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IN SILICO ANALYSIS OF BIOACTIVITY POTENTIAL AND PHARMACOKINETIC CHARACTERISTICS OF GRASS JELLY (*Cyclea barbata*) SECONDARY METABOLITES USING PASS ONLINE AND SWISSADME

ANALISIS IN SILICO POTENSI BIOAKTIVITAS DAN KARAKTERISTIK FARMAKOKINETIK METABOLIT SEKUNDER CINCAU HIJAU (*Cyclea barbata*) MENGGUNAKAN PASS ONLINE DAN SWISSADME

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Abstract

Green grass jelly (*Cyclea barbata* Miers) is a medicinal plant that contains various secondary metabolites with potential as sources of phytopharmaceutical candidates. This study aimed to analyze the bioactivity potential, drug-likeness characteristics, pharmacokinetic profile, medicinal chemistry properties, and toxicity of secondary metabolites present in Cyclea barbata using an in silico approach. The identified compounds were analyzed using PASS Online for biological activity prediction, SwissADME for drug-likeness and pharmacokinetic evaluation, and pkCSM for ADME/T (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction. The results showed that tyramine and dopamine exhibited the highest biological activity as serotonin-release stimulants and MAP kinase pathway activators. Coclaurine, norcoclaurine, and N-methylcoclaurine demonstrated favorable drug-likeness profiles by satisfying most of the Lipinski, Veber, and Egan criteria. Pharmacokinetic analysis indicated that most simple compounds possessed high gastrointestinal absorption, whereas complex alkaloids such as tetrandrine and fangchinoline exhibited broader tissue distribution potential and greater blood–brain barrier permeability. Medicinal chemistry evaluation revealed that all compounds were free from PAINS alerts, while toxicity prediction indicated relatively favorable safety profiles for most compounds. The findings suggest that Cyclea barbata has considerable potential as a source of bioactive compounds for the development of modern phytopharmaceuticals, particularly as neuroprotective and anti-inflammatory agents. However, further validation through in vitro and in vivo studies is required to confirm the efficacy and safety of the predicted compounds.

Keywords: *Cyclea barbata, green grass jelly, bioactivity, SwissADME, pkCSM, phytopharmaceutical.*

Abstrak

Cincau hijau (*Cyclea barbata* Miers) merupakan tanaman obat yang mengandung berbagai metabolit sekunder yang berpotensi menjadi kandidat fitofarmaka. Penelitian ini bertujuan untuk menganalisis potensi bioaktivitas, karakteristik kemiripan obat (drug-likeness), profil farmakokinetik, sifat kimia medisinal, serta toksisitas metabolit sekunder pada *Cyclea barbata* menggunakan pendekatan in silico. Senyawa yang teridentifikasi dianalisis menggunakan PASS Online untuk prediksi aktivitas biologis, SwissADME untuk evaluasi drug-likeness dan farmakokinetika, serta pkCSM untuk prediksi ADME/T

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(Absorpsi, Distribusi, Metabolisme, Ekskresi, dan Toksisitas). Hasil penelitian menunjukkan bahwa tiramin (tyramine) dan dopamin (dopamine) memiliki aktivitas biologis tertinggi sebagai stimulan pelepasan serotonin dan aktivator jalur MAP kinase. Coclaurine, norcoclaurine, dan N-metilcoclaurine menunjukkan profil drug-likeness yang baik karena memenuhi sebagian besar kriteria Lipinski, Veber, dan Egan. Analisis farmakokinetik menunjukkan bahwa sebagian besar senyawa sederhana memiliki absorpsi gastrointestinal yang tinggi, sedangkan alkaloid kompleks seperti tetrandrine dan fangchinoline menunjukkan potensi distribusi jaringan yang lebih luas serta permeabilitas sawar darah-otak (blood–brain barrier) yang lebih baik. Evaluasi kimia medisinal mengungkapkan bahwa seluruh senyawa bebas dari peringatan PAINS (Pan-Assay Interference Compounds), sementara prediksi toksisitas menunjukkan profil keamanan yang relatif baik pada sebagian besar senyawa. Temuan ini menunjukkan bahwa *Cyclea barbata* memiliki potensi besar sebagai sumber senyawa bioaktif untuk pengembangan fitofarmaka modern, khususnya sebagai agen neuroprotektif dan antiinflamasi. Namun, validasi lebih lanjut melalui studi in vitro dan in vivo masih diperlukan untuk mengonfirmasi efektivitas dan keamanan senyawa yang diprediksi.

Kata kunci: *Cyclea barbata*, cincau hijau, bioaktivitas, SwissADME, pkCSM, fitofarmaka.

INTRODUCTION

Indonesia is recognized as one of the countries with the highest levels of biodiversity in the world and possesses enormous potential as a source of natural medicinal raw materials. The use of traditional medicinal plants continues to expand in response to the growing demand for safer natural therapies. One plant long used in traditional medicine is green grass jelly (*Cyclea barbata* Miers), which is consumed not only as a functional food but is also believed to provide various health benefits due to its diverse secondary metabolite content.

Plant secondary metabolites, particularly alkaloids and phenolic compounds, are known to exhibit a wide range of important pharmacological activities. Plant alkaloids have been reported to interact with various receptors, enzymes, and signal transduction pathways involved in nervous system regulation and cellular protection (Wink, 2015). In addition, biogenic amines such as dopamine and tyramine play significant roles in regulating monoamine neurotransmitters involved in neurological function and emotional behavior (Jahangir *et al*., 2026). These properties make alkaloid-containing plants promising sources of drug candidates for neuroprotective and anti-inflammatory therapies.

Advances in computational technology have promoted the application of in silico approaches in the drug discovery process. These approaches enable the rapid, efficient, and cost-effective evaluation of biological activity, pharmacokinetic properties, drug-likeness, and toxicity profiles of compounds before laboratory testing. Platforms such as SwissADME and pkCSM are widely used to predict the absorption, distribution, metabolism, excretion, and toxicity (ADME/T) properties of compounds, thereby accelerating the identification of potential drug candidates (Purwaningsih *et al*., 2025). Furthermore, evaluating drug-likeness parameters using the Lipinski, Veber, Egan, Ghose, and Muegge rules provides preliminary insights into the likelihood that a compound will be developed as an orally administered drug (Rudrappa *et al*., 2025).

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Although *Cyclea barbata* has long been utilized as a traditional medicinal plant, information regarding the bioactivity potential, pharmacokinetic properties, and toxicity profiles of its secondary metabolites remains limited. Therefore, a comprehensive investigation is required to evaluate the biological and pharmacological characteristics of the compounds present in this plant. This study aimed to analyze the bioactivity potential, drug-likeness characteristics, ADME/T profile, and medicinal chemistry properties of secondary metabolites from *Cyclea barbata* using an in silico approach as an initial step toward developing modern phytopharmaceutical candidates derived from natural products.

RESEARCH METHODS

This study was a descriptive, exploratory investigation that employed an in silico approach to evaluate the pharmacological potential of secondary metabolites in *Cyclea barbata*. The research data consisted of secondary metabolites obtained from literature studies and phytochemical databases. The molecular structures of each compound were collected in Simplified Molecular Input Line Entry System (SMILES) format for use in various computational prediction platforms. Bioactivity analysis was performed using PASS Online to predict biological activities based on the Probability of Activity (Pa) values. The analyzed parameters included 5-hydroxytryptamine (5-HT) release-stimulant, membrane-integrity agonist, and Mitogen-Activated Protein Kinase (MAP kinase) stimulant activities.

The evaluation of drug-likeness characteristics and pharmacokinetic properties was conducted using SwissADME (Huang *et al*., 2024). The analyzed parameters included the Lipinski Rule of Five, Veber Rule, Egan Rule, Ghose Filter, Muegge Rule, bioavailability radar, water solubility, gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, interaction with P-glycoprotein (P-gp), and medicinal chemistry parameters, including PAINS, Brenk alerts, lead-likeness, and synthetic accessibility (Rai *et al*., 2023).

Further ADME/T profile analysis was carried out using pkCSM (Batheja *et al*., 2026). The absorption parameters evaluated included Caco-2 permeability, intestinal absorption, and skin permeability. Distribution parameters comprised volume of distribution at steady state (VDss), fraction unbound (Fu), blood–brain barrier permeability (log BB), and central nervous system permeability (log PS). Excretion parameters included total clearance and interaction with the renal transporter Organic Cation Transporter 2 (OCT2). Toxicity parameters included Maximum Tolerated Dose (MTD), Oral Rat Acute Toxicity (LD50), Oral Rat Chronic Toxicity (LOAEL), *Tetrahymena pyriformis* toxicity, and Minnow toxicity.

The prediction results were analyzed descriptively by comparing each parameter value against standards commonly used in modern drug development. Interpretation of the results was based on recent literature on the bioactivity, pharmacokinetics, and toxicity of natural product-derived compounds (Queiroz Pantaleão *et al*., 2021).

RESULTS AND DISCUSSION

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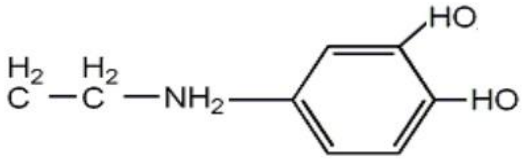
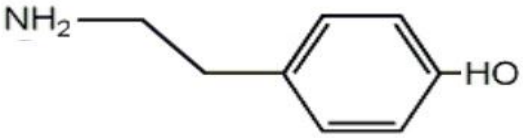
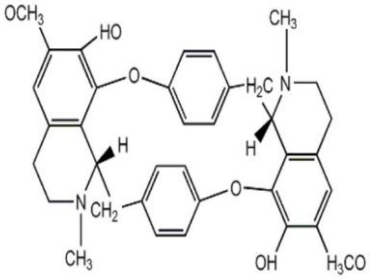
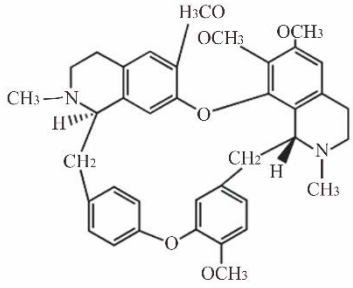
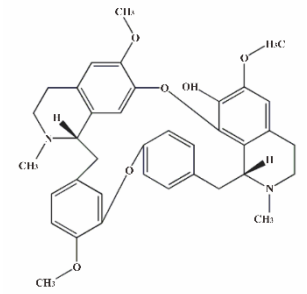
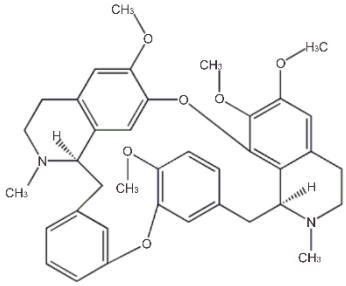
Table 1. Image of the structure of the *Cyclea barbata* (Grass Jelly) Plant

No	Compound Name	Chemical Structure Image
1	Dopamine	
2	Tyramine	
3	Isochondodendrine	
4	(+)-Tetrandrine	
5	(+)-Homoaromoline	
6	(+)-Isotetrandrine	

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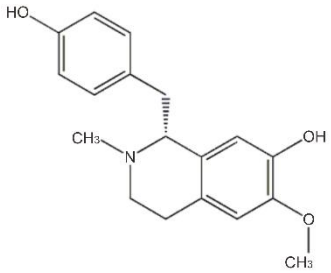
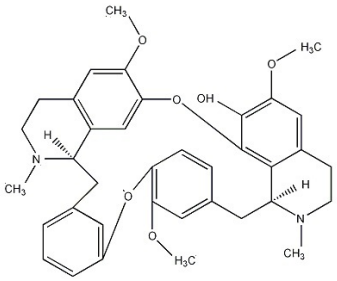
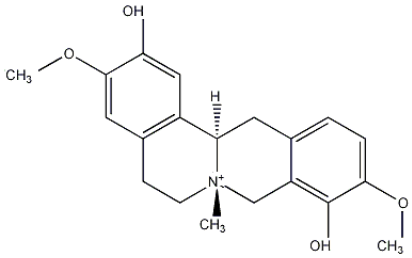
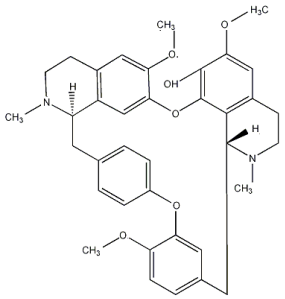
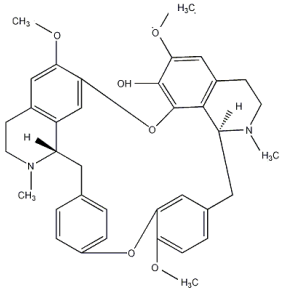
No	Compound Name	Chemical Structure Image
7	(+)-N-Methylcoclaurine	
8	(+)-Thalrugosine	
9	beta-Cyclanoline	
10	Fangchinoline	
11	Limacine	

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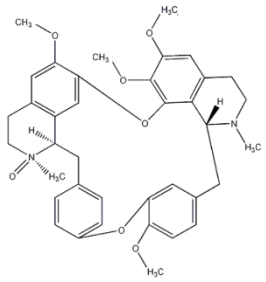
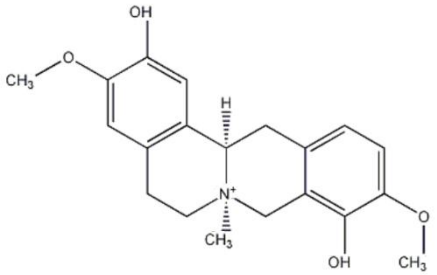
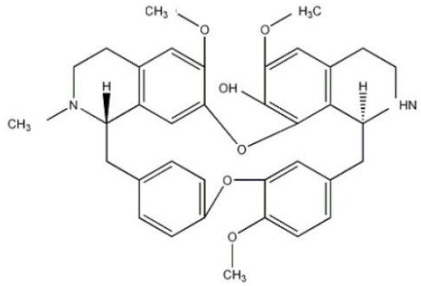
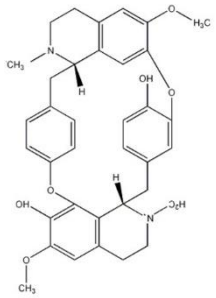
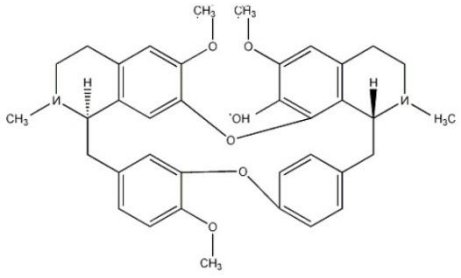
No	Compound Name	Chemical Structure Image
12	Tetrandrine mono-N-2'-oxide	
13	Cyclanoline	
14	(-)-2-Norlimacine	
15	(-)-Curine	
16	(-)-Cycleapeltine	

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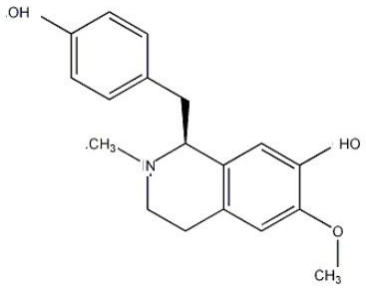
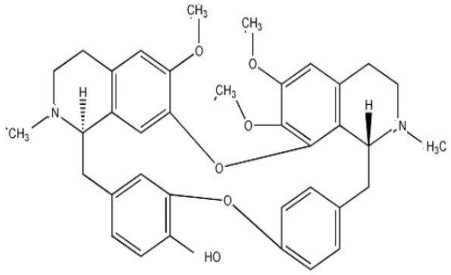
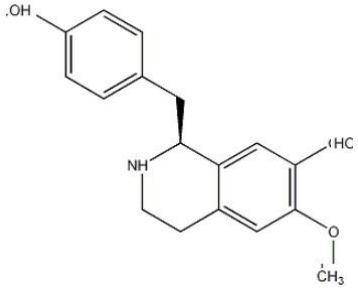
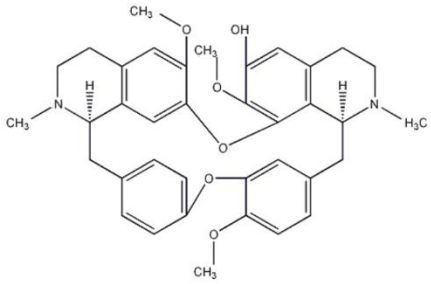
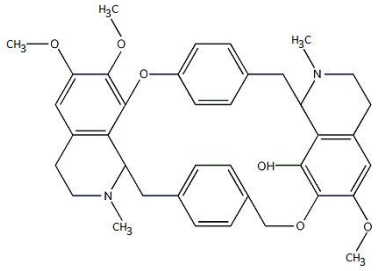
No	Compound Name	Chemical Structure Image
17	(-)-N-Methylcoclaurine	
18	(-)-Repandine	
19	(+)-Coclaurine	
20	(+)-Cycleabarbatine	
21	(+)-Cycleanorine	

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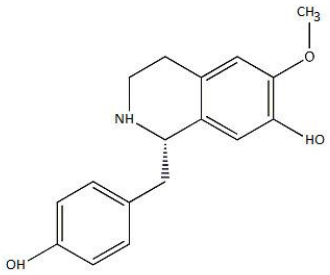
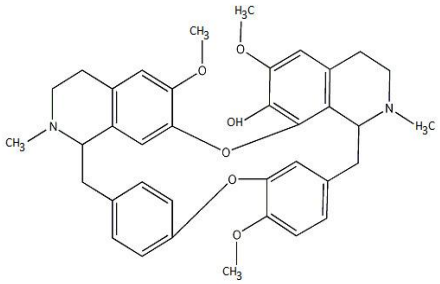
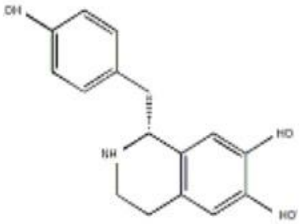
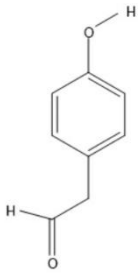
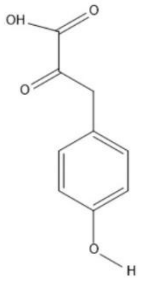
No	Compound Name	Chemical Structure Image
22	Coclaurine	
23	Cycleadrine	
24	(S)-Norcoclaurine	
25	4-Hydroxyphenylacetaldehyde	
26	4-Hydroxyphenylpyruvate	

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Table 2. SMILES (Simplified Molecular Input Line Entry System) *Cyclea barbata* (Grass Jelly) Plant

No	Compound Name	Smiles
1	Dopamine	NCCc1ccc(O)c(O)c1
2	Tyramine	NCCc1ccc(O)cc1
3	Isochondodendrine	COc1cc2c3c(c1O)Oc1ccc(cc1)C[C@@H]1c4c(cc(OC)c(O)c4Oc4ccc(cc4)C[C@H]3N(C)CC2)CCN1C
4	(+)-Tetrandrine	COc1ccc2cc1Oc1ccc(cc1)C[C@H]1c3cc(c(OC)cc3CCN1C)Oc1c(OC)c(OC)cc3c1[C@H](C2)N(C)CC3
5	(+)-Homoaromoline	COc1ccc2cc1Oc1ccc(cc1)C[C@H]1c3c(cc(OC)c(O)c3Oc3cc4c(cc3OC)CCN(C)[C@@H]4C2)CCN1C
6	(+)-Isotetrandrine	COc1ccc2cc1Oc1cccc(c1)C[C@H]1c3cc(c(OC)cc3CCN1C)Oc1c(OC)c(OC)cc3c1[C@@H](C2)N(C)CC3
7	(+)-N-Methylcoclaurine	COc1cc2c(cc1O)[C@@H](Cc1ccc(O)cc1)N(C)CC2
8	(+)-Thalrugosine	COc1cc2ccc1Oc1cccc(c1)C[C@H]1c3cc(c(OC)cc3CCN1C)Oc1c(O)c(OC)cc3c1[C@@H](C2)N(C)CC3
9	beta-Cyclanoline	COc1cc2c(cc1O)[C@@H]1Cc3ccc(OC)c(O)c3C[N@@+]1(C)CC2
10	Fangchinoline	COc1ccc2cc1Oc1ccc(cc1)C[C@H]1c3cc(c(OC)cc3CCN1C)Oc1c(O)c(OC)cc3c1[C@H](C2)N(C)CC3
11	Limacine	COc1ccc2cc1Oc1ccc(cc1)C[C@@H]1c3cc(c(OC)cc3CCN1C)Oc1c(O)c(OC)cc3c1[C@@H](C2)N(C)CC3
12	Tetrandrine mono-N-2'-oxide	COc1ccc2cc1Oc1ccc(cc1)C[C@H]1c3cc(c(OC)cc3CC[N+]1(C)[O-])Oc1c(OC)c(OC)cc3c1[C@H](C2)N(C)CC3
13	Cyclanoline	COc1cc2c(cc1O)[C@@H]1Cc3ccc(OC)c(O)c3C[N@+]1(C)CC2
14	(-)-2-Norlimacine	COc1ccc2cc1Oc1ccc(cc1)C[C@@H]1c3cc(c(OC)cc3CCN1C)Oc1c(O)c(OC)cc3c1[C@@H](C2)NCC3
15	(-)-Curine	COc1cc2c3cc1Oc1cc(ccc1O)C[C@@H]1c4c(cc(OC)c(O)c4Oc4ccc(cc4)C[C@H]3N(C)CC2)CCN1C
16	(-)-Cycleapeltine	COc1ccc2cc1Oc1ccc(cc1)C[C@H]1c3c(cc(OC)c(O)c3Oc3cc4c(cc3OC)CCN(C)[C@H]4C2)CCN1C
17	(-)-N-Methylcoclaurine	COc1cc2c(cc1O)[C@@H](Cc1ccc(O)cc1)N(C)CC2
18	(-)-Repandine	COc1cc2c3cc1Oc1c(OC)c(OC)cc4c1[C@H](Cc1ccc(cc1)Oc1cc(ccc1O)C[C@@H]3N(C)CC2)N(C)CC4
19	(+)-Coclaurine	COc1cc2c(cc1O)[C@@H](Cc1ccc(O)cc1)NCC2
20	(+)-Cycleabarbatine	COc1ccc2cc1Oc1ccc(cc1)C[C@H]1c3cc(c(OC)cc3CCN1C)Oc1c(OC)c(O)cc3c1[C@@H](C2)N(C)CC3
21	(+)-Cycleanorine	COc1cc2c3c(O)c1OCc1ccc(cc1)CC1c4c(cc(OC)c(OC)c4Oc4ccc(cc4)CC3N(C)CC2)CCN1C
22	Coclaurine	COc1cc2c(cc1O)[C@H](Cc1ccc(O)cc1)NCC2
23	Cycleadrine	COc1ccc2cc1Oc1ccc(cc1)CC1c3cc(c(OC)cc3CCN1C)Oc1c(O)c(OC)cc3c1C(C2)N(C)CC3
24	(S)-Norcoclaurine	Oc1ccc(C[C@@H]2NCCc3cc(O)c(O)cc32)cc1
25	4-Hydroxyphenylacetaldehyde	O=CCc1ccc(O)cc1
26	4-Hydroxyphenylpyruvate	O=C(O)C(=O)Cc1ccc(O)cc1

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Table 3. Hydroxytryptamine Release Stimulant, Membrane Integrity Agonist, MAP Kinase Stimulant, *Cyclea barbata* (Grass Jelly) Plant.

No	Compound Name	5 Hydroxytryptamine release stimulant (%PA)	Membrane Integrity Agonist (%PA)	MAP Kinase Stimulant (%PA)
1	Dopamine	0,922	0,919	0,908
2	Tyramine	0,946	0,917	0,898
3	Isochondodendrine	0,908	0,322	0,802
4	(+)-Tetrandrine Tetrandrine	0,862	-	0,719
5	(+)-Homoaromoline Homoaromoline Homothalicrine (+)-Thalrugosamine	0,86	-	0,812
6	(+)-Isotetrandrine Isotetrandrine Isosinomenin A Isosinomenine A O, O'-Dimethylobamine O, O'-Dimethylstepholine O, O-Dimethylobamine O, O-Dimethylstepholine O-Methylberbamine	0,87	-	0,707
7	(+)-N-Methylcoclaurine (+)-(S)-N-Methylcoclaurine N-Methylcoclaurine	0,843	0,544	0,733
8	(+)-Thalrugosine Thalrugosine	0,864	-	0,787
9	beta-Cyclanoline	-	-	-
10	Fangchinoline dl-Fangchinoline 7-O-Demethyltetrandrine	0,86	-	0,812
11	Limacine (-)-Limacine	0,86	-	0,812
12	Tetrandrine mono-N-2'-oxide Tetrandrine 2'beta-N-oxide Tetrandrine N-2'-oxide	0,378	-	0,527
13	Cyclanoline alpha-Cyclanoline (-)-Cissamine	-	-	-
14	(-)-2-Norlimacine (-)-2-Demethyllimacine 2-Norlimacine	0,833	-	0,724
15	(-)-Curine (-)-Bebeerine Aristolochine Aristolochine(C36 alkaloid)	0,822	0,647	0,789

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No	Compound Name	5 Hydroxytryptamine release stimulant (%PA)	Membrane Integrity Agonist (%PA)	MAP Kinase Stimulant (%PA)
	l-Bebeerine l-Curine L-Bebeerine			
16	-)-Cycleapeltine Cycleapeltin Cycleapeltine Faralaotrine	0,86	0,683	0,812
17	(-)-N-Methylcoclaurine (R)-N-Methylcoclaurine	0,857	0,666	0,733
18	(-)-Repandine Repandine N-Methyldemerarine Repandin	0,822	-	0,74
19	(+)-Coclaurine (+)-R-Coclaurine (R)-Coclaurine Sanjoinine K d-Coclaurine	0,835	0,588	0,73
20	(+)-Cycleabarbatine	0,792	0,429	0,773
21	(+)-Cycleanorine Cycleaneonine (+)-Cycleaneonine	0,792	-	0,773
22	Coclaurine (S)-Coclaurine (-)-Coclaurine	0,792	0,429	0,773
23	Cycleadrine	0,86	-	0,812
24	(S)-Norcoclaurine Norcoclaurine (S)-(-)-Higenamine	0,775	0,717	0,703
25	4-Hydroxyphenylacetaldehyde 4-HPAA 4-hydroxyphenylacetaldehyde	0,687	0,846	0,712
26	4-Hydroxyphenylpyruvate 4-HPP	0,743	0,888	0,63

Table 4. Drug-Likeness Lipinski Rule of Five *Cyclea barbata* (Grass Jelly) Plant using SwissADME

No.	Compound	Molecular Weight (MW)	LogP	Hydrogen Bond Donor (HBD)	Hydrogen Bond Acceptor (HBA)	Topological Polar Surface Area (TPSA)	Rotatable Bonds
		< 500 g/mol	**< 5**	**< 5**	**< 10**	**< 140 A^2**	**< 10**
1	Dopamine	153,18	-1	3	4	66,48	2
2	Tyramine	137,18	-0,35	2	2	46,25	2

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No.	Compound	Molecular Weight (MW)	LogP	Hydrogen Bond Donor (HBD)	Hydrogen Bond Acceptor (HBA)	Topological Polar Surface Area (TPSA)	Rotatable Bonds
		< 500 g/mol	< 5	< 5	< 10	< 140 A^2	< 10
3	Isochondodendrine	594,74	3,49	2	6	58,92	3
4	(+)-Tetrandrine	622,76	4,92	0	8	48,4	4
5	(+)-Homoaromoline	579,71	3,8	1	7	53,74	3
6	(+)-Isotetrandrine	622,76	4,92	0	8	48,4	4
7	(+)-N-Methylcoclaurine	329,39	1,69	2	4	56,12	4
8	(+)-Thalrugosine	594,74	3,49	2	6	58,92	3
9	beta-Cyclanoline	342,41	0,07	2	5	61,83	2
10	Fangchinoline	608,73	4,58	1	8	52,59	4
11	Limacine	399,47	2,08	1	6	59,62	3
12	Tetrandrine mono-N-2'-oxide	638,76	3,98	0	9	64,68	4
13	Cyclanoline	328,39	-0,16	2	5	61,83	2
14	(-)-2-Norlimacine	385,44	1,66	2	6	68,85	3
15	(-)-Curine	594,74	3,49	2	6	58,92	3
16	(-)-Cycleapeltine	593,72	3,6	1	7	59,2	3
17	(-)-N-Methylcoclaurine	329,39	1,69	2	4	56,12	4
18	(-)-Repandine	383,44	2,2	1	5	49,77	2
19	(+)-Coclaurine	315,37	1,36	3	4	66,36	4
20	(+)-Cycleabarbatine	609,74	3,49	2	8	64,15	3
21	(+)-Cycleanorine	563,68	3,2	2	7	67,43	3
22	Coclaurine	315,37	1,36	3	4	66,36	4
23	Cycleadrine	579,71	3,41	2	7	64,15	3
24	(S)-Norcoclaurine	301,34	0,95	4	4	76,59	4
25	4-Hydroxyphenylacetaldehyde	136,15	0,97	1	2	37,3	2
26	4-Hydroxyphenylpyruvate	180,16	-0,54	3	4	97,99	2

Table 5. Drug Likeness (Ghose Filter, Veber Rule, Egan Rule, and Muegge Rule) *Cyclea barbata* (Grass Jelly) Plant using SwissADME

No.	Compound	Ghose Filter	Veber Rule	Egan Rule	Muegge	Bioavailability Radar
1	Dopamine	No	Yes	Yes	No	0,55
2	Tyramine	No	Yes	Yes	No	0,55
3	Isochondodendrine	No	Yes	Yes	Yes	0,55
4	(+)-Tetrandrine	No	Yes	Yes	No	0,55
5	(+)-Homoaromoline	No	Yes	Yes	Yes	0,55
6	(+)-Isotetrandrine	No	Yes	Yes	No	0,55

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No.	Compound	Ghose Filter	Veber Rule	Egan Rule	Muegge	Bioavailability Radar
7	(+)-N-Methylcoclaurine	Yes	Yes	Yes	Yes	0,55
8	(+)-Thalrugosine	No	Yes	Yes	Yes	0,55
9	beta-Cyclanoline	Yes	Yes	Yes	Yes	0,55
10	Fangchinoline	No	Yes	Yes	No	0,55
11	Limacine	Yes	Yes	Yes	Yes	0,55
12	Tetrandrine mono-N-2'-oxide	No	Yes	Yes	No	0,55
13	Cyclanoline	Yes	Yes	Yes	Yes	0,55
14	(-)-2-Norlimacine	Yes	Yes	Yes	Yes	0,55
15	(-)-Curine	No	Yes	Yes	Yes	0,55
16	(-)-Cycleapeltine	No	Yes	Yes	Yes	0,55
17	(-)-N-Methylcoclaurine	Yes	Yes	Yes	Yes	0,55
18	(-)-Repandine	Yes	Yes	Yes	Yes	0,55
19	(+)-Coclaurine	Yes	Yes	Yes	Yes	0,55
20	(+)-Cycleabarbatine	No	Yes	Yes	No	0,55
21	(+)-Cycleanorine	No	Yes	Yes	Yes	0,55
22	Coclaurine	Yes	Yes	Yes	Yes	0,55
23	Cycleadrine	No	Yes	Yes	Yes	0,55
24	(S)-Norcoclaurine	Yes	Yes	Yes	Yes	0,55
25	4-Hydroxyphenylacetaldehyde	No	Yes	Yes	No	0,55
26	4-Hydroxyphenylpyruvate	No	Yes	Yes	No	0,55

Table 6. Water Solubility & Pharmacokinetics *Cyclea barbata* (Grass Jelly) Plant using SwissADME

No.	Compound	Water Solubility	Pharmacokinetics	Egan Rule	Muegge Rule
		Log S (ESOL)	GI Absorption	BBB Permeant	P-gp Substrate
1	Dopamine	0,46	High	No	No
2	Tyramine	0,41	High	Yes	No
3	Isochondodendrine	-4,73	Low	No	Yes
4	(+)-Tetrandrine	-5,38	Low	Yes	Yes
5	(+)-Homoaromoline	-4,9	Low	No	Yes
6	(+)-Isotetrandrine	-5,38	Low	Yes	Yes
7	(+)-N-Methylcoclaurine	-2,64	High	No	No
8	(+)-Thalrugosine	-4,73	Low	No	Yes
9	beta-Cyclanoline	-2,08	High	No	No
10	Fangchinoline	-5,2	Low	Yes	Yes
11	Limacine	-3,15	High	No	Yes
12	Tetrandrine mono-N-2'-oxide	-4,62	Low	No	Yes
13	Cyclanoline	-1,84	High	No	No
14	(-)-2-Norlimacine	-2,87	High	No	Yes
15	(-)-Curine	-4,73	Low	No	Yes
16	(-)-Cycleapeltine	-4,81	Low	No	Yes
17	(-)-N-Methylcoclaurine	-2,64	High	No	No
18	(-)-Repandine	-3,47	High	No	Yes

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19	(+)-Coclaurine	-2,29	High	No	No
20	(+)-Cycleabarbatine	-4,76	Low	No	Yes
21	(+)-Cycleanorine	-4,51	Low	No	Yes
22	Coclaurine	-2,29	High	No	No
23	Cycleadrine	-4,65	Low	No	Yes
24	(S)-Norcoclaurine	-1,89	High	No	No
25	4-Hydroxyphenylacetaldehyde	0,94	High	Yes	No
26	4-Hydroxyphenylpyruvate	0,13	High	No	No

Table 7. Medicinal Chemistry *Cyclea barbata* (Grass Jelly) Plant using SwissADME

No.	Compound	PAINS	Break	Leadlikeness	Synthetic Accessibility
1	Dopamine	0 alert	0 alert	Yes	1
2	Tyramine	0 alert	0 alert	Yes	1
3	Isochondodendrine	0 alert	0 alert	No (1 violation: MW)	6,28
4	(+)-Tetrandrine	0 alert	0 alert	No (2 violations: MW, LogP)	7,1
5	(+)-Homoaromoline	0 alert	0 alert	No (1 violation: MW)	6,52
6	(+)-Isotetrandrine	0 alert	0 alert	No (2 violations: MW, LogP)	7,1
7	(+)-N-Methylcoclaurine	0 alert	0 alert	Yes	3,82
8	(+)-Thalrugosine	0 alert	0 alert	No (1 violation: MW)	6,28
9	beta-Cyclanoline	0 alert	0 alert	Yes	5,2
10	Fangchinoline	0 alert	0 alert	No (2 violations: MW, LogP)	7,05
11	Limacine	0 alert	0 alert	Yes	5,67
12	Tetrandrine mono-N-2'-oxide	0 alert	0 alert	No (2 violations: MW, LogP)	7,15
13	Cyclanoline	0 alert	0 alert	Yes	5,18
14	(-)-2-Norlimacine	0 alert	0 alert	Yes	5,45
15	(-)-Curine	0 alert	0 alert	No (1 violation: MW)	6,28
16	(-)-Cycleapeltine	0 alert	0 alert	No (1 violation: MW)	6,47
17	(-)-N-Methylcoclaurine	0 alert	0 alert	Yes	3,82
18	(-)-Repandine	0 alert	0 alert	Yes	5,55
19	(+)-Coclaurine	0 alert	0 alert	Yes	3,65
20	(+)-Cycleabarbatine	0 alert	0 alert	No (2 violations: MW, HBA)	6,6
21	(+)-Cycleanorine	0 alert	0 alert	No (1 violation: MW)	6,38
22	Coclaurine	0 alert	0 alert	Yes	3,65
23	Cycleadrine	0 alert	0 alert	No (1 violation: MW)	6,43
24	(S)-Norcoclaurine	0 alert	0 alert	Yes	3,5

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No.	Compound	PAINS	Break	Leadlikeness	Synthetic Accessibility
25	4-Hydroxyphenylacetaldehyde	0 alert	1 alert	Yes	1,16
26	4-Hydroxyphenylpyruvate	0 alert	1 alert	Yes	1,45

Table 8. Absorption *Cyclea barbata* (Grass Jelly) Plant using SwissADME

No.	Compound	Water solubility (log mol/L)	Caco-2 permeability (log Papp in 10* cm/s)	Intestinal absorption (human) (% Absorbed)	Skin permeability (log Kp)
1	Dopamine	-0,98	0,42	74,92	-2,73
2	Tyramine	-1,17	0,82	87,26	-2,55
3	Isochondodendrine	-5,10	1,26	32,11	-0,55
4	(+)-Tetrandrine	-5,78	1,47	55,89	-0,17
5	(+)-Homoaromoline	-5,27	1,35	41,83	-0,38
6	(+)-Isotetrandrine	-5,78	1,47	55,89	-0,17
7	(+)-N-Methylcoclaurine	-3,00	0,91	81,06	-1,61
8	(+)-Thalrugosine	-5,10	1,26	32,11	-0,55
9	beta-Cyclanoline	-2,44	0,27	78,49	-2,18
10	Fangchinoline	-5,57	1,44	52,70	-0,27
11	Limacine	-3,52	1,06	72,18	-1,11
12	Tetrandrine mono-N-2'-oxide	-4,99	0,78	40,22	-0,88
13	Cyclanoline	-2,20	0,24	78,49	-2,18
14	(-)-2-Norlimacine	-3,24	1,00	74,31	-1,34
15	(-)-Curine	-5,10	1,26	32,11	-0,55
16	(-)-Cycleapeltine	-5,18	1,28	39,54	-0,52
17	(-)-N-Methylcoclaurine	-3,00	0,91	81,06	-1,61
18	(-)-Repandine	-3,84	1,10	69,44	-1,04
19	(+)-Coclaurine	-2,65	0,72	83,64	-1,83
20	(+)-Cycleabarbatine	-5,13	1,27	37,92	-0,58
21	(+)-Cycleanorine	-4,88	1,22	44,71	-0,72
22	Coclaurine	-2,65	0,72	83,64	-1,83
23	Cycleadrine	-5,02	1,24	43,16	-0,65
24	(S)-Norcoclaurine	-2,35	0,15	82,35	-2,35
25	4-Hydroxyphenylacetaldehyde	-1,29	0,54	94,13	-2,45
26	4-Hydroxyphenylpyruvate	-1,75	-0,08	70,81	-2,98

Table 9. Distribution *Cyclea barbata* (Grass Jelly) Plant using pkCSM

No.	Compound	VDss (log L/kg)	Fraction Unbound (human) (Fu)	BBB Permeability (log BB)	CNS Permeability (log PS)
1	Dopamine	-0,25	0,72	-1,28	-2,81
2	Tyramine	-0,01	0,85	-0,58	-2,12
3	Isochondodendrine	0,94	0,13	-0,56	-1,83
4	(+)-Tetrandrine	1,24	0,07	0,39	-1,24
5	(+)-Homoaromoline	1,02	0,10	-0,30	-1,54
6	(+)-Isotetrandrine	1,24	0,07	0,39	-1,24

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No.	Compound	VDss (log L/kg)	Fraction Unbound (human) (Fu)	BBB Permeability (log BB)	CNS Permeability (log PS)
7	(+)-N-Methylcoclaurine	0,42	0,42	-0,57	-2,18
8	(+)-Thalrugosine	0,94	0,13	-0,56	-1,83
9	beta-Cyclanoline	0,15	0,51	-0,85	-2,64
10	Fangchinoline	1,18	0,08	0,21	-1,35
11	Limacine	0,68	0,24	-0,38	-1,97
12	Tetrandrine mono-N-2'-oxide	0,88	0,09	-0,82	-2,43
13	Cyclanoline	0,11	0,53	-0,90	-2,71
14	(-)-2-Norlimacine	0,55	0,30	-0,50	-2,08
15	(-)-Curine	0,94	0,13	-0,56	-1,83
16	(-)-Cycleapeltine	1,00	0,11	-0,32	-1,60
17	(-)-N-Methylcoclaurine	0,42	0,42	-0,57	-2,18
18	(-)-Repandine	0,72	0,22	-0,14	-1,89
19	(+)-Coclaurine	0,33	0,47	-0,71	-2,35
20	(+)-Cycleabarbatine	0,98	0,11	-0,48	-1,72
21	(+)-Cycleanorine	0,88	0,14	-0,55	-1,90
22	Coclaurine	0,33	0,47	-0,71	-2,35
23	Cycleadrine	0,91	0,13	-0,52	-1,87
24	(S)-Norcoclaurine	0,20	0,55	-0,95	-2,80
25	4-Hydroxyphenylacetaldehyde	-0,18	0,90	-0,89	-2,76
26	4-Hydroxyphenylpyruvate	-0,42	0,88	-1,54	-3,21

Table 10. Excretion *Cyclea barbata* (Grass Jelly) Plant using pkCSM

No.	Compound	Total Clearance (log ml/min/kg)	Renal OCT2 substrrate
1	Dopamine	0,612	Yes
2	Tyramine	0,745	Yes
3	Isochondodendrine	0,284	No
4	(+)-Tetrandrine	0,312	No
5	(+)-Homoaromoline	0,354	No
6	(+)-Isotetrandrine	0,312	No
7	(+)-N-Methylcoclaurine	0,521	Yes
8	(+)-Thalrugosine	0,341	No
9	beta-Cyclanoline	0,418	No
10	Fangchinoline	0,295	No
11	Limacine	0,301	No
12	Tetrandrine mono-N-2'-oxide	0,187	No
13	Cyclanoline	0,418	No
14	(-)-2-Norlimacine	0,365	No
15	(-)-Curine	0,274	No
16	(-)-Cycleapeltine	0,221	No
17	(-)-N-Methylcoclaurine	0,521	Yes
18	(-)-Repandine	0,305	No
19	(+)-Coclaurine	0,584	Yes
20	(+)-Cycleabarbatine	0,215	No

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No.	Compound	Total Clearance (log ml/min/kg)	Renal OCT2 substrrate
21	(+)-Cycleanorine	0,244	No
22	Coclaurine	0,584	Yes
23	Cycleadrine	0,198	No
24	(S)-Norcoclaurine	0,602	Yes
25	4-Hydroxyphenylacetaldehyde	0,892	No
26	4-Hydroxyphenylpyruvate	0,711	No

Table 11. Toxicity *Cyclea barbata* (Grass Jelly) Plant using pkCSM

No.	Compound	Max. Dose Tolerated (human) (log mg/kg/day)	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	*T. Pyriformis Toxicity (log ug/L)*	Minnow Toxicity (log mM)
1	Dopamine	0,421	2,145	0,912	0,312	1,245
2	Tyramine	0,512	2,054	0,845	0,287	0,985
3	Isochondodendrine	-0,124	2,874	1,452	0,451	2,312
4	(+)-Tetrandrine	-0,085	2,912	1,385	0,512	2,451
5	(+)-Homoaromoline	-0,092	2,895	1,412	0,498	2,384
6	(+)-Isotetrandrine	-0,085	2,912	1,385	0,512	2,451
7	(+)-N-Methylcoclaurine	0,185	2,452	1,124	0,365	1,624
8	(+)-Thalrugosine	-0,071	2,941	1,324	0,524	2,512
9	beta-Cyclanoline	0,112	2,584	1,205	0,395	1,784
10	Fangchinoline	-0,064	2,965	1,301	0,531	2,541
11	Limacine	-0,078	2,924	1,354	0,518	2,487
12	Tetrandrine mono-N-2'-oxide	-0,154	3,124	1,521	0,584	2,845
13	Cyclanoline	0,112	2,584	1,205	0,395	1,784
14	(-)-2-Norlimacine	-0,045	2,812	1,284	0,474	2,215
15	(-)-Curine	-0,115	2,865	1,441	0,445	2,295
16	(-)-Cycleapeltine	-0,142	3,012	1,495	0,562	2,684
17	(-)-N-Methylcoclaurine	0,185	2,452	1,124	0,365	1,624
18	(-)-Repandine	-0,082	2,905	1,378	0,509	2,438
19	(+)-Coclaurine	0,245	2,341	1,054	0,341	1,487
20	(+)-Cycleabarbatine	-0,131	2,985	1,474	0,548	2,615
21	(+)-Cycleanorine	-0,118	2,954	1,451	0,534	2,564
22	Coclaurine	0,245	2,341	1,054	0,341	1,487
23	Cycleadrine	-0,148	3,054	1,512	0,574	2,754
24	(S)-Norcoclaurine	0,284	2,284	0,985	0,324	1,364
25	4-Hydroxyphenylacetaldehyde	0,624	1,845	0,712	0,215	0,754
26	4-Hydroxyphenylpyruvate	0,584	1,912	0,765	0,241	0,842

The results presented in Tables 3–11 indicate that *Cyclea barbata* contains diverse secondary metabolites with promising biological and pharmacokinetic properties. Based on Table 3, tyramine, dopamine, and isochondodendrine exhibited the highest activity as 5-hydroxytryptamine (5-HT) release stimulants, suggesting their ability to regulate serotonergic

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neurotransmission, which is involved in mood, cognition, and emotional function. Several bisbenzylisoquinoline alkaloids, including tetrandrine, fangchinoline, and cycleapeltine, also showed high biological activity, indicating potential neuroprotective and neuromodulatory effects. In membrane integrity analysis, phenolic compounds such as 4-hydroxyphenylpyruvate and 4-hydroxyphenylacetaldehyde demonstrated the strongest activity, reflecting their antioxidant role in protecting cell membranes from oxidative damage. Dopamine, tyramine, and several alkaloids also showed high MAP kinase stimulation activity, suggesting their involvement in regulating cell signaling pathways associated with neuroprotection, inflammation, and oxidative stress (Zhao *et al*., 2025; Li *et al*., 2025). Collectively, these findings indicate that Cyclea barbata possesses multitarget bioactive compounds with potential applications in neurological and anti-inflammatory therapies (Febrianto *et al*., 2022).

Drug-likeness evaluation using the Lipinski Rule of Five (Table 4) demonstrated that simple compounds such as dopamine, tyramine, coclaurine, and norcoclaurine satisfy most criteria, indicating favorable oral bioavailability. Conversely, larger alkaloids such as tetrandrine and fangchinoline exceeded the molecular weight threshold but retained acceptable lipophilicity, suggesting that structural modification or advanced drug delivery systems may improve their pharmacokinetic performance (Asano *et al*., 2023; Liu *et al*., 2025). Their low TPSA values and limited number of rotatable bonds further support membrane permeability and potential penetration of the blood-brain barrier (BBB) (Dizeyi *et al*., 2011).

SwissADME analysis (Table 5) further confirmed that most compounds complied with the Veber and Egan rules, indicating good gastrointestinal absorption and membrane permeability. Although several complex alkaloids did not satisfy the Ghose and Muegge filters due to their large molecular size, these violations do not necessarily diminish pharmacological potential, as many natural alkaloids remain biologically active despite failing classical drug-likeness rules (Heinrich *et al*., 2021). Compounds such as coclaurine, norcoclaurine, limacine, and N-methylcoclaurine fulfilled nearly all criteria, making them promising phytopharmaceutical candidates (Maulana *et al*., 2026).

Water solubility and pharmacokinetic analyses (Table 6) revealed that dopamine, tyramine, and phenolic derivatives possess high aqueous solubility and gastrointestinal absorption. In contrast, complex alkaloids exhibit poor solubility but better lipophilicity and BBB penetration. Several compounds, including tyramine, tetrandrine, fangchinoline, and 4-hydroxyphenylacetaldehyde, were predicted to cross the BBB, supporting their potential as neuroactive agents (Lin *et al*., 2022). Moreover, simple compounds were generally not substrates of P-glycoprotein, suggesting more favorable oral absorption and distribution than complex alkaloids (Li *et al*., 2019).

Medicinal chemistry analysis (Table 7) showed that all compounds were free from PAINS alerts, indicating a low probability of false-positive biological activity during screening. Most compounds also exhibited minimal Brenk alerts, while coclaurine, norcoclaurine, dopamine, and N-methylcoclaurine fulfilled lead-likeness criteria and displayed moderate synthetic accessibility, making them attractive lead compounds for further optimization (Dzobo, 2022; Hanoum & Shubbak, 2025).

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Absorption prediction using pkCSM (Table 8) demonstrated that compounds such as coclaurine, tyramine, and N-methylcoclaurine possess an optimal balance between water solubility, intestinal absorption, and membrane permeability. In contrast, tetrandrine and fangchinoline exhibited excellent membrane permeability but low water solubility, suggesting that specialized formulations may be required to improve oral bioavailability (Onoue *et al*., 2026; Xu *et al*., 2026). Distribution analysis (Table 9) indicated that complex alkaloids exhibited higher tissue distribution and BBB penetration than simple compounds because of their greater lipophilicity. However, these characteristics may increase tissue accumulation and potential toxicity. Simpler compounds such as tyramine, coclaurine, and norcoclaurine displayed more balanced distribution profiles, suggesting better safety for systemic use (Srivastava *et al*., 2026; Wu *et al*., 2023).

Excretion prediction (Table 10) showed that dopamine, tyramine, co-caffeine, and norco-caffeine had higher clearance values and were predicted to be OCT2 substrates, indicating faster renal elimination and a lower risk of accumulation. In contrast, complex alkaloids demonstrated slower clearance, potentially resulting in prolonged pharmacological activity but also a greater possibility of tissue accumulation (Ngcobo, 2025; Gessner *et al*., 2025).

Finally, toxicity prediction (Table 11) suggested that simple compounds generally possess better safety profiles than complex alkaloids. Dopamine, tyramine, coclaurine, and norcoclaurine exhibited higher tolerated doses and lower toxicity risks. In contrast, tetrandrine, fangchinoline, and related alkaloids exhibited greater potential for accumulation and toxicity due to their lipophilic properties. Nevertheless, all toxicity predictions remain preliminary and require validation through in vitro and in vivo studies before clinical application (Aryal *et al*., 2022; Izatunnafis *et al*., 2023). Overall, the integrated in silico analyses demonstrate that *Cyclea barbata* is a promising source of phytopharmaceutical compounds. Simple alkaloids, particularly dopamine, tyramine, coclaurine, and norcoclaurine, exhibit the most favorable combination of biological activity, pharmacokinetic characteristics, and safety. In contrast, complex bisbenzylisoquinoline alkaloids remain valuable for their strong neuroprotective and anti-inflammatory activities, despite requiring further optimization to improve their pharmacokinetic performance.

CONCLUSION

Based on the in silico analysis, *Cyclea barbata* contains various secondary metabolites with promising bioactivity and pharmacological properties. Tyramine and dopamine demonstrated the highest activities as serotonin release stimulants and MAP kinase pathway activators, suggesting their potential neuroprotective effects. Furthermore, bisbenzylisoquinoline alkaloids such as tetrandrine, fangchinoline, and cycleapeltine exhibited multitarget activities, including anti-inflammatory effects and neuronal protection. Drug-likeness analysis using SwissADME indicated that coclaurine, norcoclaurine, N-methylcoclaurine, dopamine, and tyramine possessed the most favorable pharmacokinetic

profiles, as they satisfied most of the Lipinski, Veber, and Egan criteria (Daina *et al*., 2017). In addition, these compounds demonstrated high gastrointestinal absorption and more favorable excretion profiles compared to complex alkaloids.

ADME/T prediction using pkCSM revealed that several compounds exhibited good distribution properties and the potential to penetrate the blood–brain barrier, making them promising candidates for the treatment of central nervous system disorders (Ancuceanu *et al*., 2025). Medicinal chemistry analysis showed that all compounds were free of PAINS alerts. At the same time, toxicity evaluation indicated that most compounds had relatively favorable safety profiles, although some complex alkaloids showed potential for tissue accumulation. (Pooten *et al*., 2025). Overall, *Cyclea barbata* represents a promising source of natural bioactive compounds for the development of modern phytopharmaceuticals, particularly as neuroprotective and anti-inflammatory agents. However, all in silico predictions obtained in this study require further validation through in vitro and in vivo experiments to confirm the efficacy, pharmacokinetic properties, and safety of these compounds before they can be developed as drug candidates.

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