H_{30}O_8$
16	Nimbinene	44715635	$C_{15}H_{20}$
17	Azadirone	10906239	$C_{28}H_{36}O_4$

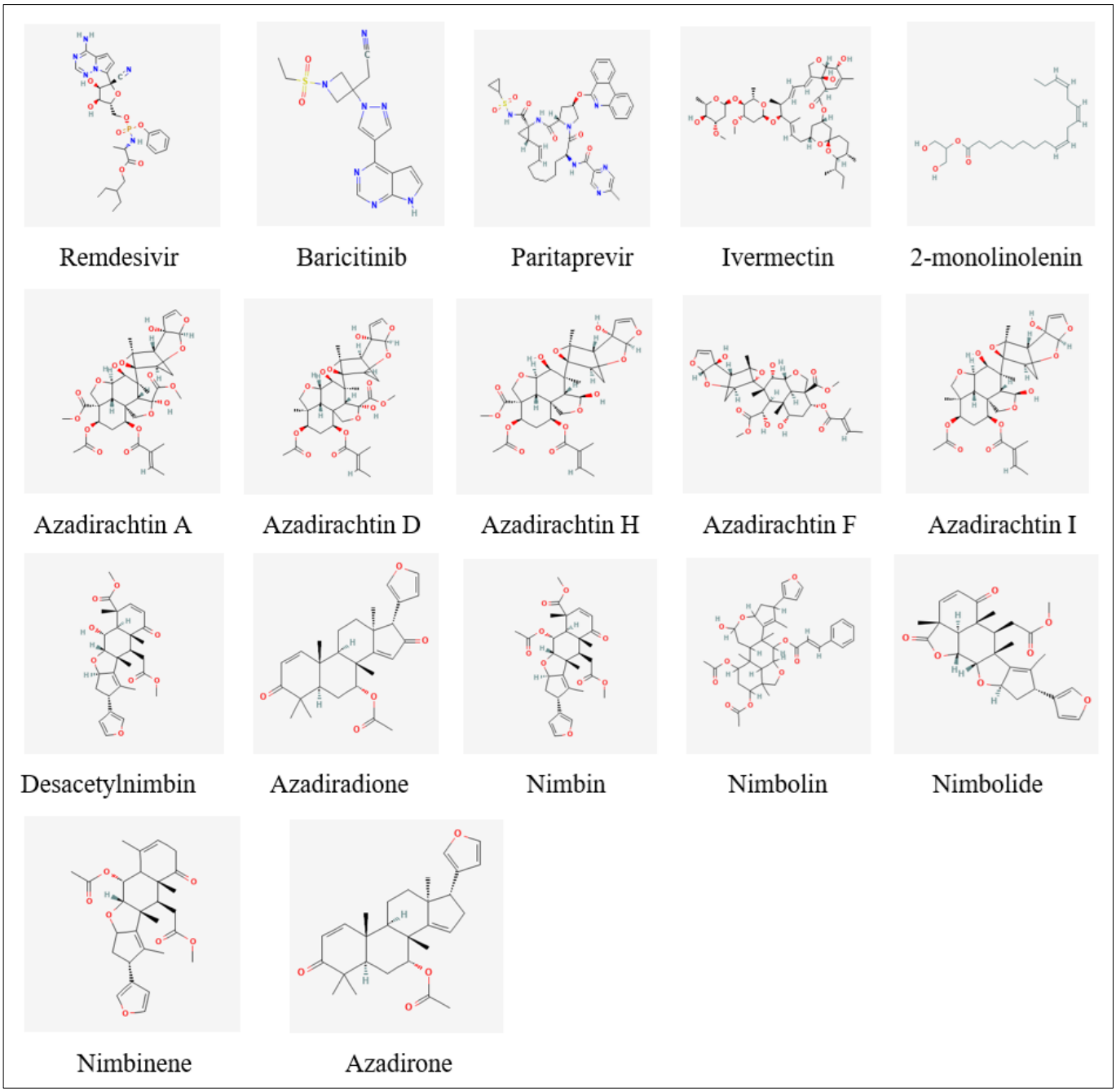

Fig 1: The 2-D Chemical Structures of the Ligands

Table 2: The Water Solubility of the Molecules

Properties / Ligands	ESOL S (mg/ml)	ESOL Class	Ali S (mg/ml)	Ali Class	Silicos IT S (mg/ml)	Silicos IT Class
Remdesivir[2]	0.184	Soluble	0.004	M Soluble	0.0115	M Soluble
Baricitinib[1]	7.31	V Soluble	10.60	V Soluble	0.0174	M Soluble
Paritaprevir[4]	0.000049	P Soluble	0.000022	P Soluble	0.00000014	P Soluble
Ivermectin[4]	0.0000016	P Soluble	0.00000017	P Soluble	0.113	Soluble
2-monolinolenin[2]	0.0316	M Soluble	0.000261	M Soluble	0.0404	Soluble
Azadirachtin A[2]	0.0333	M Soluble	0.0045	M Soluble	28.60	V Soluble
Azadirachtin D[2]	0.0106	M Soluble	0.00148	M Soluble	11.3	V Soluble
Azadirachtin H[2]	0.034	M Soluble	0.00738	M Soluble	42.70	V Soluble
Azadirachtin F[2]	0.0319	M Soluble	0.00319	M Soluble	68.30	V Soluble
Azadirachtin I[2]	0.0107	M Soluble	0.00242	M Soluble	16.90	V Soluble
Desacetylnimbin[2]	0.0961	M Soluble	0.0103	M Soluble	0.076	V Soluble
Azadiradione[4]	0.00117	M Soluble	0.000359	P Soluble	0.000223	P Soluble
Nimbin[3]	0.0345	M Soluble	0.0214	M Soluble	0.0019	M Soluble
Nimbolin[4]	0.0000182	P Soluble	0.0000431	P Soluble	0.0000745	P Soluble
Nimbolide[3]	0.0530	M Soluble	0.0857	M Soluble	0.00249	M Soluble
Nimbinene[3]	0.0719	M Soluble	0.1210	Soluble	0.00219	M Soluble
Azadirone[4]	0.000373	P Soluble	0.0000926	P Soluble	0.000162	P Soluble

KEY: M = moderately; P = poorly; S = solubility.

The results of the solubility of the ligands using various models are displayed in Table 2 above. According to the following log S scale, the qualitative estimate of the solubility class is given: insoluble 10 badly, 6 moderately, 4 soluble, 2 extremely, and 0 highly. In Swiss ADME, the decimal logarithm of the molar solubility in water (log S) is used to predict all of the values. Here, it is argued that the ligands denoted by the superscripts 1, 2, 3, and 4 are, respectively, extremely soluble, soluble, moderately soluble, and poorly soluble.

Table 3: The Physicochemical Properties of the Ligands

Properties / Ligands	MW(g/mol)	No HA	No Ar HA	RB No	No HBD	MR	TPSA
Remdesivir	606.61	42	15	15	5	153.39	215.59
Baricitinib	375.45	26	14	7	2	101.47	131.17
Paritaprevir	765.88	55	20	9	3	211.96	198.03
Paritaprevir	765.88	55	20	9	3	211.96	198.03
2-monolinolenin	352.51	25	0	17 4	2	105.25	66.76
Azadirachtin H	662.68	47	0	8	3	154.98	189.04
Azadirachtin F	664.69	47	0	9	4	157.18	200.04
Azadirachtin F	664.69	47	0	9	4	157.18	200.04
Azadirachtin I	618.67	44	0	6	3	148.89	162.74
Desacetylnimbin	498.56	36	5	6 8	1	129.07	112.27
Azadiradione	450.57	33	5	3 5	0	125.48	73.58
Nimbin	540.6	39	5	8 9	0	138.81	118.34
Nimbolin	674.78	49	11	9	1	178.44	130.73
Nimbolide	466.52	34	5	4 7	0	120.00	92.04
Nimbinene	482.57	35	5	6 7	0	128.17	92.04
Azadirone	436.58	32	5	3 4	0	125.28	56.51

KEY: MW= Molecular weight; No HA= Number of heavy atoms; No Ar HA= Number of aromatic heavy atoms; F= fraction; No RB= Number of rotatable bonds; No HBA= Number of hydrogen bond acceptors; No of HBD= Number of hydrogen bond donors; MR= molecular refractivity; TPSA= Topological polar surface area.

Table 4: The Lipophilicity of the Ligands

Models / Ligands	ILOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{o/w}$
Remdesivir	3.71	1.02	1.65	0.26	-0.41	1.24
Baricitinib	1.81	-0.73	1.23	-0.51	0.24	0.41
Paritaprevir	2.03	4.65	3.89	0.88	2.28	2.75
2-monolinolenin	4.73	4.99	4.47	3.33	5.76	4.66
Azadirachtin A	3.90	1.09	-0.20	-0.47	1.07	1.08
Azadirachtin H	3.09	1.38	0.25	-0.09	1.02	1.13
Azadirachtin F	2.84	1.51	-0.11	-0.50	1.14	0.98
Azadirachtin I	3.63	2.35	1.10	0.49	1.15	1.81
Azadirachtin I	3.63	2.35	1.10	0.49	1.15	1.81
Desacetylnimbin	3.61	1.71	3.35	1.69	3.43	2.76
Azadiradione	3.17	4.82	5.42	3.28	5.00	4.34
Nimbin	3.98	2.28	3.92	2.04	3.96	3.24
Nimbolin	3.84	4.72	5.64	3.16	4.96	4.46
Nimbolide	3.51	2.17	3.74	2.28	3.83	3.11
Nimbinene	3.83	2.04	4.52	2.48	4.32	3.44
Azadirone	3.86	5.72	6.24	4.19	5.30	5.06

Table 5: The Drug-likeness and Medicinal Chemistry of the Molecules

Parameters / Ligands	Lip V	GV	Veber V	EV	MV	B Score	PAINS Alert	Brenk Alert	LL	SA
Remdesivir	2	3	3	1	3	0.17	0	1	2	6.59
Baricitinib	0	0	0	0	0	0.55	0	0	1	3.21
Paritaprevir	2	3	1	1	3	0.17	0	2	3	6.97
Ivermectin	2	4	1	1	4	0.17	0	1	3	10.00
2-monolinolenin	0	0	1	0	1	0.55	0	1	3	3.65
Azadirachtin A	2	3	1	1	4	0.17	0	3	3	8.11
Azadirachtin D	2	3	1	1	4	0.17	0	3	2	7.96
Azadirachtin H	2	3	1	1	4	0.17	0	3	2	7.87
Azadirachtin F	2	3	1	1	3	0.17	0	3	2	7.50
Azadirachtin I	2	3	1	1	4	0.17	0	3	1	7.74
Desacetylnimbin	0	1	0	0	0	0.55	0	2	1	6.32
Azadiradione	0	0	0	0	0	0.55	0	0	2	5.89
Nimbin	1	3	0	0	0	0.55	0	2	2	6.54
Nimbolin	1	4	0	0	1	0.55	0	3	3	7.47
Nimbolide	0	0	0	0	0	0.55	0	2	1	6.07
Nimbinene	0	1	0	0	0	0.55	0	2	1	6.21
Azadirone	1	1	0	1	1	0.55	0	1	2	5.87

Key: Lip V= Lipinski Violation; B= Bioavailability; LL= lead likeness; GV= = Ghose Violation; MV = Muegge Violation; EV = Egen Violation; SA= Synthetic accessibility.

Table 6: The Metabolism and Distribution of the Ligands

Properties / Molecules	GIA	BBB P	P-gp S	C1A2I	C2C19I	C2C9I	C2D6I	C3A4I	Log K_p(cm/s)
Remdesivir	Low	No	Yes	No	No	No	No	Yes	-9.28
Baricitinib	High	No	Yes	No	No	No	No	No	-9.11
Paritaprevir	Low	No	Yes	No	No	No	No	Yes	-7.67
Ivermectin	Low	No	Yes	No	No	No	No	No	-7.14
2-monolinolenin	High	Yes	No	No	No	No	Yes	Yes	-4.91
Azadirachtin A	Low	No	Yes	No	No	No.	No	No	-9.92
Azadirachtin D	Low	No	Yes	No	No	No	No	No	-8.97
Azadirachtin H	Low	No	Yes	No	No	No	No	No	-9.36
Azadirachtin F	Low	No	Yes	No	No	No	No	No	-9.28
Azadirachtin I	Low	No	Yes	No	No	No	No	No	-8.41
Desacetylnimbin	High	No	No	No	No	No	No	Yes	-8.13
Azadiradione	High	No	Yes	No	No	No	No	No	-5.63
Nimbin	High	No	No	No	No	No	No	No	-7.98
Nimbolin	Low	No	Yes	No	No	No	No	No	-7.06
Nimbolide	High	No	Yes	No	No	No	No	No	-7.61
Nimbinene	High	No	No	No	No	No	Yes	Yes	-7.8
Azadirone	High	No	No	No	No	Yes	No	No	-4.9

KEY: GIA= gastrointestinal absorption; P= permeant; P-gp= P-glycoprotein; S=substrate, I= inhibitor; C=CYP (cytochrome P-450); Log K_p= skin permeation.

Table 7: Excretion and Toxicity of the Ligand

Parameters / Ligands	Excretion			Toxicity				
	T1/2(Hr) (mL/min/kg) CL			hERG Blocker	H-HT	AMES	SkinSen	LD50 (log[1/mol/kg])
Remdesivir	1.39	0.74	1	1	0	0	2 99	1
Baricitinib	1.47	1.16	0	1	0	0	2.52	1
Paritaprevir	2.19	0.82	1	0	0	0	3.10	1
Ivermectin	2.43	1.04	1	0	0	0	3.68	0
2-monolinolenin	1.80	1.60	1	0	0	1	1.46	0
Azadirachtin A	2.05	1.37	0	0	0	0	3.74	0
Azadirachtin D	1.94	1.38	0	0	0	0	3.73	0
Azadirachtin H	1.92	1.49	0	0	0	0	3.86	0
Azadirachtin F	1.99	1.53	0	0	0	0	3.94	0
Azadirachtin I	1.75	1.46	0	0	0	0	3.98	0
Desacetylnimbin	1.45	1.77	0	0	0	0	3.76	0
Azadiradione	1.73	1.88	0	1	0	0	3.59	0
Nimbin	1.69	1.65	0	1	0	0	3.76	1
Nimbolin	2.15	1.60	1	1	0	0	4.25	1
Nimbolide	1.41	1.92	0	0	0	0	3.94	1
Nimbinene	1.41	1.77	0	1	0	0	3.70	0
Azadirone	1.87	1.70	1	1	0	0	3.42	0

Keys; $T^1/_2$ =Half-time; CL= clearance; hERG=human ether-a-go-go-related gene; H-HT= human hepatotoxicity; AMES= Ames mutagenicity; SkinSen= skin sensitivity; LD_{50}= median lethal dose; DILI=drug induced liver injury.

Table 8: Bioactivity Prediction of the Ligands using Molinspiration Software

Bioactivity / Ligands	Bioactivity Scores					
	GPCR L	ICM	Kinase I	NRL	Protease I	Enzyme I
Remdesivir	0.35	-0.27	0.26	-0.46	0.54	0.44
Baricitinib	0.52	0.12	0.80	-0.69	0.15	0.28
Paritaprevir	-0.78	-2.24	-1.79	-2.15	0.22	-1.24
Ivermectin	-2.49	-2.86	-3.23	-2.94	-1.89	-2.53
2-monolinolenin	0.38	0.13	0.02	0.26	0.20	0.43
Azadirachtin A	-0.71	-1.51	-1.46	-0.67	-0.35	-0.71
Azadirachtin D	-0.36	-1.00	-1.02	-0.16	-0.10	-0.28
Azadirachtin H	-0.17	-0.81	-0.89	-0.03	0.13	-0.12
Azadirachtin F	-0.20	-0.79	-0.94	-0.06	0.03	-0.08
Azadirachtin I	0.07	-0.42	-0.57	0.34	0.29	0.21
Desacetylnimbin	0.31	0.21	-0.22	0.35	0.16	0.43
Azadiradione	0.08	0.07	-0.51	0.44	-0.01	0.41
Nimbin	0.24	0.14	-0.30	0.26	0.10	0.36
Nimbolin	-0.45	-1.11	-1.12	-0.59	-0.23	-0,47
Nimbolide	0.22	0.20	-0.36	0.32	0.04	0.36
Nimbinene	0.21	0.18	-0.30	0.37	0.04	0.33
Azadirone	0.13	0.11	-0.54	0.47	0.06	0.44

Keys: GPCRL= G-protein coupled receptor ligand; ICM= Ion channel modulator; I= inhibitor; NRL= Nuclear receptor ligand

All of our compounds fell within the confines of Lipinski's Rule of 5, which states that an oral medication should have a LogP value of less than 5. For good oral and intestinal absorption of a compound, lipophilicity should ideally fall between 1.35-1.8. Thus from this result, all the ligands have LogP values less than 5 with exception of azadirone.

The numbers, 0, 1, 2, 3 and 4 were categorical values which respectively indicates no (zero), one, two, three and four violations of the rules. Any ligands that do not have more than one violation could be said to have a good drug-likeness and possibly lead-likeness. From this result, baricitinib, 2-monolinolenin, desacetylnimbin, azadiradione, nimbin, nimbolin, nimbolide, nimbinene and azadirone have one or no violation.

Yes and No respectively connote higher probability of the ligand to be substrate and non-substrate of P-gp and inhibitor and non-inhibitor of given P450 isoforms. Note that 1 and 0 are categorical which mean positive and negative respectively with different probabilities (although not shown here). For instance, hERG 0 means non-blocker while 1 means blocker. The blue coloured values signify the ligands with significant bioactivity as predicted by Molinspiration Software, which increases as the value increases.

Discussion and Conclusion

Discussion

When compared to FDA-approved COVID-19 medications in this study, the results of this *In-silico* ADMET and bioactivity prediction of important secondary metabolites from *A. indica* leaf from Loganathan *et al*. (2021) [20] revealed noteworthy results. Two (40%) of the five FDA COVID-19 medications and three (25%) of the twelve secondary metabolites from *A. indica* leaf were deemed to be poorly soluble according to the solubility prediction (Table 2). Similar to what was found in this work, the physicochemical characteristics of the ligands (Table 3) predict that the fraction of carbon Sp3 will fall between 0.25 and 1. For the purpose of determining the unsaturation and flexibility of the chosen ligands or compounds, the number of rotatable bonds should not be greater than 9. Furthermore, molecules with TPSAs greater than 140 angstroms squared (A^2) have a propensity to have poor cell membrane penetration. A TPSA of less than 90 A^2 is often required for molecules to pass through the BBB and act on receptors in the central nervous system, as illustrated in the case of the 2-monolinolenin molecule (Fig. 3). The likelihood that an oral medication candidate would be developed successfully and the number of aromatic rings are not inversely related. Oral medication candidates with more than three aromatic rings are less likely to be developed successfully than those with fewer.

The capacity of a molecule to differentially dissolve in a mixture of water and lipids or organic solvents is known as lipophilicity (LogP), and it can be difficult to empirically establish for a large number of substances. P is therefore intended to lessen risks and failures related to novel drug candidates by helping to prioritize the synthesis of the appropriate compounds. In fact, LogP is a key component of Lipinski's Rule of Five suggestions, which determine how drug-like a novel synthetic molecule will be. All of our compounds satisfied Lipinski's Rule of 5, which states that an oral medication should have a LogP value of less than 5. An optimal range for lipophilicity for a compound's oral and intestinal absorption is 1.35–1.8. Thus from this result (Table 4), all the ligands have Log*P* values less than 5 with exception of azadirone.

To improve the prediction accuracy by consensus log Po/w, the models supporting the predictors for lipophilicity should be as diverse as is practical [27]. As a result, SwissADME gave users access to five publicly accessible predictive models, including XLOGP3, an atomistic approach with corrective variables and a knowledge-based library [28], WLOGP, an internal implementation of an atomistic approach based on the Wildman and Crippen fragmental system [29], and MLOGP, an illustrative topological approach relying on a linear relationship with 13 molecules. The consensus log Po/w is the arithmetic mean of the values projected by the five indicated techniques; therefore, the LogP numbers are rather correct.

The drug ability or drug-likeness of ligands was estimated through structural or physicochemical examinations of development compounds that were sufficiently advanced to be recognized as oral drug candidates. It is common practice to utilize this method to screen chemical libraries for molecules with properties that are most likely incompatible

with a desired pharmacokinetic profile. In this study, the Swiss ADME Model gave researchers access to five different rule-based filters, each of which has a distinct set of characteristics that distinguish a molecule as being drug-like. These filters typically originate from large pharmaceutical corporations' research initiatives to improve the caliber of their own chemical libraries. The rule-of-five was initially applied using the Lipinski (Pfizer) filter [25]. The approaches used by Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) were adapted from Ghose *et al*. [30], Veber *et al*. [31], Egan *et al*. [32], and Muegge *et al*. [33], in that order. As a result of the availability of many estimates, it is possible to reach a consensus or choose the tactics best suited to the end user's unique requirements in terms of chemical space or project-related parameters. In order to determine if a chemical will have at least 10% oral bioavailability in rats or measurable Caco-2 permeability in rats, the Abbot Bioavailability Score [34] was also created. This semi-quantitative rule-based score generates four classifications of compounds with probabilities of 11%, 17%, 56%, or 85% based on total charge, TPSA, and Lipinski filter violation. Baricitinib, 2-monolinolenin, desacetylnimbin, azadiradione, nimbin, nimbolin, nimbolide, nimbinene, and azadirone all have bioactivity scores in this study that are greater than 50%, which is consistent with their drug-likeness.

The detection of potentially problematic components is made possible by two complementary pattern recognition techniques, which aid medicinal (bio)chemists in their continual quest to find new medications. In assays, ligands or substances with substructures known as PAINS (pan-assay interference chemicals) exhibit potent reactivity regardless of the protein target. They are also known as promiscuous compounds or frequent hits. After examining six orthogonal tests, Baell and Holloway [35] discovered elements that result in biological output that is mistakenly positive. Another aspect of Swiss ADME tools is Structural Alert, a list of 105 fragments that Brenk *et al*. [36] discovered to be potentially hazardous, chemically reactive, metabolically unstable, or to have properties that lead to poor pharmacokinetics. Swiss ADME developed a rule-based technique for lead likeness that was adopted from Teague *et al*. [37] because it is essential for a biochemist to determine whether a specific molecule is suitable to begin lead optimization. Based on this finding, only Brenk Alert has a PAIN Alert. Only 5 of the compounds under investigation (Table 5) exhibit less than 2 LL breaches in a way similar to this. The ability to pick the most promising virtual compounds to be manufactured and examined in biological testing or other research is a significant component of computer-aided drug design (CADD) techniques. Another important element to take into account in lead optimization is synthetic accessibility (SA). The parameters used to describe size and complexity, such as macrocycles, chiral centers, or spiro functions as described by Ertl and Schuffenhauer in 2009, are added together for a specific molecule to calculate the fragmental contributions to SA. The SA Score, which has undergone standardization, goes from 1 (extremely easy) to 10 (very tough). So, the simpler the chemical can be produced, the lower the SA Score.

Potts and Guy [38] found that the skin permeability coefficient (Kp) was directly connected to molecule size and lipophilicity (R^2 = 0.67), which led to the development of the multiple linear regression method used to predict Kp. The molecule becomes less permeable to skin as log Kp (with Kp in cm/s) becomes more negative. As a result, the values in red on Table 6 had comparatively low skin sensitivity, whereas the values in blue had significant skin sensitivity. Knowing which substances are substrates or non-substrates of the permeability glycoprotein (P-gp, the most vital member among ATP-binding cassette transporters, or ABC-transporters) is also necessary for assessing active efflux via cellular membranes, such as from the brain or from the gastrointestinal wall to the lumen [39]. P-gp has a number of important functions, one of which is the selective transportation of xenobiotics away from the central nervous system (CNS) [40]. Understanding how chemicals interact with cytochromes P450 (CYP) is also crucial. Through metabolic biotransformation, this isoenzyme superfamily greatly contributes to drug clearance [41, 42] shown that CYP and P-gp can digest minute molecules in a synergistic way to enhance tissue and organism defense. These isoenzymes' inhibition unquestionably contributes significantly to drug-drug interactions that are connected to pharmacokinetics [43, 44], which can have toxic or other undesirable side effects [45]. This is brought on by the decreased excretion and buildup of medicines or their metabolites. There are many CYP isoform inhibitors available. Others exhibit selectivity for specific isoenzymes, whereas some have an impact on a number of CYP isoforms [46]. Therefore, it is essential to predict a molecule's propensity to inhibit CYPs and cause major drug interactions as well as identify which isoforms are affected during the drug development process (Table 6). Only remdesivir, paritaprevir, 2-monolinolenin, desacetylnimbin, and nimbinene inhibited one or more isoforms, as stated in Table 6 above. The FDA has approved 2-monolinolenin for the treatment of COVID-19, but it is the only medicine that can cross the blood-brain barrier (BBB; Table 6).

With the exception of remdesivir and nimbolin, the majority of the medicines exhibited low toxicity according to the toxicity prediction (Table 7). Similar to this, all the compounds, with the exception of 2-monolinolenin, showed little oral acute toxicity [47]. With the exception of remdesivir and paritaprevir, all of the medications have an excretion half-life of 1 to slightly less than 3 hours and a clearance time of around 2 mL/min/kg (Table 7). In the study of bioactivity prediction, the ligands with significant bioactivity as predicted by Molinspiration Software are represented by blue-colored values; the value rises as the value rises (Table 8). This discovery indicates that nimbolin, ivermectin, azadirachtin A, azadirachtin D, azadirachtin H, and azadirachtin F did not display any bioactivity. This was not unexpected given the comparatively subpar ADMET characteristics of these ligands. Many of the ligands under investigation may also function as inhibitors of enzymes and nuclear receptor ligands. Only two substances, remdesivir and baricitinib, might, however, inhibit kinases (Table 8).

Significance of the Study

This work has shown that many distinct bioactive substances found in *A. indica* leaves, when isolated and investigated (via molecular docking, *in-vitro*, and *in-vivo* experiments), could result in the discovery of drug(s) for treating COVID-19. Examples of these compounds are azadiradione and nimbolide.

Conclusion

The majority of the *A. indica* bioactive secondary metabolites exhibited favorable ADMET and bioactivity characteristics. Ivermectin, azadirachtin A, azadirachtin D, azadirachtin H, azadirachtin F, azadirachtin I, and nimbolin, on the other hand, have shown comparatively subpar properties. Additionally, the *A. indica* compounds outperformed the FDA-approved COVID-19 medication in terms of their characteristics. Similar to this, all of the substances except for remdesivir and nimboline have a relatively low level of toxicity. With the exception of 2-monolinolenin, their oral acute toxicity can be deemed to be rather modest.

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