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DNA Barcoding, GC-MS Analysis, and Biological Activity Prediction of Bioactive Compounds in the Seeds of *Celastrus paniculatus*: A Source of Lead Compounds for Neurological Disorders

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Abstract

Background: Neurodegenerative disorders are multifactorial by nature and are difficult to treat. Limitations of existing drugs due to narrow therapeutic profiles have led to the consideration of alternative strategies, including natural products and their derivatives. *Celastrus paniculatus* is an endangered medicinal plant widely used in *Ayurveda* and is known for multiple therapeutic benefits, including effectiveness against cognitive impairment and possessing anti-epileptic, memory-enhancing, and anti-inflammatory properties. **Aim:** The present study aimed to identify the secondary metabolites present in the seeds of *C. paniculatus* and to estimate their pharmacological parameters to act as leads using computational predictive analysis. **Methods:** Seed extracts were prepared using methanol and ethanol and analysed using GC–MS to identify compounds. The identified compounds were evaluated using the Lipinski filter and computational predictive analysis of pharmacological parameters, including absorption, distribution, metabolism, excretion, toxicity, and blood–brain barrier crossing potential, along with biological activity prediction. **Results:** A total of 32 compounds were identified from the methanol extract, and 18 compounds from the ethanol extract. Among these, 47 compounds exhibited drug-likeness based on the Lipinski filter. Out of these, five compounds—phenethylamine, trans-tetrahydro-3,4-furandiol mononitrate, extroamphetamine, 13-alpha-benzoyloxylupanine, and 2-palmitoylglycerol—satisfied pharmacological parameters of absorption, distribution, metabolism, excretion, and toxicity and exhibited blood–brain barrier crossing potential. These compounds also showed a higher probability of activity as neuroprotective agents. **Conclusion:** GC-MS analysis of *C. paniculatus* seed extracts identified 49 phytochemicals, among which phenethylamine, trans-tetrahydro-3,4-furandiol mononitrate, dextroamphetamine, 13α-benzoyloxylupanine, and 2-palmitoylglycerol showed promising drug-like and neuroprotective potential based on Lipinski, ADMET, and neurological activity predictions. The study highlights *Celastrus paniculatus* seeds as a potential source of bioactive lead molecules for neurological disorder research.

Major Findings: GC–MS analysis of *C. paniculatus* seed extracts identified 49 phytochemicals, of which 47 exhibited favourable drug-likeness properties. ADMET, BBB permeability, and biological activity prediction analyses highlighted phenethylamine, trans-tetrahydro-3,4-furandiol mononitrate, dextroamphetamine, 13α-benzoyloxylupanine, and 2-palmitoylglycerol as promising neuroprotective lead candidates for neurodegenerative disorder research.

Keywords: *Celastrus paniculatus*, *In Silico* Predictions, Neurological Disorders, Phytochemicals, Pharmacokinetics, Traditional Medicine

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1. Introduction

Drug discovery for chronic disorders is challenging due to the multifactorial nature of the disease. Neurological disorders are one such kind, where the disease progression occurs through molecular, cellular, genetic, pathological, physiological, and psychological misregulations. Due to this, most of the efforts to

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develop potent drug molecules end in failure[1]. In addition to this, the complexity of brain signalling, the difficulty of getting experimental specimens, and the poor pharmacological parameters of drug candidates make this an unmet clinical need. Due to high structural diversity and various bioactivities such as anti-oxidant, anti-inflammatory, and immune modulatory effects, considerable efforts have been made in recent decades to explore the therapeutic potential of natural products as promising agents for neurological disease management[2]. From a pharmaceutical perspective, medicinal plants with a long history of use in traditional practice can be a rich source of bioactive compounds for the treatment of various disorders. They are considered large repositories of lead candidates having therapeutic importance[3].

Celastrus paniculatus (CP), commonly known as intellect tree/ *Jotishmati,* is an important medicinal plant extensively used in the Indian traditional system of medicine, *Ayurveda*[4]. In *Ayurveda*, CP is known as the 'Tree of life' and is claimed to be enriched with remarkable therapeutic activities against diseases such as skin disorders, respiratory system disorders, cardiac problems, genitourinary disorders, neurological disorders and inflammation[5]. CP seeds are used in the Ayurvedic formulation Medhya Rasayana, which is specifically indicated for improving cognitive functions[6]. Along with this traditional indication, experimental data confirm the neuroprotective effects of CP seed extracts through *in vitro* and *in vivo* experiments. Some of the proven medicinal properties of CP seed extracts relevant to neurological disorders are summarised in Table 1.

Table 1. Medicinal properties of *Celastrus paniculatus* seed extract with respect to neurological disorders

Sr. No.	Properties
1	Anticonvulsant[7]
2	Anti-inflammatory[8]
3	Free radical scavenger[9]
4	Cholinergic activity[10]
5	Cognitive enhancement[11]
6	Neurotransmitter regulation[12]
7	Enhance learning and memory[13]
8	Neuromuscular stimulant[14]
9	Modulating glutamate receptor function[15]
10	Anxiolytic[16]

The above data clearly indicate the potential of CP seeds as a source of potent therapeutic agents for neurological disorders. Even though the extracts are found to be effective for cognitive disorders, efforts to analyse the plant constituents to develop potent drugs are very rare due to the unexplored biological activity and adverse effects. Understanding the pharmacokinetic profile of lead candidates is an important factor in the process of drug development. Problems with molecular weight, lipophilicity, hydrogen bond donors and acceptors, Absorption, Distribution, Metabolism, Elimination, and Toxicity (ADMET) have been recognised as major reasons for the rejection in the late-stage of the drug development process[17]. Also, the inability of small molecules to cross the Blood-Brain Barrier (BBB) is one of the major challenges in CNS drug discovery[18]. Parallel evaluation of these parameters in the initial stage of drug discovery is highly recommended. The effective application of *in silico* predictions may be employed to predict these properties so that the compounds with the best features can be filtered out for further analysis in a time and cost-effective way[17]. Hence, the present study aimed to identify potent compounds present in the CP seeds using the GC-MS method and to estimate their pharmacological parameters of biological activity using *in silico* predictive analysis to explore the possibility of considering them as neuroprotective agents.

2. Materials and Methods

2.1 Plant Authentication

Plant authentication is critical to identify the exact species and to consider them for further evaluation based on their medicinal properties. Since classical Ayurvedic texts use *Sanskrit* synonyms of medicinal plants and do not convey exact taxonomical features, the botanical identification becomes controversial. Hence, scientific identification is required for the authentication of exact plant species.

2.1.1 Morphological Identification

The plant, along with the seeds of CP, was collected from the government. *Ayurveda* College, Trivandrum, was

identified and authenticated by the taxonomist at the Department of Botany, University of Kerala. The plant specimen was labelled and preserved in a herbarium sheet for which a herbarium voucher number was assigned.

2.1.2 DNA Barcoding

The plant was further taken for species-level identification using DNA barcoding. The fresh seeds of CP were submitted for sequencing at Rajiv Gandhi Centre for Biotechnology (RGCB), Trivandrum. The rbcL gene was amplified using universal primers rbcL-aF (5′-ATGTCACCACAAACAGAGACTAAAGC-3′) and rbcL-aR (5′-GTAAAATCAAGTCCACCRCG-3′), which are widely used for plant DNA barcoding studies. DNA isolation was done using the NucleoSpin® Plant II Kit. The quality of the DNA isolates was checked using agarose gel electrophoresis. The gels were visualised using a UV transilluminator (Genei) and the images were captured using a Gel documentation system (Bio-Rad). Sanger Sequencing was done in a PCR thermal cycler (GeneAmp PCR System 9700, Applied Biosystems) using the BigDye Terminator v3.1 Cycle sequencing Kit (Applied Biosystems, USA) based on the manufacturer's protocol. The quality of the sequence was checked using Sequence Scanner Software v1 (Applied Biosystems). Sequence alignment and editing were carried out using Geneious Pro v5.1. The sequence was assembled to form the consensus sequence and aligned with the existing sequences using BLAST[19] to identify the related species. The identified sequence was deposited in GenBank[20].

2.2 GC-MS Analysis

The plant seed extracts were taken by the Soxhlet extraction method (Lopez, 2020). The collected seed sample was washed with distilled water and shade-dried at room temperature. Crushed seeds were weighed to 25 gm. each and extracted with 250 mL of organic solvents, methanol and ethanol using the standard protocol. The extracts were filtered using Whatman No. 1 filter paper and concentrated under reduced pressure with a rotary evaporator. Further, the extracts were freeze-dried in a lyophilizer and stored in sterile pre-weighed screw cap bottles at 4°C.

The extracts were further taken for phytochemical analysis using GC-MS (GC-MS Shimadzu, Model QP2020) with Column SH-Rxi-5Sil MS. The oven temperature was kept at 60°C for 8 minutes and 1.0µl of the sample was loaded for the analysis. Helium gas of 99.99% purity was used as a carrier as well as eluent. The flow rate of helium gas was set to 1 ml/min. The sample injector temperature was maintained at 250°C, and the split ratio was 10 throughout the experiment. The ionisation mass spectroscopic analysis was done with 70eV. The mass spectra were recorded over a scan range of 40-600 m/z for approximately 8 minutes. As individual compounds eluted from the gas chromatographic column, they entered the electron ionisation detector, where they were bombarded with a stream of electrons, causing them to break apart into fragments. The fragments are charged ions with a certain mass. The m/z ratio obtained was calibrated from the graph, which is the fingerprint of the molecules. Compounds were tentatively identified by comparing their mass spectra with data from the National Institute of Standards and Technology (NIST) 17 Library.

2.3 Biological Activity Prediction

2.3.1 Drug Likeness Assessment

The Lipinski filter protocol of Discovery Studio (DS)[21] was used to estimate the drug-likeness of the identified compounds. Lipinski's rule of five (RO5) determines small molecules' chemical and physical properties to assess their pharmacological potential as orally active drugs in humans[22]. The number of Hydrogen Bond Donors (HBD), number of Hydrogen Bond Acceptors (HBA), Molecular Weight (MW) in dalton (Da), and log value of octanol-water partition coefficient (AlogP) were calculated. According to Lipinski's rule, an orally active drug should have the number of HBD <=5; the number of HBA <=10; MW <=500 daltons; octanol-water partition coefficient (AlogP) <=5.

2.3.2 ADMET and BBB Crossing Potential

The pharmacokinetic parameters ADMET of drug candidates play important roles in drug discovery. A qualified drug candidate should have appropriate ADMET properties at a therapeutic dose to avoid toxicity. ADMET descriptors of Discovery Studio provide computational predictions of pharmacokinetic properties based on chemical structure; therefore, the results represent *in silico* estimates that require experimental validation[17]. The parameters include

intestinal absorption, aqueous solubility, Blood-Brain Barrier penetration (BBB), plasma protein binding, cytochrome P4502D6 inhibition, and hepatotoxicity. Selected compounds were screened based on the ADMET protocol of DS.

2.3.3 Neurological Activity Prediction

The compounds that satisfied pharmacological parameters were screened for estimating their potential as neuroprotective agents using the computer program PASS (Prediction of Activity Spectra for biologically active Substances)[23]. PASS is a web-based program that predicts pharmacological activity and possible biochemical mechanisms for the given compounds based on the structure-activity relationships. The prediction result returns the corresponding probability activation of values, p(a), and inactivation values, p(i), with an accuracy of 89%. If p(a)<0.5, the compound is unlikely to exhibit the activity; if 0.5<p(a)<0.7, the compound is likely to exhibit the activity; and if p(a)> 0.7, the substance is very likely to exhibit the activity.

3. Results

3.1 Plant Authentication

The plant identified based on the morphological features was preserved in a herbarium sheet with voucher number 'KUBH11101' (Figure 1A). The image of CP seeds is given in Figure 1B.

The annotated DNA sequence of CP was submitted to GenBank with accession number 'ON146360'. The FASTA sequence of the same is provided below.

>ON146360.1 Celastrus paniculatus ribulose-1,5-bisphosphate carboxylase/oxygenase large subunit (rbcL) gene, partial cds; chloroplast

ACAGAGACTAAAGCGAGTGTTGGAT
TCAAGGCTGGCGTTAAAGATTATAAATT
GACTTATTATACTCCTG

AATATGAAACCAAAGATACTGATATCTTG
GCAGCATTCCGAGTAACTCCTCAACCTG
GAGTTCCGCCTGA

AGAAGCAGGGGCGGCGGTAGCTGCT
GAATCTTCTACTGGTACATGGACAACTGT
GTGGACCGATGGGCTT

ACCAGTCTTGATCGTTACAAAGGACGAT
GCTACCACATCGAGCCCGTTGCTGGAGA
AGAAACTCAATTTA

TTGCTTATGTAGCTTATCCTTTAGA
CCTTTTCGAAGAAGGTTCTGTTACTAA
CATGTTTACTTCCATTGT

GGGTAATGTCTTTGGTTTCAAAGCCCTGC
GTGCTCTACGTCTGGAGGATTTGCGAAT
CCCCCCTGCTTAT

TCTAAAACTTTCCAAGGCCCGCCGCATG
GTATCCAAGTTGAGAGAGATAAATTGAA
CAAGTATGGACGCC

CTCTATTGGGATGTACTATTAAACCTAAATT
GGGATTATCCGCTAAGAATTATGGTAGAGCAG
TTTATGA

ATGTCTCCG

3.2 GC-MS Analysis

GCMS analysis of the methanol and ethanol extracts of CP seeds revealed the presence of 32 and 18 compounds, respectively. GCMS chromatograms

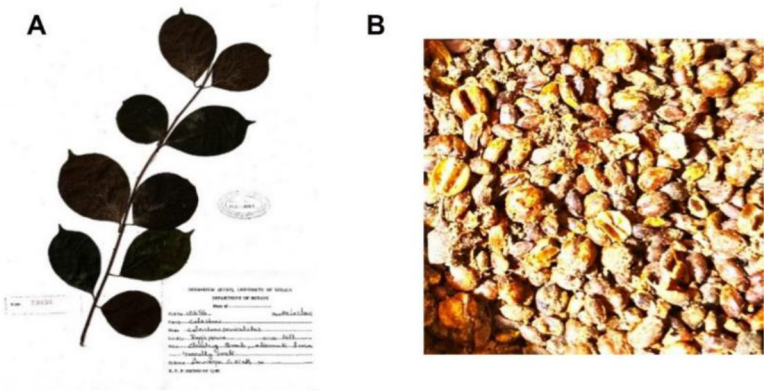


Figure 1. **(A).** Herbarium specimen of *Celastrus paniculatus* and **(B).** dried seeds of *Celastrus paniculatus*.

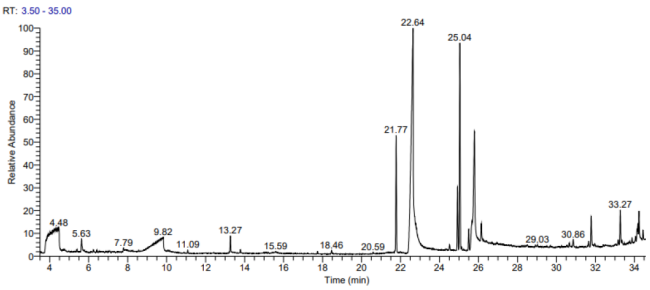


Figure 2. GC-MS Chromatogram of methanol extract of *C. paniculatus*. The compounds detected were represented as peaks. The X-axis represents retention Time (RT), and the Y-axis represents the relative abundance of the compounds.

of these compounds are depicted in Figures 2 and 3, respectively. The compounds with their name, Retention Time (RT), percentage of area, and height are presented in Tables 2 and 3.

3.3 Drug Likeness

RO5 predicts the probability of drug-likeness of small molecules in terms of oral bioavailability. The molecular descriptors of RO5 for the identified compounds are listed in Table 4.

According to the Lipinski filter protocol implemented in Discovery Studio, 47 compounds satisfied the Rule of Five criteria. Although a few

Table 2. Phytochemicals identified in the methanol extract of *C. paniculatus* seeds using the GC-MS method

Sr. No.	Compound Name	RT	Area %	Height
1	Trans-Tetrahydro-3,4-Furandiol Mononitrate	4.16	1.22	9238169
2	1-Ethyl-3-methylcyclohexane (c,t)	4.47	0.96	926875
3	Mesitylene	4.55	0.86	592587
4	Octane, 3,6-dimethyl-	9.81	0.79	534739
5	Cyclohexane, propyl-	13.27	0.79	771171
6	Heptane, 3-ethyl-2-methyl-	21.77	5.38	521409
7	13alpha-Benzoyloxylupanine	22.64	29.99	9470719
8	Nonane, 4-methyl-	24.93	2.84	282223
9	3,4-Furandiol, tetrahydro-, trans-	25.04	9.85	926825
10	1,2,3,4-Butanetetrol, [S-(R*,R*)]-	25.50	0.93	9380988
11	L-Arabinitol	25.67	1.62	1162921
12	Benzene, 1-ethyl-3-methyl-	25.79	11.12	5115486
13	Cyclohexane, 1-methyl-2-propyl-	26.15	1.01	781630
14	Cyclohexane, 1-methyl-4-(1-methylethyl)-, cis-	31.78	1.69	1372043
15	3-Hexen-1-ol, benzoate, (Z)-	33.27	1.63	15609553
16	Octane, 3,5-dimethyl-	34.24	1.64	1366157
17	Benzene, (2-ethenyl-1,4,4-trimethylpentyl)-	35.23	3.19	2234587
18	2,4-Di-tert-butylphenol	35.30	2.99	3081135
19	Benzene, 1-ethyl-2-methyl-	35.56	1.75	1904550
20	Cyclohexane, butyl-	37.21	4.07	3544928
21	Phenol, 3,5-bis(1,1-dimethylethyl)-	37.36	1.54	1457574
22	Ribitol	37.55	3.57	2185289
23	Benzene, 1-methyl-3-propyl-	37.69	0.91	840554
24	Benzene, 1,4-diethyl-	38.13	1.76	126465
25	Dodecane, 4,6-dimethyl-	38.22	0.89	758894
26	Benzene, 1-methyl-4-propyl-	38.77	2.92	2365259
27	Nonane, 5-butyl-	39.04	1.21	8957320
28	Benzene, 2-ethyl-1,4-dimethyl-	39.55	1.21	852124
29	Phenol, 2,6-bis(1,1-dimethylethyl)-	39.89	0.77	715213
30	Pentadecanoic acid, 14-methyl-, methyl ester	44.04	0.56	848456
31	Formic acid, benzoyl-, (8'-phenylmenthyl) ester	44.16	1.23	923816
32	Diglycerol	3.87	0.77	7152138

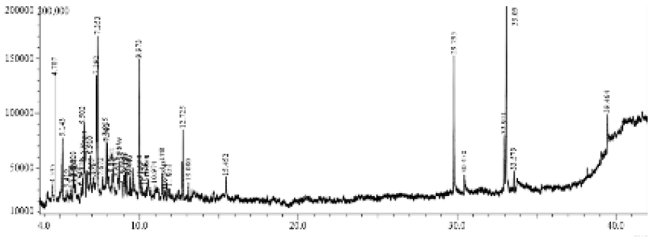


Figure 3. GC-MS Chromatogram of ethanol extract of *C. paniculatus*. The compounds detected were represented as peaks. The X-axis represents retention Time (RT), and the Y-axis represents the relative abundance of the compounds.

compounds showed AlogP values slightly greater than 5, they did not exceed the allowable limit of one violation and therefore were still considered acceptable in terms of oral drug-likeness.

3.4 ADMET

The ADMET protocol of DS filters the relevant compounds with promising pharmacokinetic parameters. The results of ADMET prediction for the identified compounds are listed in Table 5.

ADMET parameters assessment for the identified phytochemicals of *C. paniculatus* was done using the ADMET protocol of Discovery Studio version 4.0. The range of ADMET descriptors is as follows:

Solubility: 0- extremely low,1-low but possible, 2- possible, 3- good, 4- optimal, 5- too soluble. BBB level: 0-very high penetrant,1- high penetrant, 2 -medium penetrant, 3 - penetrant, 4 -undefined. Intestinal absorption: 0- good, 1- moderate, 2- poor, 3- very poor. (BBB: Blood-brain barrier; CYP2D6: Cytochrome P450 2D6 binding).

ADMET prediction results suggest that out of 47 screened compounds, five compounds exhibit favourable predicted pharmacokinetic parameters, including adequate solubility, good intestinal absorption, absence of predicted hepatotoxicity, and potential BBB permeability. These compounds were found to have no long-term interaction with plasma proteins and cytochrome P450 2D6 and were found to be able to cross the BBB. The details of compounds that satisfied ADME parameters are shown in Table 6.

3.5 Neurological Activity Prediction

The possible neurological activities of the identified compounds with favourable pharmacokinetic

Table 3. Phytochemicals identified in the ethanol extract of *C. paniculatus* seeds using the GC-MS method

Sr. No.	Compound Name	RT	Area %	Height
1	Mesitylene	4.53	1.26	15547
2	Octane, 3,5-dimethyl-	4.70	7.07	108923
3	N,N'-Bis(Carbobenzyloxy)-lysine methyl(ester)	5.14	3.78	53374
4	Phenethylamine	5.41	0.87	10290
5	Dextroamphetamine	5.82	1.26	26042
6	trans-Verbenyl isovalerate	5.97	0.75	12836
7	Tridecane	6.34	0.37	8350
8	2-Palmitoylglycerol	6.42	0.63	14546
9	trans-Verbenyl isovalerate	6.50	3.95	64636
10	Dodecane	6.57	1.93	32014
11	.gamma.-Asarone	6.68	2.83	38718
12	Dodecane, 2,6,11-trimethyl-	4.69	7.76	114888
13	1H-Cyclopropa[a] naphthalene, 1a,2,3,5,6,7,7a,7b-octahydro-1	5.12	4.51	55831
14	(1R,7S,E)-7-Isopropyl-4,10-dimethylenecyclodec-5-enol	5.82	1.46	24613
15	Naphthalene, 1,2,3,4-tetrahydro-1,5,7-trimethyl-	6.48	4.16	62688
16	Silphiperfola-4,7(14)-diene	6.55	1.57	26633
17	(1S,3aS,4S,5S,7aR,8R)-5-Isopropyl-1,7a-dimethyloctahydro-1	6.66	3.56	40881
18	Spirojatamol	6.89	2.37	33846

From the results, it was observed that the compound 'mesitylene' was common in both methanol and ethanol extracts. A total of 47 putatively annotated compounds were taken for further analysis based on spectral similarity matching with the NIST library.

parameters were predicted using the PASS server. PASS interprets the activity of a substance based on its 2D structure and generates the activity spectra at various threshold levels based on the probability scores. Among the predicted biological properties, the likelihood of neurological activities of compounds was noted and is presented in Table 7.

The biological activity spectra of selected phytochemicals of *C. paniculatus* were estimated using the PASS server. PASS predicts the pharmacological

Table 4. Molecular descriptors of identified phytocompounds of *C. paniculatus* that passed the Lipinski filter

Sr. No.	PubChem ID	MW (in Dalton)	HBA	HBD	AlogP
1	1001	122.188	0	1	0.252
2	107252	140.266	0	0	4.153
3	10955174	222.366	1	1	3.427
4	11053257	222.366	1	1	3.854
5	11903	120.192	0	0	3.258
6	12100	120.192	0	0	3.258
7	12260646	149.102	5	1	1.257
8	12388	184.361	0	0	6.302
9	13304974	220.35	1	1	4.086
10	139989	142.282	0	0	4.524
11	14095	134.218	0	0	3.714
12	15505	126.239	0	0	3.901
13	15506	140.266	0	0	4.357
14	15653	134.218	0	0	3.744
15	21205	270.451	2	0	6.414
16	28455	142.282	0	0	4.729
17	300476	184.361	0	0	6.097
18	31405	206.324	1	1	4.388
19	35412	126.239	0	0	3.696
20	35768	212.415	0	0	6.601
21	42953	166.172	5	4	-2.05
22	439255	152.146	5	5	-2.43
23	529436	174.282	0	0	4.567
24	5370859	190.281	1	0	2.999
25	545627	198.388	0	0	6.349
26	569258	216.362	0	0	5.168
27	577060	364.477	3	0	5.947
28	5826	136.214	0	1	0.629
29	636750	208.254	3	0	2.788
30	6430112	369.477	3	1	0.933
31	6432176	204.351	0	0	4.123
32	6912	152.146	5	5	-2.43
33	70825	206.324	1	1	4.388
34	7311	206.324	1	1	4.388
35	7459	140.266	0	0	3.948
36	7668	120.192	0	0	3.228
37	7734	134.218	0	0	3.714
38	7947	120.192	0	0	3.288
39	8182	170.335	0	0	5.846
40	85238955	202.335	0	0	3.927
41	85927	142.282	0	0	4.524
42	8998	122.12	4	4	-1.919
43	90803	104.105	3	2	-1.153
44	91710272	236.35	2	0	3.592
45	12303891	222.366	1	1	3.338
46	123409	330.503	4	2	5.568
47	75487878	428.478	6	2	3.96

The molecular descriptors of 47 phytochemicals of *Celastrus paniculatus* seeds identified through GC-MS analysis were evaluated using the Lipinski filter protocol of Discovery Studio version 4.0. Results indicate that 47 compounds passed the filter. The criterion for Lipinski filter is: MW</= 500 Da, HBD</=5, HBA</=10, AlogP</=5, (MW: Molecular Weight; HBD: H-bond Donors; HBA: H-bond Acceptors; AlogP: octanol-water partition coefficient; RB: Rotatable bonds).

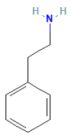
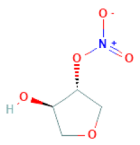
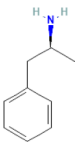
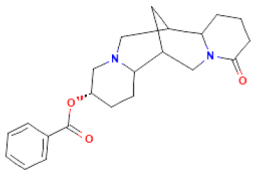
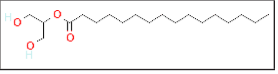
Table 5. ADMET parameters calculated for the identified phytochemicals of *C. paniculatus*

Sr. No.	Compound (PubChem. Id)	Solubility	BBB level	CYP2D6	Hepatotoxicity	Absorption	PPB
1	1001	4	3	false	false	0	false
2	107252	2	0	false	false	0	true
3	10955174	2	1	false	true	0	true
4	11053257	2	0	false	true	0	true
5	11903	3	0	false	false	0	true
6	12100	3	0	false	false	0	true
7	12260646	5	3	false	false	0	false
8	12388	2	0	false	false	2	true
9	13304974	2	0	false	false	0	true
10	139989	2	0	false	true	1	true
11	14092	3	0	false	false	0	true
12	14095	3	0	false	false	0	true
13	15505	3	0	false	false	0	true
14	15506	2	0	false	false	0	true
15	15653	2	0	false	false	0	true
16	21205	2	0	false	false	1	true
17	222285	5	4	false	true	1	false
18	28455	2	0	false	false	1	true
19	300476	2	0	false	true	1	true
20	31405	2	0	true	true	0	true
21	35412	3	0	false	false	0	true
22	35768	2	0	false	false	2	true
23	42953	5	4	false	false	1	false
24	439255	5	4	false	false	3	false
25	529436	2	0	false	true	1	true
26	5370859	2	1	false	false	0	true
27	545627	2	0	false	false	2	true
28	569258	2	0	true	false	1	true
29	577060	1	0	true	false	1	true
30	5826	4	2	false	false	0	false
31	636750	3	1	false	true	0	true
32	6430112	3	3	false	false	0	false
33	6432176	2	0	false	true	0	true
34	6912	5	4	false	false	3	false
35	70825	2	0	true	true	0	true
36	7311	2	0	true	true	0	true
37	7459	2	0	false	true	0	true
38	7668	3	0	false	false	0	true
39	7734	3	0	false	true	0	true
40	7947	3	0	false	true	0	true
41	8182	2	0	false	false	1	true
42	85238955	2	0	false	false	0	true
43	85927	2	0	false	true	1	true
44	8998	5	4	false	true	1	false
45	90803	5	4	false	true	1	false
46	91710272	2	1	false	false	0	true
47	12303891	2	1	false	true	0	true
48	123409	3	1	false	false	1	false
49	75487878	3	4	false	false	0	true

activity based on the structure-activity relationship. The results are expressed in terms of the probability values, probability of activity (Pa) and probability of inactivity (Pi). The range of likelihood of activity is calculated by the following parameters:

P(a) < 0.5 - likely to be inactive; 0.5 < P(a) < 0.7 - likely to be active, P(a) > 0.7 - more likely to be active. (P(a): probability of activity, P(i): probability of inactivity)

Table 6. Bioactive compounds with favourable pharmacological profiles identified in the seeds of *C. paniculatus*

Sr. No.	Name	(PubChem. Id)	2D Structure
1	Phene thylamine	1001	
2	trans-Tetrahydro-3,4-furandiol mononitrate	12260646	
3	Dextroam phetamine	5826	
4	13alpha-Benzoylo xylupanine	6430112	
5	2-Palmito ylglycerol	123409	

Biological activity prediction showed that all five compounds exhibit a higher probability of activity in relation to neurological disease management. From the results, it can be seen that phenethylamine may be suitable for anxiety disorders. trans-tetrahydro-3,4-furandiol mononitrate can be an anti-ischemic agent and may be used for phobic disorders treatment. Also, the compound is more likely to be a G Protein-Coupled Receptor (GPCR) inhibitor. The compound, dextroamphetamine, can be used for phobic disorder treatment. The compound, 13alpha-Benzoyloxylupanine, has a high probability of acting as a neuroprotective agent and acetylcholine antagonist. The compound, 2-palmitoylglycerol, is more likely to be a GABA aminotransferase inhibitor.

4. Discussion

Drug discovery for nervous system disorders faces challenges due to the complex nature of the disease and poor pharmacological features of drug candidates. In the present study, by leveraging the traditional practice and the scientific data that support the neuroprotective effect of Ayurvedic medicinal plant *C. paniculatus*, the present study attempted to explore the phytochemicals of the plant seeds with favourable pharmacological profiles.

In our effort to identify the bioactive compounds present in the methanolic and ethanolic extracts of CP seeds, we obtained 32 compounds from the methanol and 18 compounds from the ethanolic extracts. The pharmacokinetic parameters of these molecules play a key role in considering them as functional leads, and they must be bioavailable and efficiently

Table 7. Neurological activity prediction of selected compounds of *C. paniculatus* using the PASS server

Sr. No.	Compound	P(a)	P(i)	Activity
1	Phenethylamine	0.93	0.00	Anxiety *disorder*
2	trans-Tetrahydro-3,4-furandiol mononitrate	0.96 0.81 0.76	0.00 0.03 0.01	Anti-ischemic, cerebral Phobic disorders treatment GPCR inhibitor
3	Dextroamphetamine	0.87 0.75	0.01 0.00	Phobic disorders treatment
4	13alpha-Benzoyloxylupanine	0.86 0.81	0.00 0.00	Nootropic Acetylcholine antagonist
5	2-Palmitoylglycerol	0.71	0.00	GABA aminotransferase inhibitor

delivered to reach their molecular target in an adequate concentration. The effective application of *in silico* predictions can assess these properties before taking them for screening against disease targets. The Lipinski's filter approves the molecules as orally administrable, and the ADMET parameters filter the molecules based on drug metabolism and toxicity. Virtual prediction of the components identified from *C. paniculatus* seeds using the GC-MS method conveys that:

(a) 47 compounds possess drug-like properties in terms of oral bioavailability based on their physicochemical characteristics.
(b) Out of 47 screened compounds, five compounds, phenethylamine, trans-tetrahydro-3,4-furandiol mononitrate, dextroamphetamine, 13alpha-benzoyloxylupanine, and 2-palmitoylglycerol, passed the ADMET filter with adequate solubility, good intestinal absorption, with no hepatotoxicity and exhibited BBB crossing potential.
(c) Neurological activity prediction indicates that these compounds have a higher probability of activity, to consider them as therapeutic agents for chronic neurological disorders.

The CNS stimulant property of the identified compound, phenethylamine, was reported previously[24]. The compound belongs to the class of illicit drugs that come under the class of monoamine alkaloids. Studies indicate that the compound can be used for mood disorders, which justifies the result of the neurological activity prediction of this study. Reports show that it could also act as a neurotransmitter in the human brain to a lesser extent[25]. The other compound, dextroamphetamine, belongs to the class of CNS stimulant drugs and is used for attention deficit hyperactivity disorder and narcolepsy[26]. 2-Palmitoylglycerol is a fatty acid ester, and studies show that it could increase the binding affinity of 2-arachidonoylglycerol to cannabinoid receptors in the brain[27]. This correlates with the neurological activity prediction of this study, where the result showed a possible inhibitory effect of 2-Palmitoylglycerol against GABA aminotransferase. Also, *in vivo* experiments evidence that 2-Palmitoylglycerol could increase the inhibitory effect of 2-arachidonylglycerol against tumour necrosis factor-α (TNF-α) to reduce pain and inflammation[28]. No therapeutic indications are reported for the compound trans-tetrahydro-3,4-furandiol mononitrate and dextroamphetamine.

It should be noted that compound annotation in the present study was based on GC-MS spectral library matching and therefore represents tentative identification. The compounds such as dextroamphetamine and phenethylamine are not commonly reported as natural metabolites of *C. paniculatus*, and their detection may be attributed to spectral similarity with structurally related phytochemicals, co-elution, or database overmatching. Hence, confirmation using authentic reference standards or advanced analytical techniques such as LC–MS/MS or NMR is required before definitive assignment. Future targeted metabolomic analyses are required to confirm the identity of selected bioactive compounds. Also, the ADMET properties reported in this study are derived from computational prediction models and therefore represent preliminary pharmacokinetic estimates that require validation through experimental studies. Additionally, since PASS predictions are derived from structure–activity relationship modelling, the reported neurological activities represent probability-based estimates and should be interpreted as preliminary indicators requiring validation through docking studies and experimental assays.

Here, the effective application of *in silico* methods helped to identify five potent compounds that are orally bioavailable, least toxic, and have BBB crossing potential from a set of 49 compounds. Since the compounds with unexplored biological activities are marked with promising pharmacological parameters based on computational predictions, their possibility to act as neuroprotective agents can be studied by estimating their interactions with corresponding molecular targets of CNS disorders. This considerable reduction in the number of compounds to be tested in the next level of screening could also help in minimising the number of animal sacrifices in pre-clinical studies.

5. Conclusion

This study evaluated the biological activity of phytochemicals present in the methanol and ethanol extracts of seeds of the Ayurvedic medicinal plant *C. paniculatus,* considering its therapeutic potential as a neuroprotective agent. Based on the computational predictions, the plant seeds can be an important source for leads with drug-like properties. Out of 49 compounds identified through GC-MS analysis, five

compounds, phenethylamine, trans-tetrahydro-3,4-furandiol mononitrate, dextroamphetamine, 13alpha-benzoyloxylupanine, and 2-palmitoylglycerol were found as promising candidates based on Lipinski filter, ADMET and neurological activity predictions. The identified compounds with favourable predicted pharmacological features represent preliminary candidates from computational screening and may be taken forward for target-based molecular docking, *in vitro* assays, and *in vivo* validation to assess their suitability as potential lead molecules for neurological disorders.

Traditionally employed medicinal plants are known to be beneficial for chronic disorders, including neurological disorders. Still, limited analysis has been performed by the research community to explore their therapeutic properties and develop successful drug candidates. The lack of knowledge about their biological activities prevented them from further screening and development. The findings of this study raise new possibilities to overcome these impediments and to identify promising compounds of natural origin with desirable therapeutic potential.

6. References

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