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Review

Evaluation of phytochemicals from *Azadirachta indica* for drug-like properties: A computational insight into natural product-based drug discovery

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ABSTRACT:

Introduction: The growing interest in natural products for drug discovery has strengthened the exploration of various phytochemicals from traditional medicinal plants like *Azadirachta indica* (Neem), known for its excellent therapeutic benefits. **Methodology**: This current study uses computerised tools to appraise drug-like potential for the medicinal plant *Azadirachta indica-derived* phytochemicals. Few parameters, such as molecular weight, lipophilicity (Log P), hydrogen bond donors or acceptors, and Drug Likeness score, were analysed using IMPPAT and Molsoft L.L.C database highlighting on Lipinski's Rule of Five. **Results**: Phytochemical compounds such as nimbin, nimbolide, azadirachtin, and quercetin exhibited favourable drug-like properties and better oral bioavailability. Major phytochemicals that are analysed have complied with standards of drug-likeness, reinforcing their viability as potential orally administered therapeutic drug candidates. **Conclusion**: These results emphasize the value of phytochemicals present in *Azadirachta indica* for modern drug development and emphasize the usefulness of computerised tools in the early stage of drug screening and evaluation for future pharmacological studies.

KEYWORDS: *Azadirachta indica*, phytochemicals, drug-likeness, Lipinski's Rule of Five, bioavailability, computational drug discovery.

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1. INTRODUCTION

Azadirachta indica, known as *Nimba* in the local language, is an age-old medicinal plant widely used for therapeutic purpose in traditional systems of medicine such as Ayurveda, Unani, and traditional Chinese medicine. Neem has medicinal properties in of its parts i.e *Panchanga* (five parts of the plant), which includes stem, bark, roots, leaves, fruits, and flowers. Neem has been used in various traditional systems of medicine like Ayurveda, Siddha, Unani, and as a polyherbal preparation in medicine since ancient times. It is currently utilized in the production of contemporary pharmaceuticals, toiletries, and a variety of cosmetics. [1] Various chemical components like alkaloids, ketones, flavonoids, carotenoids, phenolic compounds, azadirachtin, etc, from different parts of the plant exhibit a wide range of pharmacological action, like antipyretic, analgesic, anti-filarial, hepatoprotective, anti-inflammatory, anti-cancer, anti-microbial, and anti-malarial effects. [2,3] For a compound to be a strong drug candidate, a molecule must exhibit few qualities, like solubility, permeability, and bioavailability. For a drug molecule to reach its target site in the body at certain therapeutic concentrations, various properties are necessary. [4] According to Lipinski's Rule of Five, there are various parameters and normal standards that include molecular weight, Partition Coefficient (Log P), Hydrogen bond acceptor, Hydrogen bond donor, which are most used to predict the drug likeness of a compound. When a compound does not meet the standard criteria of each parameter i.e, usually more than one, it is considered an orally inactive medication. [5] An application in computerised drug discovery, that is Computer-Aided Drug Design (CADD), is widely applied due to its increased process efficiency. [6] Researchers can rapidly screen and optimize the potential drugs by application of various techniques like pharmacophore modelling, molecular docking, and quantitative structure-activity relationship (QSAR). Application of computational tools like IMPAAT, MolSoft, etc fastens the process of drug development also improves the precision of predicting drug-like properties of a phytochemical along with its therapeutic efficacy. [7] Based on a chemical structure, a QSAR model can predict the biological activity of phytochemicals. Whereas the models of molecular docking can specifically estimate how well a compound can fit or bind to target proteins. [8] In regard to the assessment of therapeutic potential and drug-like characteristics for a phytochemical of *Azadirachta indica*, current studies have also given due importance to the in-silico method of analysis. [9] A potent bioactive compound of *Azadirachta indica* named Nimbolide, according to molecular docking studies; this compound shows significant binding affinity towards several target proteins in relation to cancer, which includes VEGFR-2, PI3K, and NF-κB. [10] These conclusions support the efficacy of nimbolide as an effective anticancer drug. [11] Computational approaches have limits, even if they have several benefits for predicting drug-like characteristics. The reliability of the data depends upon both the quality of the data and the techniques/methods adopted for its collection. In vitro

and in vivo studies must also ensure in silico predictions to guarantee relevance and application. [12]

2. MATERIALS AND METHODS - Software and Servers used - IMPAAT database is used for the collection of canonical smiles, the selection of appropriate phytochemicals, and downloading SDF files. Molsoft software is used to evaluate the drug-likeness of compounds**.**

List of Phytochemicals -

The list of selected phytochemicals included in the study are 6-Deacetylnimbin, Azadirachtanin, Isomargosinolide, Nimbinene, Isoazadirolide, Nimbocinolide, 28-Deoxonimbolide, 1-Nonacosanol, Tetradecanal, Azadirachtin, alpha-Patchoulene, Quercetin, Germacrene B, Isomeldenin, Corosolic acid, Margosinolide, Meldenin, 1-Hexacosanol,2',3'-Dehydrosalannol, Hexadecanal, Isorhamnetin, Nonacosane, beta-Elemene, Nimocinol, Vilasinin, 3-Deacetylsalannin, Scopoletin, Lutein, beta-Carotene, Humulene, gamma-Muurolene, Nicotiflorin, Sterol, gamma-Elemene, delta-Elemene, Triterpenoids, Quercetin-3-glucoside, beta-Caryophyllene, beta-Sitosterol, Daucosterol, Stigmasterol, Hyperoside, Rutin, Quercitrin,beta-Sitosterol-beta-D-glucoside,alpha-Copaene, Allo-Aromadendrene, Azadirone, Gedunin, 24-Methylenecycloartanol, Nimbin, D-Glucose, D-Fructose, D-Xylose, Nimbiol, 6-Deacetylnimbin, Kulinone, Methyl kulonate, Kulactone, Kulolactone, 6beta-Hydroxystigmast-4-en-3-one, Methyl 2,5-dihydroxycinnamate, Nimbionol, Sugiol, Nimbionone, Epoxyazadiradione, Nimbosone, Margolonone, Deacetylgedunin, Nimbidiol, Myristic acid, Triterpenoid, Limbocidin, Azadirol, Nimbanal, 1,3-Diacetylvilasinin, 6-Acetylnimbandiol, Ohchinolide B, Corosolic acid, Dipropyl disulfide, 7-Deacetoxy-7-hydroxygedunin, 17-Hydroxyazadiradione, Salannin, Nimbinol, 2-Methyl-2pentenal,11HydroxyazadirachtinB,Linoleicacid, 1Docosene,cinnamoylmelianolone, kaempferol, Docosane, Melianoninol, Nimolinone, 6-Hydroxycyclohexa-2,4-dien-1-one, Nimolicinol, 5-Hydroxymethylfurfural, Salimuzzalin, Azadiradionol.

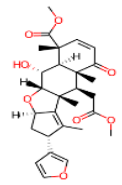
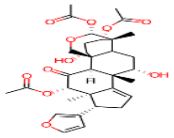
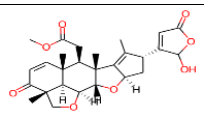
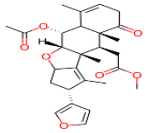
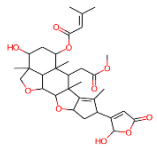
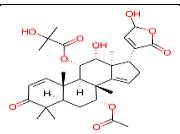
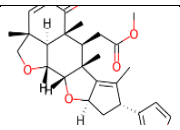
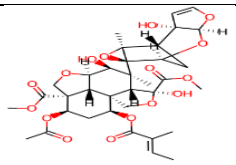
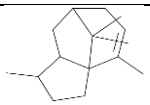
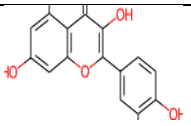
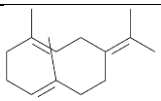
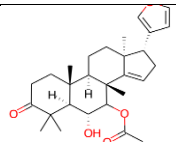
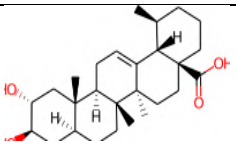
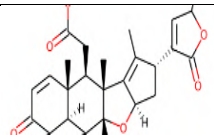
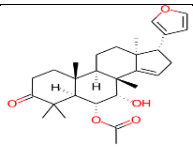
Collection of Canonical SMILES of selected Phytochemicals from IMPPAT Database - In order to collect canonical SMILES for selected phytochemicals, we have used the IMPPAT website and searched using each phytochemical's synonyms. There, select the phytochemical option. Later, add the name of the specific medicinal plant and click on the search button. The results display various phytochemicals based on the plant parts that is selected.

Click on the name of the individual phytochemical to view its details. Under the category of chemical structure information, the canonical SMILES will be displayed. Copy it, and repeat the same process for all the phytochemicals."

Chemical structures of selected phytochemicals from neem – Firstly, copy the notation of canonical SMILES from the IMPPAT database for the selective compound. Open Molsoft L.L.C. and proceed to the Import option, paste the copied canonical SMILES string into the input field, and click on OK. The molecular structure will be generated and displayed. The image is now copied and pasted into a Word document.

Determination of Drug Likeness Scores - MolSoft web servers (https://molsoft.com/mprop/) were used to predict the drug-like characteristics of phytocompounds. Lipinski's rule of five was used to determine drug-like qualities, which states that molecules should have a molecular weight of 500, a C log P of 5, fewer than 10 hydrogen bond acceptors, and fewer than 5 hydrogen bond donors. To anticipate drug-like features of compounds, the canonical Simplified Molecular Line-Entry Systems (SMILES) were retrieved from the IMPPAT Database and entered into the MolSoft online server. [13]

Table 1: Chemical structures of selected phytochemicals from *Azadirachta indica*

S.no	Phytochemicals	Structure
1	6-Deacetylnimbin	
2	Azadirachtanin	
3	Isomargosinolide	
4	Nimbinene	
5	Isoazadirolide	
6	Nimbocinolide	
7	28-Deoxonimbolide	
8	1-Nonacosanol	
9	Tetradecanal	
10	Azadirachtin	
11	alpha-Patchoulene	
12	Quercetin	
13	Germacrene B	
14	Isomeldenin	
15	Corosolic acid	
16	Margosinolide	
17	Meldenin	
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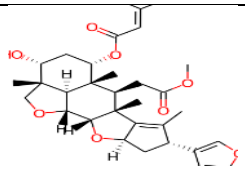
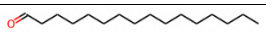
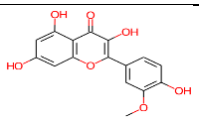
19	2',3'-Dehydrosalannol	
20	Hexadecanal	
21	Isorhamnetin	
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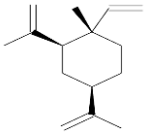
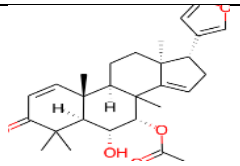
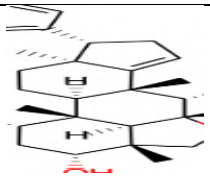
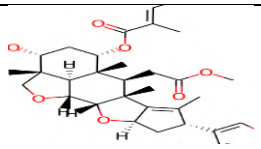
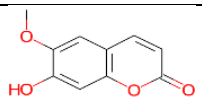
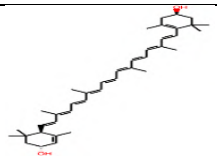
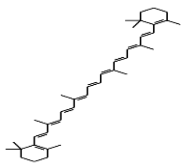
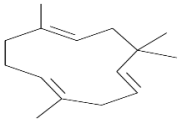
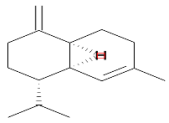
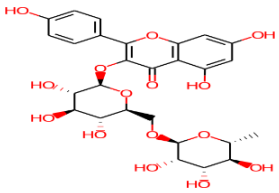
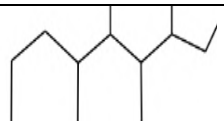
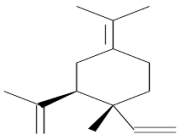
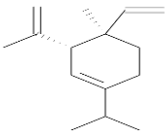
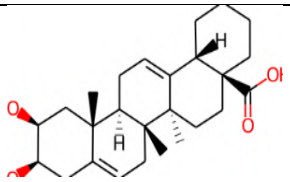
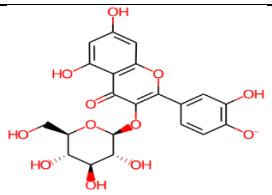
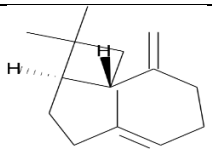
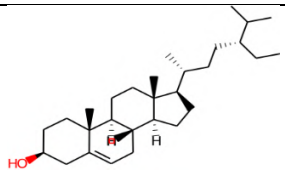
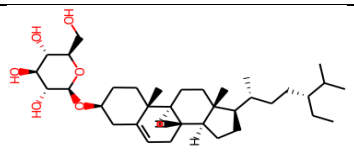
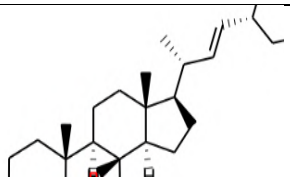
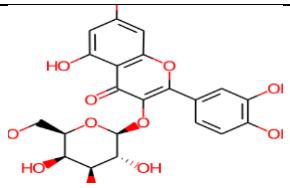
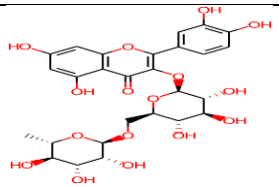
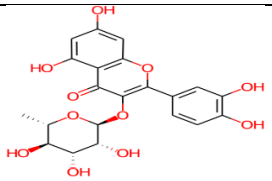
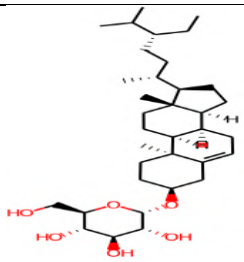
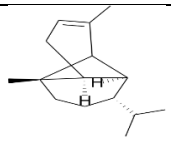
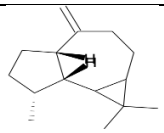
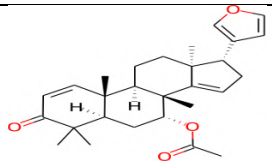
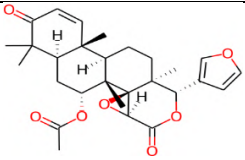
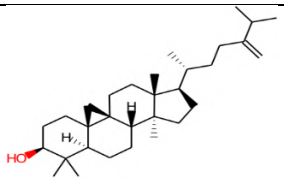
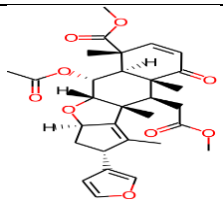
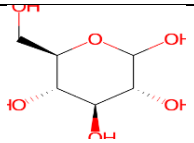
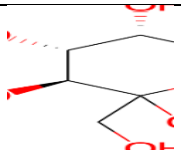
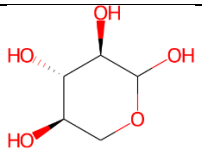
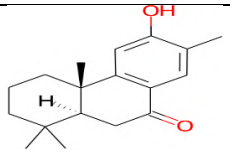
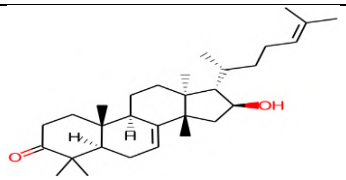
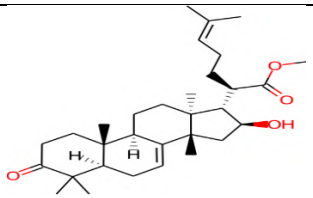
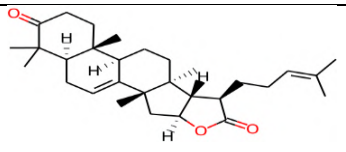
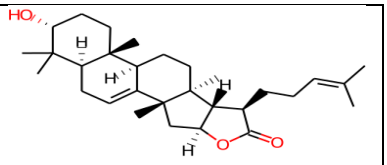
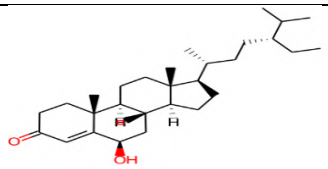
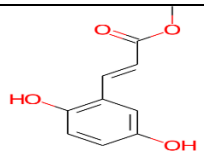
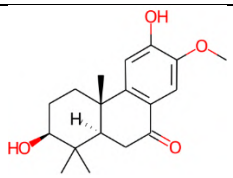
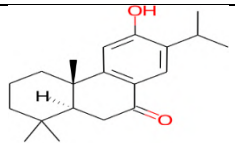
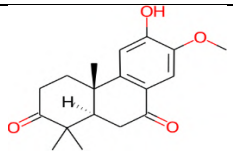
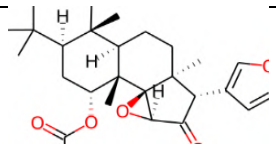
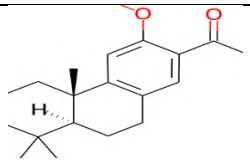
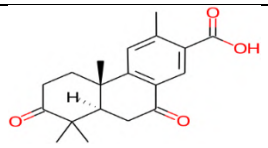
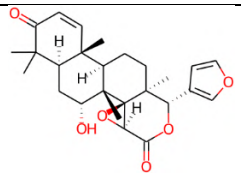
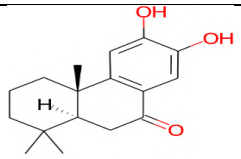
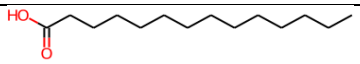
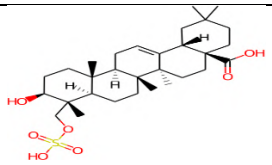
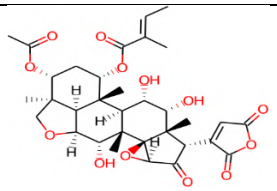
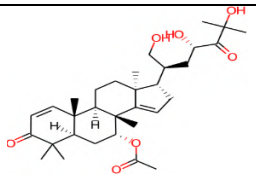
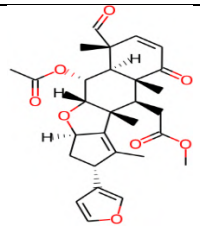
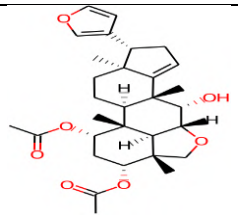
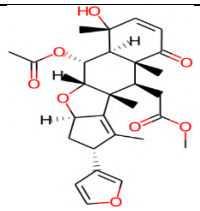
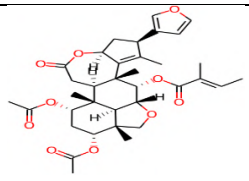
23	beta-Elemene	
24	Nimocinol	
25	Vilasinin	
26	3-Deacetylsalannin	
27	Scopoletin	
28	Lutein	
29	beta-Carotene	
30	Humulene	

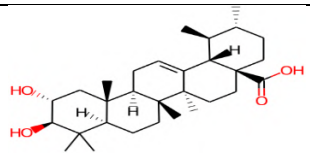
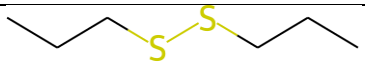
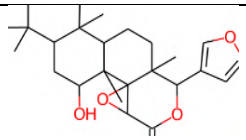
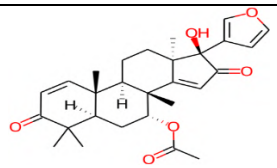
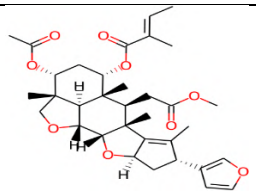
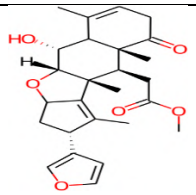
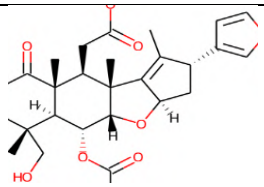
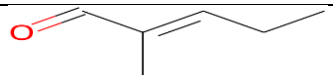
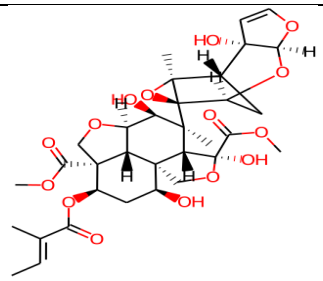
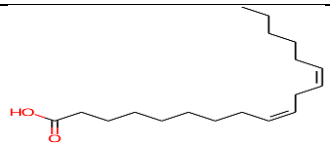
31	gamma-Muurolene	
32	Nicotiflorin	
33	Sterol	
34	gamma-Elemene	
35	delta-Elemene	
36	Triterpenoids	
37	Quercetin-3-glucoside	
38	beta-Caryophyllene	
39	beta-Sitosterol	
40	Daucosterol	

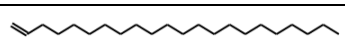
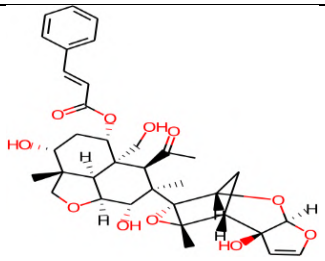
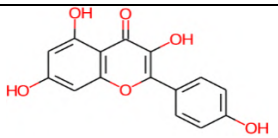
41	Stigmasterol	
42	Hyperoside	
43	Rutin	
44	Quercitrin	
45	beta-Sitosterol-beta-D-glucoside	
46	alpha-Copaene	
47	Allo-Aromadendrene	
48	Azadirone	
49	Gedunin	

50	24-Methylenecycloartanol	
51	Nimbin	
52	D-Glucose	
53	D-Fructose	
54	D-Xylose	
55	Nimbiol	
56	Kulinone	
57	Methyl kulonate	
58	Kulactone	

59	Kulolactone	
60	6beta-Hydroxystigmast-4-en-3-one	
61	Methyl 2,5-dihydroxycinnamate	
62	Nimbionol	
63	Sugiol	
64	Nimbionone	
65	Epoxyazadiradione	
66	Nimbosone	
67	Margolonone	
68	Deacetylgedunin	

69	Nimbidiol	
70	Myristic acid	
71	Triterpenoid	
72	Limbocidin	
73	Azadirol	
74	Nimbanal	
75	1,3-Diacetylvilasinin	
76	6-Acetylnimbandiol	
77	Ohchinolide B	

78	Corosolic acid	
79	Dipropyl disulfide	
80	7-Deacetoxy-7-hydroxygedunin	
81	17-Hydroxyazadiradione	
82	Salannin	
83	6-Deacetylnimbinene	
84	Nimbinol	
85	2-Methyl-2-pentenal	
86	11-Hydroxyazadirachtin B	
87	Linoleic acid	

88	1-Docosene	
89	1-cinnamoylmelianolone	
90	kaempferol	
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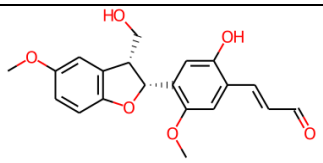
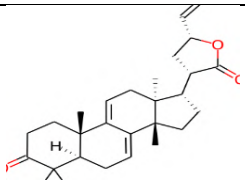
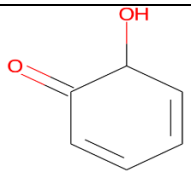
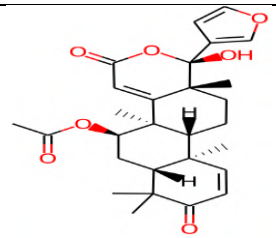
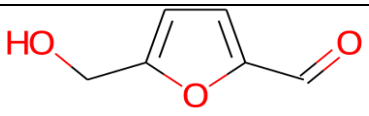
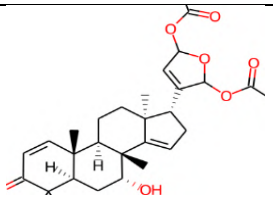
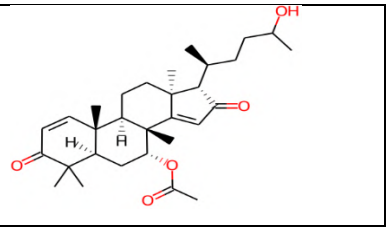
92	Melianoninol	
93	Nimolinone	
94	6-Hydroxycyclohexa-2,4-dien-1-one	
95	Nimolicinol	
96	5-Hydroxymethylfurfural	
97	Salimuzzalin	

98	Azadiradionol	

3. RESULTS -

Drug design depends critically on the concept of "drug likeness," which is particularly defined in terms of bioavailability, how closely a chemical resembles the characteristics of a conventional drug. Many drug-related properties are measured for different phytochemicals to understand how well they can be absorbed and used by the human body. The main objective of the study was to investigate whether these plant compounds have the right qualities to be used in the development of medicine. The drug-likeness of the compounds was evaluated using several physicochemical criteria, including Molecular Weight (MW), Hydrogen Bond Acceptors (HBA), Hydrogen Bond Donors (HBD), partition coefficient (Log P), and compliance with Lipinski's rule of five (RO5). The acceptable ranges for these values are listed below, which show adequate oral bioavailability: MW<500 Daltons, HBA≤10, HBD≤5, Log P≤5, and RO5 violations≤1. Utilizing the MolSoft web server, the potential of the specified medicines and phytoconstituents to be used as drugs was evaluated. The results, as presented in Table 1, indicate that the majority of the Table 2 represents the drug Likeness Profile of Phytochemicals from *Azadirachta indica*

Table 2. Drug Likeness Profile of Phytochemicals from *Azadirachta indica*.

S.no	CHEMICAL NAME	MW (> 500)	Clog *P(> 5)*	HBA (> 10)	HBD (> 5)	Number of Violations	DLS
1.	6-Deacetylnimbin	498.23	2.59	8	1	0	0.07
2.	Azadirachtanin	600.26	1.31	11	2	2	-0.07
3.	Isomargosinolide	484.21	1.53	8	1	0	-0.2
4.	Nimbinene	482.23	3.72	7	0	0	-0.29
5.	Isoazadirolide	586.28	2.52	10	2	1	0.01
6.	Nimbocinolide	586.28	1.97	10	3	1	0.41
7.	28-Deoxonimbolide	452.22	3.29	6	0	0	-0.51
8.	1-Nonacosanol	424.56	13.72	1	1	1	-0.92
9.	Tetradecanal	211.21	6.07	1	0	1	-1.19
10.	Azadirachtin	720.26	1.26	16	3	2	-0.16
11.	alpha-Patchoulene	204.19	5.01	0	0	1	0.12
12.	Quercetin	302.04	1.19	7	5	0	0.52
13.	Germacrene B	204.19	6.49	0	0	1	-1.6
14.	Isomeldenin	454.27	5.11	5	1	1	0.46
15.	Corosolic acid	472.36	5.3	4	3	1	0.6
16.	Margosinolide	484.21	1.35	8	1	0	-0.39

17.	Meldenin	454.27	5.2	5	1	1	0.49
18.	1-Hexacosanol	382.42	12.2	1	1	1	-0.92
19.	2',3'-Dehydrosalannol	257.11	2.68	3	1	0	0.29
20.	Hexadecanal	240.25	7.08	1	0	1	-1.19
21.	Isorhamnetin	316.06	1.34	7	4	0	0.39
22.	Nonacosane	408.47	15.45	0	0	1	-1.03
23.	beta-Elemene	204.19	5.84	0	0	1	-1.15
24.	Nimocinol	452.26	4.68	5	1	0	0.51
25.	Vilasinin	428.26	2.62	5	3	0	-0.2
26.	3-Deacetylsalannin	554.29	33.59	8	1	2	-0.38
27.	Scopoletin	192.04	0.93	4	1	0	-1.23
28.	Lutein	568.43	11.81	2	2	2	-0.33
29.	beta-Carotene	536.44	13.93	0	0	2	0.64
30.	Humulene	204.19	6.23	0	0	1	-1.42
31.	gamma-Muurolene	204.19	5.32	0	0	1	-1.09
32.	Nicotiflorin	594.14	-1.13	15	9	3	0.9
33.	Sterol	248.21	4.09	1	1	0	-1.07
34.	gamma-Elemene	204.19	5.54	0	0	1	-0.69
35.	delta-Elemene	204.19	5.51	0	0	1	-1.19
36.	Triterpenoids	472.32	4.04	5	4	0	0.56
37.	Quercetin-3-glucoside	463.09	-0.32	12	7	2	0.64
38.	beta-Caryophyllene	204.19	5.35	0	0	1	-1.74
39.	beta-Sitosterol	414.39	8.45	1	1	1	0.78
40.	Daucosterol	576.44	6.31	6	4	2	0.5
41.	Stigmasterol	412.37	7.74	1	1	1	0.62
42.	Hyperoside	464.1	-0.54	12	8	2	0.68
43.	Rutin	610.15	-1.55	16	10	3	0.91
44.	Quercitrin	448.1	0.32	11	7	2	0.82
45.	Beta-Sitosterol-beta-D-glucoside	576.44	6.31	6	4	2	0.5
46.	alpha-Copaene	204.19	4.89	0	0	0	-0.89
47.	Allo-Aromadendrene	204.19	5.22	0	0	1	-1.3
48.	Azadirone	432.26	5.52	4	0	1	0.14
49.	Gedunin	482.23	4.2	7	0	0	-0.44

50.	24-Methylene-cycloartanol	440.4	8.49	1	1	1	-0.48
51.	Nimbin	540.24	3.13	9	0	1	-0.02
52.	D-Glucose	180.06	-3.02	6	5	0	-0.12
53.	D-Fructose	180.06	-2.75	6	5	0	-0.52
54.	D-Xylose	150.05	-2.93	5	4	0	-1.37
55.	Nimbiol	272.18	4.24	2	1	0	0.37
56.	Kulinone	440.37	7.89	2	1	1	0.58
57.	Methyl kulonate	484.36	6.95	4	1	1	0.7
58.	Kulactone	452.33	7.42	3	0	1	0.24
59.	Kulolactone	454.34	7.34	3	1	1	0.26
60.	6beta-Hydroxy-stigmast-4-en-3-one	428.37	7.36	2	1	1	1.22
61.	Methyl 2,5-dihydroxycinnamate	194.06	1.76	4	2	0	-0.66
62.	Nimbionol	304.17	3.58	4	2	0	0.43
63.	Sugiol	300.21	5.1	2	1	1	0.46
64.	Nimbionone	257.11	2.68	3	1	0	0.29
65.	Epoxyazadiradione	466.24	4.04	6	0	0	-0.2
66.	Nimbosone	300.21	5.11	2	0	1	-0.37
67.	Margolonone	314.15	4.13	4	1	0	0.46
68.	Deacetylgedunin	440.22	3.71	6	1	0	-6.09
69.	Nimbidiol	274.16	3.44	3	2	0	0.3
70.	Myristic acid	228.21	5.63	2	1	1	-0.54
71.	Triterpenoid	552.31	2.6	7	3	1	0.29
72.	Limbocidin	644.25	-0.1	13	3	2	-0.24
73.	Azadirol	544.34	3.48	7	3	1	0.64
74.	Nimbanal	510.23	2.77	8	0	1	-0.25
75.	1,3-Diacetylvilasinin	257.11	2.64	3	1	0	0.29
76.	6-Acetylnimbandiol	498.23	2.79	8	1	0	-0.08
77.	Ohchinolide B	624.29	3.77	10	0	1	-0.1
78.	Corosolic acid	472.36	5.3	4	3	1	0.6
79.	Dipropyl disulfide	150.05	3.18	2	0	0	-1.29
80.	7-Deacetoxy-7-	440.22	3.71	6	1	0	-0.69

	hydroxygedunin						
81.	17-Hydroxyazadiradione	466.24	3.63	6	1	0	0.43
82.	Salannin	596.3	4.15	9	0	1	-0.45
83.	6-Deacetylnimbinene	440.22	3.19	6	1	0	-0.19
84.	Nimbinol	512.24	2.92	8	1	1	-0.05
85.	2-Methyl-2-pentenal	98.07	2.05	1	0	0	-1.54
86.	11-Hydroxyazadirachtin B	678.25	0.7	15	4	2	-0.17
87.	Linoleic acid	280.24	6.6	2	1	1	-0.3
88.	1-Docosene	308.34	11.66	0	0	1	-1.25
89.	1-cinnamoylmelianolone	638.27	2.23	11	4	2	-0.12
90.	kaempferol	286.05	1.61	6	4	0	0.5
91.	Docosane	310.36	11.91	0	0	1	-1.03
92.	Melianoninol	356.13	2.27	6	2	0	-0.61
93.	Nimolinone	422.28	6.08	3	0	1	-0.01
94.	6-Hydroxycyclohexa-2,4-dien-1-one	110.04	-0.2	2	1	0	-1.16
95.	Nimolicinol	482.23	3.72	7	1	0	0.23
96.	5-Hydroxymethylfurfural	126.03	0.23	3	1	0	-1.64
97.	Salimuzzalin	512.28	4.14	7	1	1	0.31
98.	Azadiradionol	484.32	4.46	5	1	0	0.9

Data Analysis: Drug-Likeness Evaluation of Selected Phytochemicals

Evaluation of Drug-likeness of selected phytochemicals was assessed for physicochemical properties using a few parameters that influence the bioavailability of a substance in a human body. These parameters are Molecular Weight (MW), partition coefficient (Log P), Hydrogen Bond Acceptors (HBA), Hydrogen Bond Donors (HBD), and adherence to Lipinski's rule of five (RO5). The MolSoft web server was used to evaluate whether these plant compounds could be effective drug candidates.

Molecular Weight (MW) - This is a crucial parameter in drug design as it influences pharmacokinetic activity, that is, how a phytochemical is absorbed, distributed, metabolised, and eliminated from the body. In general, those phytochemicals which has a lower molecular weight have a greater bioavailability and can pass across the cell membranes. To ensure optimal oral absorption, MW should be below 500 Daltons. While most of the selected compounds have met the molecular weight limit, a few were over 500 Daltons, which could reduce their bioavailability.

Hydrogen Bond Acceptors (HBA) - The amount of hydrogen bond acceptors in a molecule affects the

solubility and permeability. A high number of HBAs can increase solubility but reduce the ability to pass through cell membranes. (A good medicine candidate should have no more than ten hydrogen bond acceptors.) As per the investigation, most compounds met the HBA limit; some exceeded it, which would lower their bioavailability and permeability.

Hydrogen Bond Donors (HBD) - Hydrogen bond donors help drugs stick to their targets in the body. The hydrogen bonds with the receptors help the drug work better. However, an excess amount of HBDs makes it harder for a compound to cross the cell membranes. An optimal medication should have five or fewer hydrogen bond donors. Most of the drug compounds had safe levels of hydrogen bond donors and were within the limit, indicating a satisfactory balance of solubility and membrane permeability.

Partition Coefficient (Log P) - Log P measures the hydrophobicity metric that shows how well a compound can pass through the lipid bilayer of cell membranes. It also influences the compound's solubility in water vs organic solvents. A Log P value below 5 shows an optimal membrane permeability and solubility balance. The majority of the phytochemicals analysed had Log P values within the acceptable range, indicating high permeability and bioavailability. Compounds having Log P values greater than 5 may be excessively hydrophobic, making them poorly soluble in water.

Lipinski's Rule of Five (RO5) - Lipinski's Rule provides a set of parameters to check if a selected phytochemical possesses better oral bioavailability. Phytochemicals which don't adhere to the standard values i.e, beyond one standard parameter, are considered less likely to show their potential oral bioavailability. A Phytochemical compound shouldn't possess more than one violation of the Lipinski's rule of five. The present investigation has shown that the majority of the phytochemical compounds adhere to the standard values for all the parameter components of Lipinski's rule of five, which highlights the potency of a drug compound showing its effective oral bioavailability. Although only a minimal number of phytochemicals deviate to meet multiple parameters, this reveals that there is a need for optimisation to achieve better compatibility with drug-like characters.

Most of the phytochemicals have excellent drug-likeness properties based on their analysis over Lipinski's rule. Multiple phytochemicals have complied with the standards of all the parameters of Lipinski's rule, suggesting their potential for future development of a drug. A very minimal number of compounds did not comply with the parameters of Lipinski's rule. The phytochemicals that are beyond the normal standards of Lipinski's rule need changes in their structures to exhibit drug-like properties.

A total of 98 phytochemicals which belong to Azadirachta indica was analysed for drug-likliness properties these analysis reveal clear distinction among the compounds with favourable drug likeliness and those with multiple violations. Compounds like azadiradione, gedunin, corosolic acid, nimbin, nimbinol, isomargolonide, quercetin and nimocinol have compiled with the lipinskis rule of five with no violations and and positive drug likeliness scores. However rutin,

nicotiflorin, azadirachtin and tetracosolic acid showed strong compliance with all the parameters.

The current evaluation highlighting the necessity of computational techniques/tools in highlighting the importance of early drug development, as they pave the way for better insights into experimental procedures. In-depth experimental research studies, including in vivo and invitro investigations, are crucial to analyse and validate the results and to discover the clinical relevance of phytochemical compounds.

4. Discussion -

The evaluation of various phytochemicals for their drug likeness related to *Azadirachta indica* exhibits its suitable potential for the development of a viable oral therapeutic medication. Most of phytochemicals that are screened comply the standard ranges of Lipinski's rule that shows conducive to better oral bioavailability traits such as molecular weight <5000 Da, log P 1–2, and a balanced number of hydrogen bond donors and as well as hydrogen bond acceptors. Few prominent compounds, such as Nimbinene, 6-Deacetylnimbin and Quercetin have exhibited either zero or one deviation from the normal standards this, which indicates better solubility and permeability of the drug with higher probability for effective absorption of the drug. A very limited number of phytochemical compounds like azadirachtin and azadirachtanin exhibit certain deviations in their standard due to their traits such as molecular bond and abundance of hydrogen acceptor bond and hydrogen donor bond; this reflects the limitations in the oral absorption of the drug, yet still doesn't affect the therapeutic efficacy through any of the other alternative routes of drug administration. The range of variations in values of drug-likeliness profiles of various phytochemicals reveals its complexity and richness of phytochemicals of *Azadirachta indica*, thus providing a varied range of effective bioactive compounds/potent therapeutic agents for future pharmacological exploration. Computerised databases/tools such as IMPAAT and MolSoft powdered platforms are meant to accelerate faster in silico screening, which enables the identification of pinpoint phytochemicals that are suitable for drug likeliness. However, the application of computational tools should be evaluated by various methods of experimental studies to affirm both safety and efficacy of a drug. Moreover, the docking studies point out stronger targets shown by nimbolide and nimbolide-like compounds for cancer, emphasizing its stronger potential for neem phytochemicals, underscoring an anticancer drug development. [14]Quecetin compound which is complied with lipinskis rule of five is well documented for its ancticancer activity and antioxidant potential. [15] Rutin possessing high hydrogen bond count and high molecular weight it retains its pharmacological significance because of its vascular protective activity. [16] Corosolic acid have shown minor variation but it is well established for its anti-diabetic action. [17] Gedunin and limonoids demonstrate favourable properties ans are reported for its antimalarial and anticancer propertied. [18] These findings reveal that although few phytochemicals show violations but the therapeutic activity of the compounds

is supported by its pharmacological evidences highlighting the drug discovery potential.

To sum up, the findings of this study show the relevance of drug discovery based on various phytochemicals from *Azadirachta indica* while also considering the limitations of applications of computational methods and the need for pharmacological validation.

5. Conclusion - Advanced natural product-based drug discovery offers an opportunity for new potential drug discoveries. The current study aims to identify promising drug-like phytochemical compounds from *Azadirachta indica*. Assessment of various phytochemicals of *Azadirachta indica* highlights compounds like nimbolide and quercetin exhibiting high potential for orally active therapeutic medication. Although few phytochemicals exhibit very modest deviation from Lipinski's rule yet they continue to exhibit potential therapeutic benefits. During the preliminary phase, screening is done by application of analysis by application of computerised methods to find out bioactive components, facilitating a quicker process for drug development. However, to confirm the therapeutic potential, experimental investigations which include, invitro and in vivo kinds of studies are necessary to establish their validation for their pharmacokinetic profiles, safety, and efficacy of a compound.

Abbreviations –

CADD (Computer-Aided Drug Design)

QSAR (Quantitative Structure–Activity Relationship)

IMPAAT (In-silico Molecular Properties and ADMET Analysis Tool)

SMILES (Simplified Molecular Input Line Entry System)

MW (Molecular Weight)

HBA (Hydrogen Bond Acceptor)

HBD (Hydrogen Bond Donor)

RO5 (Rule of Five - Lipinski's Rule of Five for drug-likeness)

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