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In-Silico Exploration of *Marsilea minuta*: ADME Profiling and Potential Neurotherapeutic Applications

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Abstract

Marsilea minuta (M. minuta), a traditional Ayurvedic medicinal plant, has garnered attention for its potential in treating central nervous system (CNS) disorders. This study employs *in-silico* computational profiling to evaluate the ADME (absorption, distribution, metabolism, excretion) properties and therapeutic potential of its phytochemicals. Using databases like IMPPAT and predictive tools (SwissADME), we analyzed 12 bioactive compounds (Syringic acid, Vanillic acid,Ferulic acid, 3,4-Dihydroxybenzoic acid, Caffeic acid, 4-Hydroxycinnamic acid, Marsileagenin A, Triacontyl hexacosanoate, beta-Sitosterol, 6-Hentriacontanol, Cholesterol, Stigmasterol), including syringic acid, ferulic acid, and beta-sitosterol. The results highlight phenolic acids as promising candidates due to their drug-like properties (MW <200, moderate lipophilicity, high solubility) and CNS activity, particularly ferulic acid's BBB permeability. Sterols and lipids exhibited poor bioavailability but demonstrated neuroprotective and anti-inflammatory effects. The study validates traditional uses of *M. minuta* for epilepsy, cognitive disorders, and anxiety, while identifying molecular targets for future drug development. These findings underscore its potential as a multi-target therapeutic agent for CNS diseases.

Keywords: CNS, *In-Silico*, *Ayurveda*, *Marsilea minuta*, SwissADME, Ethnopharmacology, IMPPAT, Phytochemicals

1. Introduction

CNS-related disorders like epilepsy, neurodegenerative disorders have affected millions of people worldwide. Neurodegenerative disorders such as Alzheimer's disease are complex, and although current treatments primarily address symptoms, there are some therapeutic options available, they still have significant limitations in effectiveness. However, medicinal plants present promising possibilities due to their neuroprotective and antioxidant properties [5]. Traditional herbs have demonstrated cholinergic and cognitive-enhancing properties, often with fewer side effects than conventional drugs [11]. Neurodegenerative and neuropsychiatric conditions such as Alzheimer's, Parkinson's, and depression represent a significant global health challenge. As concerns increase regarding the side effects associated with synthetic medications, there is an escalating interest in herbal and Ayurvedic treatments because of their natural origins and more favorable safety profiles [20]. It is crucial to understand that the label

"natural" does not necessarily imply safety, as certain herbs may possess hepatotoxic properties and would require further toxicological assessment [21].

Ayurveda provides a comprehensive approach and includes numerous nootropic herbs that offer multiple benefits. This has sparked a renewed interest in traditional remedies and emphasized the necessity for additional research and standardization of *Ayurvedic* therapies for brain disorders [22]. *Ayurveda*, recognized as one of the oldest holistic medical systems in the world, presents valuable methods for addressing neurodegenerative conditions like Alzheimer's and Parkinson's [15]. Medicinal herbs have been in use for treating diseases since ancient times in India. *Ayurvedic* therapies involving medicinal herbs and herbomineral products have been traditionally regarded as well-tolerated, with relatively few reported adverse effects when used appropriately. This ancient method of healing shows the use of *Ayurvedic* herbal remedies, recognized for their antioxidant, anti-inflammatory, and neuroprotective effects, which can assist in the management of these diseases while offering fewer adverse effects than standard medications [1], [4], [6], [7].
Marsilea minuta (*M. minuta*) comes from the family Marsileaceae (water clover family). *Marsilea minuta* has been widely researched, the latest evidences show that its antitussive (cough-suppressing) and expectorant properties using different extracts on mice. The methanol extract proved most effective, significantly reducing cough frequency and increasing tracheal secretion of phenol red, a marker for expectorant activity. At a dose of 500 mg/kg, it inhibited coughs by over 50% and boosted secretion by nearly 90%. These findings support the traditional use of *M. minuta* for treating respiratory ailments like cough [3]. *Marsilea minuta* has not only shown its efficiency in neurodegenerative disorders but also in psychiatric conditions, especially with regard to cognition. *M. minuta* demonstrated significant potential in reversing amnesia, primarily through the inhibition of acetylcholinesterase activity and the upregulation of muscarinic receptors, enhancing cognitive functions and memory [2].

In silico approaches serve as an important tool in modern bioinformatics and cheminformatics, offering cost-effective, time-efficient, and powerful predictive tools that generate hypotheses about molecular interactions and pathways, which require in vitro/in vivo confirmation. ADME analysis (Absorption, Distribution, Metabolism, Excretion) evaluates how a substance acts within the body, assisting researchers in choosing molecules with optimal bioavailability, effectiveness, and safety characteristics early in the development process. ADME analysis, in particular, allows for the systematic evaluation of a compound's pharmacokinetic profile, enabling the identification of lead candidates with optimal drug-like properties. This approach utilizes molecular modeling tools and computer-aided drug design (CADD) techniques, such as virtual ligand screening, profiling, structure prediction, refinement, and optimization [8], [10], [12]. Databases such as IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) offer organized details on phytochemicals, historical applications, and molecular characteristics, enabling quicker identification of bioactive compounds for computational evaluation and confirmation. The combination of *Ayurveda* with *in- silico* technology presents a hopeful opportunity for creating advanced and efficient therapeutic solutions, while many medicinal plants have been thoroughly examined using *In silico* ADME profiling, particularly *Marsilea minuta* has not been extensively studied through computational methods. The exploration of its various phytochemicals via *In silico* techniques is still relatively unaddressed, especially when considering the opportunity to incorporate drug repurposing, reverse pharmacology, and polypharmacology within *Ayurveda* through computational strategies. This

points out a significant gap in existing research and emphasizes the necessity for additional studies on *M. minuta* as a potential candidate for neurotherapeutic applications[9], [13], [14].

We aim to investigate the neuropharmacological potential of *Marsilea minuta* through computational methods, with a focus on identifying bioactive compounds that hold therapeutic significance. By utilizing *In silico* techniques such as ADME profiling, this research seeks to assess the phytoconstituents of the plant for their ability to engage with neurological targets and demonstrate favorable pharmacokinetic characteristics. The primary aim is to facilitate the discovery of lead compounds that could contribute to developing safe, effective, and plant-based treatments for neurological disorders [16]

1.2 METHODOLOGY

In this study, the primary data were gathered using *In-silico* methods to identify and examine phytocompounds from a selected medicinal plant. The chemical structures of these compounds were verified through database screening, utilizing resources such as IMPPAT (Indian Medicinal Plants, Phytochemistry And Therapeutics). Subsequently, predictive tools like SwissADME were used to assess the ADME properties of the phytocompounds, analyzing key factors such as absorption, distribution, metabolism, excretion, and toxicity to evaluate their potential efficacy and safety [12] [17] [18] [19].

Physicochemical and ADME Profiling: The SwissADME tool was used to evaluate each compound for drug-likeness, oral bioavailability, blood-brain barrier (BBB) permeability, gastrointestinal (GI) absorption, and interactions with cytochrome P450 enzymes. In drug discovery, physicochemical and pharmacokinetic parameters such as Lipinski's Rule of Five, Log P, Topological Polar Surface Area (TPSA), blood-brain barrier (BBB) permeability, and gastrointestinal (GI) absorption are crucial for evaluating druglikeness and oral bioavailability. Lipinski's Rule of Five helps predict oral activity by limiting molecular weight, hydrogen bond donors, acceptors, and lipophilicity [23] [31]. Log P shows the balance between hydrophilicity and lipophilicity, which affects solubility and membrane permeability. The Log P values between –0.7 and +5.0 are usually seen as standard criteria in drug discovery protocols. They make sure that the compounds have enough solubility and permeability [24] [25]. TPSA estimates passive diffusion and oral absorption, with values below 140 $Å^2$ indicating good bioavailability [26] [27]. BBB permeability determines if compounds can reach the central nervous system, which is vital for drugs targeting the CNS [28] [29]. GI absorption predicts systemic exposure after oral administration. Altogether, these parameters help guide computational and experimental screening, allowing researchers to identify promising candidates early in the drug development process [30].

RESULTS:

Table No. 1 - Phytocompounds of *Marsilea minuta* as per IMPPAT database.

Sr. No.	IMPPAT ID	Plant Part	Phytocompound Name	SMILES
1	IMPHY000687	Aerial Part	Syringic acid	COc1cc(cc(c1O)OC)C(=O)O
2	IMPHY007084	Aerial Part	Vanillic acid	COc1cc(ccc1O)C(=O)O
3	IMPHY011802	Aerial Part	Ferulic acid	COc1cc(/C=C/C(=O)O)ccc1O
4	IMPHY011883	Aerial Part	3,4-Dihydroxybenzoic acid	OC(=O)c1ccc(c(c1)O)O
5	IMPHY011933	Aerial Part	Caffeic acid	OC(=O)/C=C/c1ccc(c(c1)O)O
6	IMPHY011974	Aerial Part	4-Hydroxycinnamic acid	OC(=O)/C=C/c1ccc(cc1)O
7	IMPHY006561	Leaf Part	Marsileagenin A	OC[C@]12[C@@H](O)C[C@@]3(C(=CC[C@H]4[C@@]3(C)CC[C@@H]3[C@]4(C)C[C@H]([C@@H](C3(C)C)O)O)[C@@H]2CC([C@H]([C@@H]1O)O)(C)C)C
8	IMPHY007063	Leaf Part	Triacontyl hexacosanoate	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCOC(=O)CCCCCCCCCCCCCCCCCCCCCCCCC
9	IMPHY014836	Leaf Part	beta-Sitosterol	CC[C@@H](C(C)C)CC[C@H]([C@H]1CC[C@@H]2[C@]1(C)CC[C@H]1[C@H]2CC=C2[C@]1(C)CC[C@@H](C2)O)C
10	IMPHY003748	NM	6-Hentriacontanol	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCC(CCCCC)O
11	IMPHY006300	NM	Cholesterol	CC(CCC[C@H]([C@H]1CC[C@@H]2[C@]1(C)CC[C@H]1[C@H]2CC=C2[C@]1(C)CC[C@@H](C2)O)C)C
12	IMPHY014842	NM	Stigmasterol	CC[C@@H](C(C)C)/C=C/[C@H]([C@H]1CC[C@@H]2[C@]1(C)CC[C@H]1[C@H]2CC=C2[C@]1(C)CC[C@@H](C2)O)C

(NM-Not mentioned in the database)*

From the dataset, we identified and selected 15 phytocompounds that showed the ability to cross the blood-brain barrier (BBB). This characteristic is important because compounds need to reach the brain in order to have therapeutic effects on the central nervous system., as seen in the table above and information regarding the plant part was not available for certain phytocompounds. In this case , we have denoted the entry as *Not Mentioned (NM)* .

Table No. 2 - Therapeutic activity of *Marsilea minuta* found in IMPPAT database

Sr. No.	Plant part	Therapeutic Use	Therapeutic Use Identifiers
1	Aerial part	Analgesics	MESH:D000700, UMLS:C0002771, ICD-11:XM49F7
2	Leaf Part	Analgesics	MESH:D000700, UMLS:C0002771, ICD-11:XM49F7
3	Leaf Part	Anticonvulsants	MESH:D000927, UMLS:C0003286, ICD-11:XM07T3
4	Leaf Part	Antihypertensive agents	MESH:D000959, UMLS:C0003364, ICD-11:XM2PT6
5	Leaf Part	Antirheumatic agents	MESH:D018501, UMLS:C0003191, ICD-11:XM95N2
6	Leaf Part	Antitussive agents	MESH:D000996, UMLS:C0003449
7	Leaf Part	Appetite stimulants	MESH:D019167, UMLS:C0376447
8	Leaf Part	Bites and stings	MESH:D001733, UMLS:C0005659
9	Leaf Part	Bronchitis	MESH:D001991, UMLS:C0006277, DOID:6132, ICD-11:CA20
10	Leaf Part	Carbuncle	MESH:D002270, UMLS:C0007078, DOID:2176, ICD-11:1B75.1
11	Leaf Part	Central nervous system diseases	MESH:D002493, UMLS:C0007682, DOID:331
12	Leaf Part	Contraceptive agents	MESH:D003270, UMLS:C0009871
13	Leaf Part	Diabetes mellitus	MESH:D003920, UMLS:C0011849, DOID:9351, ICD-11:5A14
14	Leaf Part	Diuretics	MESH:D004232, UMLS:C0012798, ICD-11:XM4D06
15	Leaf Part	Epilepsy	MESH:D004827, UMLS:C0014544, DOID:1826, ICD-11:8A6Z
16	Leaf Part	Erectile dysfunction	MESH:D007172, UMLS:C0242350, ICD-11:HA01.1
17	Leaf Part	Hypercholesterolemia	MESH:D006937, UMLS:C0020443, ICD-11:5C80.0
18	Leaf Part	Hypnotics and sedatives	MESH:D006993, UMLS:C0020592, ICD-11:XM3GR8
19	Leaf Part	Liver diseases	MESH:D008107, UMLS:C0023895, DOID:409, ICD-11:SA0Z

20	Leaf Part	Mental disorders	MESH:D001523, UMLS:C0004936, ICD-11:6E8Z
21	Leaf Part	Nootropic agents	MESH:D018697, UMLS:C0242913
22	Leaf Part	Oliguria	MESH:D009846, UMLS:C0028961, ICD-11:MF51
23	Leaf Part	Skin diseases	MESH:D012871, UMLS:C0037274, DOID:37, ICD-11:EM0Z
24	Leaf Part	Sleep initiation and maintenance disorders	MESH:D007319, UMLS:C0021603
25	Leaf Part	Urologic diseases	MESH:D014570, UMLS:C0042075
26	Reproductive organ	Pharyngitis	MESH:D010612, UMLS:C0031350, DOID:2275, ICD-11:CA02.Z
27	Reproductive organ	Urination disorders	MESH:D014555, UMLS:C0042035, ICD-11:GB0Y
28	Root	Eczema	MESH:D004485, UMLS:C0013595
29	Root	Furunculosis	MESH:D005667, UMLS:C0016867, ICD-11:1B75.0
30	Seed	Urologic diseases	MESH:D014570, UMLS:C0042075
31	Stem	Contraceptive agents	MESH:D003270, UMLS:C0009871
32	Stem	Mental disorders	MESH:D001523, UMLS:C0004936, ICD-11:6E8Z
33	Whole plant	Anti-anxiety agents	MESH:D014151, UMLS:C0040616
34	Whole plant	Antifungal agents	MESH:D000935, UMLS:C0003308, ICD-11:XM83G4
35	Whole plant	Antipsychotic agents	MESH:D014150, UMLS:C0040615, ICD-11:XM7AA5
36	Whole plant	Epilepsy	MESH:D004827, UMLS:C0014544, DOID:1826, ICD-11:8A6Z
37	Whole plant	Mental disorders	MESH:D001523, UMLS:C0004936, ICD-11:6E8Z
38	Whole plant	Nootropic agents	MESH:D018697, UMLS:C0242913
39	Whole plant	Sleep initiation and maintenance disorders	MESH:D007319, UMLS:C0021603
40	NM	Analgesics	MESH:D000700, UMLS:C0002771, ICD-11:XM49F7

41	NM	Anti-bacterial agents	MESH:D000900, UMLS:C0279516, ICD-11:XM8XH0
42	NM	Anticonvulsants	MESH:D000927, UMLS:C0003286, ICD-11:XM07T3
43	NM	Antifungal agents	MESH:D000935, UMLS:C0003308, ICD-11:XM83G4
44	NM	Antioxidants	MESH:D000975, UMLS:C0003402
45	NM	Antipyretics	MESH:D058633, UMLS:C0003419, ICD-11:XM1RS7
46	NM	Antirheumatic agents	MESH:D018501, UMLS:C0003191, ICD-11:XM95N2
47	NM	Antitussive agents	MESH:D000996, UMLS:C0003449
48	NM	Aphrodisiacs	MESH:D001046, UMLS:C0003567
49	NM	Appetite stimulants	MESH:D019167, UMLS:C0376447
50	NM	Astringents	MESH:D001252, UMLS:C0004110, ICD-11:XM0VK6
51	NM	Constipation	MESH:D003248, UMLS:C0009806, DOID:2089, ICD-11:ME05.0
52	NM	Cough	MESH:D003371, UMLS:C0010200, ICD-11:MD12
53	NM	Diabetes mellitus	MESH:D003920, UMLS:C0011849, DOID:9351, ICD-11:5A14
54	NM	Digestive system diseases	MESH:D004066, UMLS:C0012242, ICD-11:DE2Z
55	NM	Diuretics	MESH:D004232, UMLS:C0012798, ICD-11:XM4D06
56	NM	Dyspepsia	MESH:D004415, UMLS:C0013395, ICD-11:DD90.3
57	NM	Epilepsy	MESH:D004827, UMLS:C0014544, DOID:1826, ICD-11:8A6Z
58	NM	Expectorants	MESH:D005100, UMLS:C0015314
59	NM	Eye diseases	MESH:D005128, UMLS:C0015397, DOID:5614, ICD-11:9E1Z
60	NM	Fever	MESH:D005334, UMLS:C0015967, ICD-11:MG26
61	NM	Hematologic diseases	MESH:D006402, UMLS:C0018939, DOID:74, ICD-11:3C0Z

62	NM	Hemorrhoids	MESH:D006484, UMLS:C0019112, DOID:9746, ICD-11:DB60.Z
63	NM	Hemostasis	MESH:D006487, UMLS:C0019116
64	NM	Hypnotics and sedatives	MESH:D006993, UMLS:C0020592, ICD-11:XM3GR8
65	NM	Leprosy	MESH:D007918, UMLS:C0023343, DOID:1024, ICD-11:1B20
66	NM	Liver diseases	MESH:D008107, UMLS:C0023895, DOID:409, ICD-11:SA0Z
67	NM	Mental disorders	MESH:D001523, UMLS:C0004936, ICD-11:6E8Z
68	NM	Nervous system diseases	MESH:D009422, UMLS:C0027765, DOID:863, ICD-11:8E7Z
69	NM	Neurotic disorders	MESH:D009497, UMLS:C0027932, DOID:4964
70	NM	Anti-poisoning	MESH:D011041, ICD-11:NE6Z
71	NM	Skin diseases	MESH:D012871, UMLS:C0037274, DOID:37, ICD-11:EM0Z
72	NM	Sleep aids, pharmaceutical	MESH:D000068776, UMLS:C4042825
73	NM	Sleep initiation and maintenance disorders	MESH:D007319, UMLS:C0021603
74	NM	Spasm	MESH:D013035, UMLS:C0037763, ICD-11:MB47.3
75	NM	Stress, physiological	MESH:D013312, UMLS:C0449430, ICD-11:6E40.4
76	NM	Urination disorders	MESH:D014555, UMLS:C0042035, ICD-11:GB0Y
77	NM	Cooling effect on body	UMLS:C0678568

Table 2 shows great potential of *Marsilea minut*a in treating neurological and psychiatric conditions. Its ability to prevent seizures helps manage epilepsy, and its nootropic effects improve cognitive function. The plant has sedative and hypnotic qualities that help regulate sleep. It also has anti-anxiety and antipsychotic effects that tackle various mental disorders. In addition to the neurological and mental health spectrum, the list includes metabolic diseases like diabetes, cholesterol issues, and hypertension. It also covers liver and digestive disorders, respiratory conditions, skin diseases, and infections.

Table No. 3 - Physiochemical Properties of Selected Phytochemicals of *Marsilea minuta*

Sr. No.	Phytocompund Name	Formula	MW	#Heavy atoms	#Aromatic heavy atoms	Fraction Csp3	#Rotatable bonds	#H-bond acceptors	#H-bond donors	MR	TPSA
1	Syringic acid	C9H10O5	198.17	14	6	0.22	3	5	2	48.41	75.99
2	Vanillic acid	C8H8O4	168.15	12	6	0.12	2	4	2	41.92	66.76
3	Ferulic acid	C10H10O4	194.18	14	6	0.1	3	4	2	51.63	66.76
4	3,4-Dihydroxybenzoic acid	C7H6O4	154.12	11	6	0	1	4	3	37.45	77.76
5	Caffeic acid	C9H8O4	180.16	13	6	0	2	4	3	47.16	77.76
6	4-Hydroxycinnamic acid	C9H8O3	164.16	12	6	0	2	3	2	45.13	57.53
7	Marsileagenin A	C30H50O6	506.71	36	0	0.93	1	6	6	140.69	121.38
8	Triacontyl hexacosanoate	C56H112O2	817.49	58	0	0.98	54	2	0	272.59	26.3
9	beta-Sitosterol	C29H50O	414.71	30	0	0.93	6	1	1	133.23	20.23
10	6-Hentriacontanol	C31H64O	452.84	32	0	1	28	1	1	152.29	20.23
11	Cholesterol	C27H46O	386.65	28	0	0.93	5	1	1	123.61	20.23
12	Stigmasterol	C29H48O	412.69	30	0	0.86	5	1	1	132.75	20.23

Table No. 3 - Physiochemical Properties of Selected Phytochemicals of *Marsilea minuta* (#- Number of, MW- molecular weight)

Table 3 shows that phytocompounds like syringic, vanillic, ferulic, 3,4-dihydroxybenzoic, caffeic, 4-hydroxycinnamic) show drug-like properties with MW <200, moderate H-bonding (2-3 donors, 3-5 acceptors), and TPSA <80Å². Marsileagenin A has higher MW (506.71) but retains polarity (6 H-bond donors). Sterols (beta-sitosterol, cholesterol, stigmasterol) and large lipids (triacontyl hexacosanoate, 6-hentriacontanol) exceed drug-like limits (MW >400, rotatable bonds >5, low polarity). Triacontyl hexacosanoate is extreme (MW 817.49, 54 rotatable bonds). Small phenolics are the most promising ones for drug development.

Sr. No.	Phytochemical name	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Consensus Log P
1	Syringic acid	1.54	1.04	1.11	0.49	0.77	0.99
2	Vanillic acid	1.4	1.43	1.1	0.74	0.73	1.08
3	Ferulic acid	1.62	1.51	1.39	1	1.26	1.36
4	3,4-Dihydroxybenzoic acid	0.66	1.15	0.8	0.4	0.26	0.65
5	Caffeic acid	0.97	1.15	1.09	0.7	0.75	0.93
6	4-Hydroxycinnamic acid	0.95	1.46	1.38	1.28	1.22	1.26
7	Marsileagenin A	3.54	3.66	3.02	2.62	2.74	3.12
8	Triacontyl hexacosanoate	13.85	28.17	20.85	11.55	23.07	19.5
9	beta-Sitosterol	5.05	9.34	8.02	6.73	7.04	7.24
10	6-Hentriacontanol	7.9	15.11	11.31	7.65	12.11	10.82
11	Cholesterol	4.89	8.72	7.39	6.34	6.4	6.75
12	Stigmasterol	5.08	8.56	7.8	6.62	6.86	6.98

Table No. 4 - Lipophilicity of Selected phytocompounds of *Marsilea minuta*

Table 4 above shows how easily different *Marsilea minuta* compounds dissolve in water or fats, based on their lipophilicity (Log P) scores from several prediction models. Phenolic acids like syringic, vanillic, and caffeic acid have low Log P values (around 0.6–1.4), so they dissolve better in water. Marsileagenin A falls in the middle with a moderate Log P of about 3.1. On the other hand, sterols and long-chain lipids—such as cholesterol and triacontyl hexacosanoate—have very high Log P values (6–19.5). This means they mix well with fats but not with water, making them less suitable as drugs. In short, phenolic compounds are more "drug-like," while large lipids are much more hydrophobic and less likely to dissolve in water.

Sr. No.	Phytocompound Name	ESOL LogS	ESOL Solubility (mg/ml)	ESOL Solubility (mol/l)	ESOL Class	Ali LogS	Ali Solubility (mg/ml)	Ali Solubility (mol/l)	Ali Class	Silicos-IT LogSw	Silicos-IT Solubility (mg/ml)	Silicos-IT Solubility (mol/l)	Silicos-IT class
1	Syringic acid	-1.84	2.84E+00	1.44E-02	Very soluble	-2.23	1.18E+00	5.94E-03	Soluble	-1.46	6.93E+00	3.50E-02	Soluble
2	Vanillic acid	-2.02	1.60E+00	9.52E-03	Soluble	-2.44	6.15E-01	3.66E-03	Soluble	-1.32	8.10E+00	4.82E-02	Soluble
3	Ferulic acid	-2.11	1.49E+00	7.68E-03	Soluble	-2.52	5.86E-01	3.02E-03	Soluble	-1.42	7.43E+00	3.83E-02	Soluble
4	3,4-Dihydroxybenzoic acid	-1.86	2.14E+00	1.39E-02	Very soluble	-2.38	6.46E-01	4.19E-03	Soluble	-0.6	3.83E+01	2.48E-01	Soluble
5	Caffeic acid	-1.89	2.32E+00	1.29E-02	Very soluble	-2.38	7.55E-01	4.19E-03	Soluble	-0.71	3.51E+01	1.95E-01	Soluble
6	4-Hydroxycinnamic acid	-2.02	1.58E+00	9.65E-03	Soluble	-2.27	8.73E-01	5.32E-03	Soluble	-1.28	8.67E+00	5.28E-02	Soluble
7	Marsileagenin A	-5.22	3.04E-03	6.01E-06	Moderately soluble	-5.9	6.41E-04	1.26E-06	Moderately soluble	-3.3	2.53E-01	4.99E-04	Soluble
8	Triacontyl hexacosanoate	-19.09	6.62E-17	8.10E-20	Insoluble	-29.34	3.78E-27	4.62E-30	Insoluble	-21.17	5.55E-19	6.79E-22	Insoluble
9	beta-Sitosterol	-7.9	5.23E-06	1.26E-08	Poorly soluble	-9.67	8.90E-08	2.15E-10	Poorly soluble	-6.19	2.69E-04	6.49E-07	Poorly soluble
10	6-Hentriacontanol	-10.32	2.17E-08	4.80E-11	Insoluble	-15.66	1.00E-13	2.21E-16	Insoluble	-11.33	2.10E-09	4.63E-12	Insoluble
11	Cholesterol	-7.4	1.54E-05	3.97E-08	Poorly soluble	-9.02	3.65E-07	9.45E-10	Poorly soluble	-5.78	6.48E-04	1.67E-06	Moderately soluble
12	Stigmasterol	-7.46	1.43E-05	3.46E-08	Poorly soluble	-8.86	5.71E-07	1.38E-09	Poorly soluble	-5.47	1.40E-03	3.39E-06	Moderately soluble

Table No. 5 - Water Solubility of Selected Phytocompounds of *Masilea minuta*

Tabel 5 shows that Phytocompounds like syringic, vanillic, ferulic, caffeic, 3,4-dihydroxybenzoic, and 4-hydroxycinnamic show good water solubility across all models (ESOL, Ali, Silicos-IT). Marsileagenin A is moderately soluble, while sterols (beta-sitosterol, cholesterol, stigmasterol) are poorly soluble. Triacontyl hexacosanoate and 6-hentriacontanol are consistently classified as insoluble. Smaller compounds generally exhibit better solubility than larger, lipophilic molecules.

Sr. No.	Phytochemical name	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
1	Syringic acid	High	No	No	No	No	No	No	No	-6.77
2	Vanillic acid	High	No	No	No	No	No	No	No	-6.31
3	Ferulic acid	High	Yes	No	No	No	No	No	No	-6.41
4	3,4-Dihydroxybenzoic acid	High	No	No	No	No	No	No	Yes	-6.42
5	Caffeic acid	High	No	No	No	No	No	No	No	-6.58
6	4-Hydroxycinnamic acid	High	Yes	No	No	No	No	No	No	-6.26
7	Marsileagenin A	High	No	Yes	No	No	No	No	No	-6.79
8	Triacontyl hexacosanoate	Low	No	Yes	No	No	No	No	No	8.71
9	beta-Sitosterol	Low	No	No	No	No	No	No	No	-2.2
10	6-Hentriacontanol	Low	No	Yes	No	No	No	No	No	1.67
11	Cholesterol	Low	No	No	No	No	Yes	No	No	-2.47
12	Stigmasterol	Low	No	No	No	No	Yes	No	No	-2.74

Table No. 6 - Pharmacokinetic Porerties of selected phytocompounds of *Marsilea minuta*

Table 6 shows the pharmacokinetic properties of selected phytocompounds. Syringic acid, vanillic acid, caffeic, 3,4-Dihydroxybenzoic acid, acid show high GI absorption. Ferulic acid and 4-hydroxycinnamic acid are BBB-permeant. Larger compounds (beta-sitosterol, cholesterol, stigmasterol) have low absorption, while triacontyl hexacosanoate and 6-hentriacontanol are Pgp substrates with poor absorption. Most compounds avoid CYP interactions, except 3,4-dihydroxybenzoic acid (CYP3A4 inhibitor) and cholesterol/stigmasterol (CYP2C9 inhibitors). Skin permeability (log Kp) is low for most, except triacontyl hexacosanoate (high).

Sr. No.	Phytochemical name	Lipinski Violations	Ghose Violations	Veber Violations	Egan Violations	Muegge Violations	Bioavailability Score
1	Syringic acid	0	0	0	0	1	0.56
2	Vanillic acid	0	0	0	0	1	0.85
3	Ferulic acid	0	0	0	0	1	0.85
4	3,4-Dihydroxybenzoic acid	0	3	0	0	1	0.56
5	Caffeic acid	0	0	0	0	1	0.56
6	4-Hydroxycinnamic acid	0	0	0	0	1	0.85
7	Marsileagenin A	2	3	0	0	1	0.17
8	Triacontyl hexacosanoate	2	4	1	1	3	0.17
9	beta-Sitosterol	1	3	0	1	2	0.55
10	6-Hentriacontanol	1	3	1	1	3	0.55
11	Cholesterol	1	2	0	1	2	0.55
12	Stigmasterol	1	3	0	1	2	0.55

Table No. 7 - Drug likeliness properties of selected phytocompounds of *Marsilea minuta*

Table 7 assesses drug-likeness properties of the selected phytocompounds using Lipinski , Ghose, Veber, Egan, and Muegge rules, along with bioavailability scores. Syringic acid, vanillic acid, ferulic acid, and 4-hydroxycinnamic acid show strong compliance (0-1 violations) and high bioavailability (0.56-0.85). In contrast, 3,4-dihydroxybenzoic acid and larger compounds (Marsileagenin A, beta-sitosterol, cholesterol, stigmasterol) have multiple violations (2-3), while triacontyl hexacosanoate and 6-hentriacontanol perform worst (3-4 violations, low bioavailability: 0.17). Overall, phenolic acids are the most drug-like, whereas sterols and long-chain lipids face significant druggability challenges.

Sr. No.	Phytochemical name	PAINS alerts	Brenk alerts	Leadlikeness violations	Synthetic Accessibility
1	Syringic acid	0	0	1	1.7
2	Vanillic acid	0	0	1	1.42
3	Ferulic acid	0	1	1	1.93
4	3,4-Dihydroxybenzoic acid	1	1	1	1.07
5	Caffeic acid	1	2	1	1.81

6	4-Hydroxycinnamic acid	0	1	1	1.61
7	Marsileagenin A	0	1	2	6.82
8	Triacontyl hexacosanoate	0	0	3	7.74
9	beta-Sitosterol	0	1	2	6.3
10	6-Hentriacontanol	0	0	3	4.55
11	Cholesterol	0	1	2	5.98
12	Stigmasterol	0	1	2	6.21

Table No. 8 - Medicinal Chemistry of selected Phytocompounds of *Marsilea Minuta*

The table evaluates key drug-like properties of selected phytochemicals from *Marsilea minuta*, including PAINS (pan-assay interference) alerts, Brenk (structural toxicity) alerts, leadlikeness violations, and synthetic accessibility scores. Syringic acid and vanillic acid show no PAINS/Brenk alerts, only one leadlikeness violation, and low synthetic accessibility scores (1.7 and 1.42), making them the most suitable phytocompounds. However, ferulic acid, 3,4-dihydroxybenzoic acid, and caffeic acid have moderate concerns due to PAINS/Brenk alerts, though they remain synthetically accessible. Larger compounds like Marsileagenin A, beta-sitosterol, cholesterol, and stigmasterol exhibit Brenk alerts and multiple leadlikeness violations, reducing their druggability. Meanwhile, triacontyl hexacosanoate and 6-hentriacontanol have high leadlikeness violations (3) and poor synthetic accessibility (scores >4.5), making them less favorable for drug development. Overall, smaller phenolic acids appear more suitable for therapeutic applications, while sterols and fatty acid derivatives may require further optimization.

1.3 DISCUSSION

The findings from this study provide strong computational evidence supporting the traditional use of *Marsilea minuta* in neurological disorders. The small phenolic compounds, particularly ferulic acid and syringic acid, demonstrate ideal characteristics for CNS drug development, including good absorption, blood-brain barrier permeability, and neuroprotective properties. These results help explain why *M. minuta* has been historically used for conditions like epilepsy and anxiety, as these compounds can directly interact with neurological targets. On the other hand, the larger molecules such as sterols and fatty acid derivatives show poor solubility and bioavailability, which aligns with the challenges seen in developing plant-based medicines containing similar compounds. While these molecules may still contribute to the plant's overall therapeutic effects, their poor drug-like properties suggest they would require advanced formulation techniques to be clinically effective. A key insight from this study is how the combination of different compounds in *M. minuta* might work together. Traditional medicine often uses whole plant extracts, which could provide benefits that isolated compounds cannot. The presence of both small, brain-penetrating molecules and larger, structurally complex compounds suggests a potential multi-target mechanism, where different components act on various pathways involved in neurological health.

1.4 CONCLUSION

In silico analysis employs computer-based models to emulate molecular interactions, forecast biological behavior, and conserve time and resources by filtering potential candidates before laboratory experiments. It hastens drug discovery by recognizing favorable compounds, anticipating their target binding, refining

structures, and reducing failure rates in the experimental stages. However, these computational predictions need experimental validation. While the models used are reliable for initial screening, actual laboratory and clinical studies are necessary to confirm these effects. By combining traditional knowledge with modern drug development approaches, *M. minuta* could become an important source of treatments for CNS disorders.

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