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In vivo and *in silico* studies on the nootropic effect of *Strychnos innocua* Del. (Loganiaceae) leaf ethanol extract

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Abstract

Nootropics, often referred to as cognitive enhancers, are substances that improve cognitive functions, such as memory, learning, attention, and executive processes. Memory is a fundamental cognitive function that allows individuals to encode, store, and retrieve information essential for their daily activities. Disruptions in memory processes can significantly impair learning, decision making, and overall quality of life. While synthetic nootropics have been extensively studied, their side effects and variable efficacy have sparked interest in natural alternatives, particularly plant-derived extracts rich in bioactive compounds. This study aimed to evaluate the nootropic effect of *Strychnos innocua* leaf ethanol extract using *in vivo* and *in silico* models. The bioactive compounds present in the extract were identified using GC-MS analysis. The Y-maze test was used to evaluate the *in vivo* nootropic activity of the extract in adult male Swiss albino mice. Graded extract doses (200 – 800 mg/kg) were used in this study. In the *in silico* study, the binding interactions of the bioactive constituents of the extract were evaluated using iGEMDOCK. GC-MS analysis revealed the presence of 40 compounds, including myo-inositol 4-C-methyl, vitamin E, 9,12,15-octadecatrienoic acid (Z, Z, Z), and phytol. The *in vivo* study showed a non-dose-dependent effect, with significant improvement in novel arm preference at 200 mg/kg, indicating enhanced spatial working memory. Higher doses (400–800 mg/kg) resulted in reduced cognitive performance, which aligns with the inverted-U model of cognitive function. In addition, the *in silico* study outcome showed a good binding interaction of its bioactive composition, such as myo-inositol, 4-C-methyl, 9,12,15-octadecatrienoic acid (Z, Z, Z), and phytol, to the active site of acetylcholinesterase. The results of this study show that *S. innocua* leaf ethanol extract enhances cognitive function in mice, likely through the modulation of cholinergic and monoaminergic neurotransmission.

Keywords: Nootropic, Acetylcholinesterase, *Strychnos innocua*, GC-MS

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Introduction

Nootropics, often referred to as "smart drugs" or cognitive enhancers, are substances that improve cognitive functions, such as memory, learning, attention, and executive processes. These compounds have gained significant interest in both clinical and research settings because of their potential applications in treating neurodegenerative disorders, age-related cognitive decline, and enhancing cognitive performance in healthy individuals (Suliman *et al*., 2016). While synthetic nootropics, such as piracetam and racetams, have been extensively studied, their side effects and variable efficacy have sparked interest in natural alternatives, particularly plant-derived extracts rich in bioactive compounds, such as alkaloids, flavonoids, and polyphenols (Kennedy *et al*., 2011). Traditional medicine, which relies on centuries-old knowledge of natural products, has been a cornerstone of healthcare in many cultures, particularly in regions with limited access to modern pharmaceuticals (Che *et al*., 2017). Plant extracts have long been used in traditional medicine to support cognitive health; however, their nootropic potential often lacks rigorous scientific validation.

Strychnos innocua Del., a member of the Loganiaceae family, is a deciduous shrub or small tree that is widely distributed across tropical and subtropical regions of Africa. Traditionally, various parts of *Strychnos innocua* have been used in ethnomedicine to treat a range of ailments, including fever, pain, infections, and neurological conditions (Adesina, 1982). The leaf ethanol extract of *Strychnos innocua* is of particular interest because of its rich phytochemical profile, which includes alkaloids, flavonoids, and phenolic compounds, known for their antioxidant, anti-inflammatory, and neuroprotective properties (Ojewole, 2008). These phytochemicals are hypothesized to modulate neurotransmitter systems, enhance cerebral blood flow, and protect against oxidative stress, all of which are critical mechanisms underlying nootropic activity (Mukherjee *et al*., 2007).

In vivo studies provide valuable insights into the physiological effects of plant extracts, allowing researchers to evaluate their efficacy and safety in living systems. Common models, such as rodents, are used to assess cognitive performance through behavioral tests, such as the Morris water maze, Y-maze, and novel object recognition tests, which assess spatial memory, working memory, and recognition memory, respectively (Vorhees and Williams, 2014). These studies are complemented by *in silico* approaches, which leverage computational tools such as molecular docking, pharmacophore modeling, and quantitative structure-activity relationship (QSAR) analyses. *In silico* studies can identify bioactive compounds, their potential targets, and their binding affinities to key receptors or enzymes involved in cognitive processes, such as acetylcholinesterase, N-methyl-D-aspartate (NMDA) receptors, or GABAergic pathways (Ekins *et al*., 2007). The integration of *in vivo* and *in silico* methodologies offers a comprehensive strategy for identifying and characterizing novel nootropic agents from plant extracts. Hence, this study aimed to evaluate the nootropic effect of *Strychnos innocua* leaf ethanol extract using *in vivo* and *in silico* models.

Materials and Method

Plant collection and identification

Fresh leaves of *Strychnos innocua* were collected from the Jos-North Local Government Area, Plateau State, Nigeria. The species was identified and authenticated by Mr. Jeffrey Azila, a taxonomist at the Federal College of Forestry, Jos, Plateau State, Nigeria.

Extraction

The thoroughly washed leaves were air-dried at room temperature. An electric milling machine was employed to pulverize the dried leaves, and 2 kg of the pulverized leaves were macerated in 6 litres of 70% ethanol at room temperature for 72 h with periodic agitation. The resulting solution was filtered successively through a mesh sieve, cotton wool, and 110 mm Whatman filter paper. The filtrate was concentrated using a water bath at 40°C. The obtained crude extract was stored at 4°C in a refrigerator until use.

Gas chromatography-mass spectrometry (GC-MS) analysis

The ethanol extract was analyzed by GCMS-QP2010 SE (Shimadzu Japan) comprising Shimadzu QP-2010 GC with QP-2010 Mass Selective Detector (MSD), operated in the EI mode, electron energy of 70 eV, scan range of 45-700 amu, and Shimadzu GCMS solution data system. The Gas chromatography column was an Agilent HP-5 MS fused silica capillary with a 5% phenyl-methylpolysiloxane stationary phase, with a length of 30 m, internal diameter of 0.25 mm, and film thickness of 0.25 μm. The carrier gas was helium 99.999% with a flow rate of 1.61 mL/min. The program used for gas chromatography oven temperature was 60 - 160°C at a rate of 15°C/min, then held at 160°C for 1 min, followed by160 - 280°C at a rate of 20°C/min, and then held at 280°C for 2 min. The injection port temperature was 250°C, interface temperature was 250°C while ion source temperature was 200°C. The extract was dissolved in methanol and filtered through 0.45 μm and1.0 μL was injected into the GC using autosampler and the split mode with ratio of 25:1. Individual constituents were identified by comparing their mass spectra with those of known compounds in the NIST Mass Spectral Library.

Animals

Swiss albino mice of both sexes (weight range) housed at the Animal Facility of the Department of Pharmacology, Novena University, were used. The animals were housed in

standard cages under standard laboratory conditions in accordance with the "NIH Guidelines for Laboratory Animal Care and Use" (National Research Council, 1985) and Novena University regulations for laboratory animal use.

Y-maze test

This test was carried out using a Y-maze apparatus in accordance with the method described by Dember and Fowler (1958). Twenty-five Swiss albino mice of either sex were used in the study. The animals were randomized into five groups of five animals each and treated as follows: Group 1 received distilled water (10 ml/kg), Groups 2 – 4 received the extract (200, 400, and 800 mg/kg p. o., respectively), and Group 5 was administered diazepam (2 mg/kg i.p.). After 1 h of oral administration or 30 min of i. p. administration, each animal was placed on the apparatus for 5 min, and the number of entries, total alternation, and novel arm preference were observed and recorded.

In silico studies

PASS Prediction

The possible biological activities of a chemical compound are predicted using the online software database program prediction of activity spectra for substance (PASS). The program aids in estimating the biological activities of chemicals, such as organic chemicals (having molecular weights of 50–1250 Da) or plant chemicals. In this software, compounds that must be evaluated for biological activities are analyzed for structural activity relationships using a training set containing approximately 205,000 chemical structures that show almost 3750 different biological activities (Lagunin *et al*., 2000).

Ligand retrieval and preparation

Ligands used in this research were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). These compounds were then imported into the Biovia Discovery Studio 2021 Client 21.1 software, where they were converted from SD files to PDB files, as iGEMDOCK only accepts PDB file format.

Docking

The docking of the prepared compounds and proteins was performed using IGEMDOCK software. The ligands were docked into their respective protein binding sites by standard precision (SP) protocol and post docking visualization and analysis of docked poses was also carried out with Biovia Discovery Studio 2021 Client 21.1 software (Hsu *et al*., 2011).

Statistical analysis

The results are expressed as the mean ± standard error of the mean (SEM). One-way analysis of variance (ANOVA), followed by Dunnett's post hoc test, was used to test for significance. *Statistical significance was set at* $P < 0.05$. GraphPad Prism (version 8.0) was used for analysis.

Results

Gas Chromatography- Mass Spectrometry (GC-MS)

GC-MS analysis revealed the presence of 40 compounds in the extract, including phytol, vitamin E, myo-inositol 4-C-methyl-, and 9,12,15-Octadecatrienoic acid (Z, Z, Z), which were represented by the respective peaks in the chromatogram (Figure 1). The names, retention times, peak heights, area percentages, and compositions of the identified compounds are listed in Table 1.

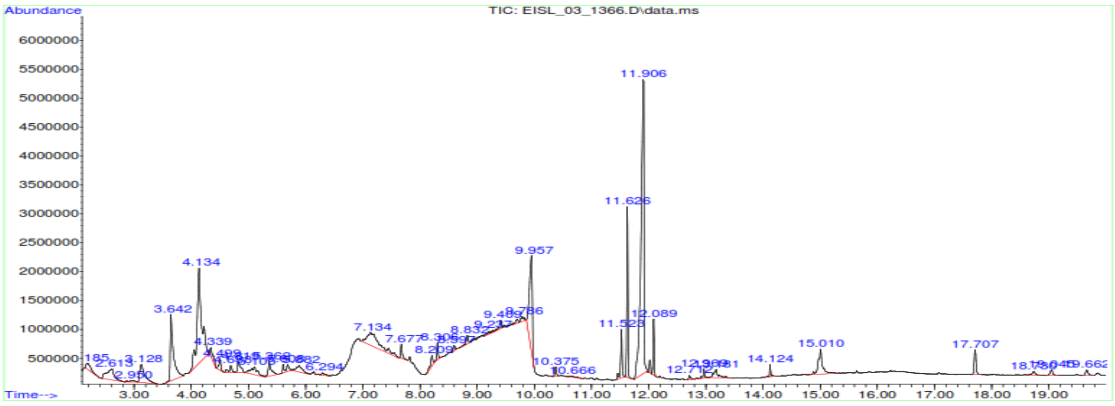

Figure 1: GC-MS chromatogram of *Strychnos innocua* ethanolic leaf extract

Table 1: Chemical composition of *Strychnos innocua* ethanolic leaf extract

Peak No.	Compound Name	Retention Time (min)	Peak Height	% Composition
1	2-Propenoic acid, 2,3-dichloro-	2.185	107109	0.88
2	dl-Threitol	2.613	191176	2.60
3	Propanenitrile, 3-amino-2,3-di(hydroxymino)-	2.950	28216	0.30
4	Thymine	3.128	310329	0.29
5	2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one	3.642	1150623	6.54
6	5-Hydroxymethylfurfural	4.134	1644437	13.82
7	Methylene chloride	4.339	141692	0.76
8	Salicylic acid	4.499	189667	0.61
9	1-Hexadecanol, 2-methyl-	4.688	121469	0.70
10	2,6-Octadienoic acid, 3,7-dimethyl -, (E)-	4.819	195944	1.06
11	Succinic acid, 2-decyl 3-methylbutylester	5.105	136455	1.53
12	Allopurinol	5.362	246772	1.43
13	Benzoic acid, 2-methoxy-	5.608	151498	0.85
14	Octanoic acid, silver (1+) salt	5.882	111347	1.21
15	Trehalose	6.294	38704	0.26
16	Methyl-. beta. -D-thiogalactoside	7.134	221548	4.91
17	3-Deoxy-d-mannoic lactone	7.677	248109	0.74
18	Cyclopropanecarboxylic acid, undecyl ester	8.209	179982	0.80
19	2H-Tetrazole, 2-(1,3-dioxolan-4-yl methyl)-	8.306	301732	0.80
20	Myo-Inositol, 4-C-methyl-	8.597	96509	0.40
21	3-O-Methyl-d-glucose	8.832	145494	0.61
22	4-O-Methylmannose	9.237	36454	0.44
23	Scyllo-Inositol,1-C-methyl-	9.409	144193	0.67
24	Thiophene, tetrahydro-2-methyl-	9.786	86432	0.81
25	n-Hexadecanoic acid	9.957	1705331	8.50
26	Docosanoic acid, ethylester	10.375	164034	0.50
27	D-chiro-Inositol,3-0-(2-amino-4-2,3,4,6-tetradeoxy-alpha-D-arabino-hexopyranosyl)-	10.666	18645	0.24
28	9,12,15-Octadecatrienoic acid, methylester, (Z,Z,Z)	11.523	837754	2.20
29	Phytol	11.626	2954462	5.78
30	9,12,15-Octadecatrienoic acid (Z, Z, Z)	11.906	5083538	26.60
31	Ethyl 9,12,15-octadecatrienoate	12.089	972260	2.50

32	9,12,15-Octadecatrien-1-ol, (Z, Z, Z)	12.712	70085	0.23
33	1,4,8-Dodecatriene, (E, E, E)	12.969	159857	0.60
34	Undecanoicacid,phenylmethylester	13.181	144662	1.24
35	Hexadecanoic acid,2-hdroxy-1-(hydroxymethyl)ethylester	14.124	211588	0.50
36	Fumaric acid, pent-4-en-2-yl tridecylester	15.010	432049	3.20
37	Vitamin E	17.707	432273	1.41
38	Methyltris(trimethylsiloxysilane)arsane	18.730	60993	0.40
39	Methyltris(trimethylsiloxy)silane	19.045	89146	0.43
40	Tetrasiloxane, decamethyl-	19.662	90545	0.43

Y maze Test

Pretreatment of the animals with the extract and diazepam increased their cognitive function, as observed by an increase in novel arm preference. The effect was however non-dose dependent with the extract as the lowest test dose (200 mg/kg) gave a better effect which was significant ($P < 0.05$) (Figure 2). The cognitive percentage also increased in the respective treated groups compared to the control group. (Table 2)

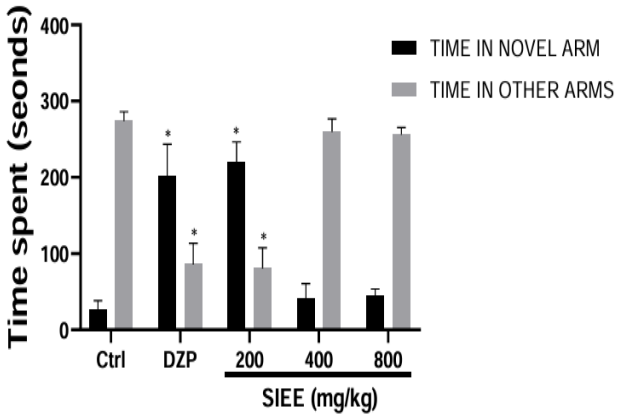

Figure 2: Nootropic effects of the extract. Values expressed as mean ± SEM, n = 5, *P < 0.05, using one-way ANOVA. Ctrl = Control, DZP= Diazepam, SIEE= *Strychnos innocua* ethanolic extract

Table 2: Nootropic effect of the extract on cognition

Treatment	Dose (mg/kg)	Total Entries	Novel preference percentage (%)
Control (Distilled water 10 ml/kg)	–	8.000 ± 1.528	8.653 ± 4.021
DZP	2	6.750 ± 3.614	71.50 ± 15.95
SIEE	200	4.500 ± 0.6455	73.17 ± 9.055
	400	3.750 ± 1.377	31.75 ± 22.66
	800	10.50 ± 3.122	33.17 ± 18.74

Values are expressed as mean ± SEM, n = 5, *P < 0.05 using one-way ANOVA test. DZP= Diazepam, SIEE= *Strychnos innocua* leaf ethanol extract

In silico studies

PASS prediction identified four bioactive compounds with good nootropic activity: vitamin E, phytol, myo-inositol 4-C-methyl, and 9,12,15-Octadecatrienoic acid (Z, Z, Z). Molecular docking studies revealed that these compounds exhibited good binding interactions with acetylcholinesterase. Vitamin E had two hydrogen bonds, one pi-sigma and akyl bonds respectively. Phytol had three akyl bonds, while myo-inositol 4-C-methyl- had three pi-donor hydrogen bonds (Figure 3 – 7; Table 3).

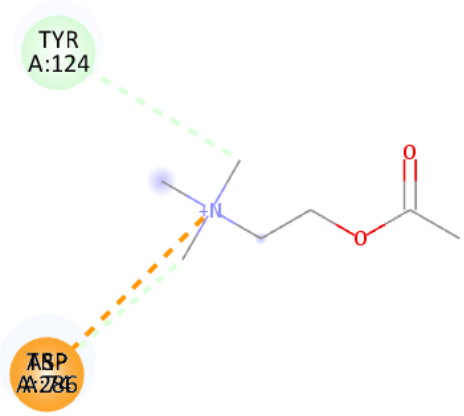

Figure 3: Binding interaction of acetylcholine with acetylcholinesterase enzyme

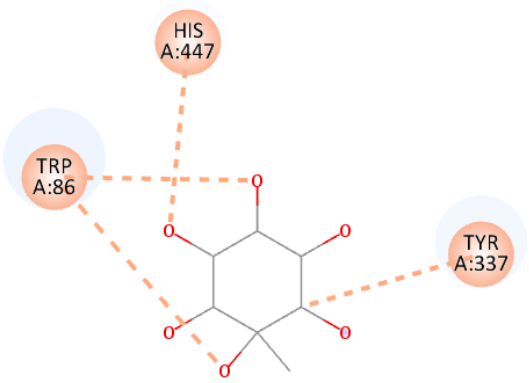

Figure 4: Binding interaction of myo-inositol, 4-c-methyl with acetylcholinesterase enzyme

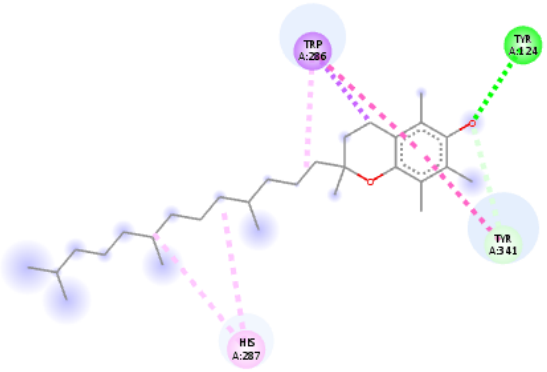

Figure 6: Binding interaction of vitamin E with acetylcholinesterase enzyme

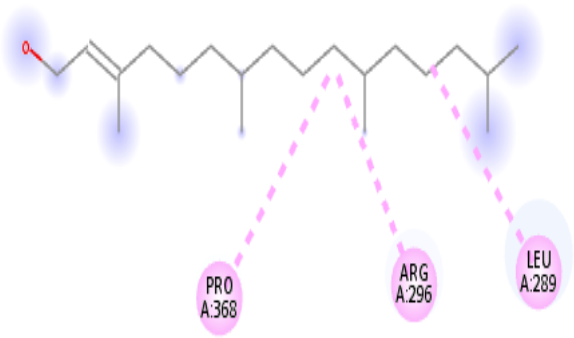

Figure 5: Binding interaction of phytol with acetylcholinesterase enzyme

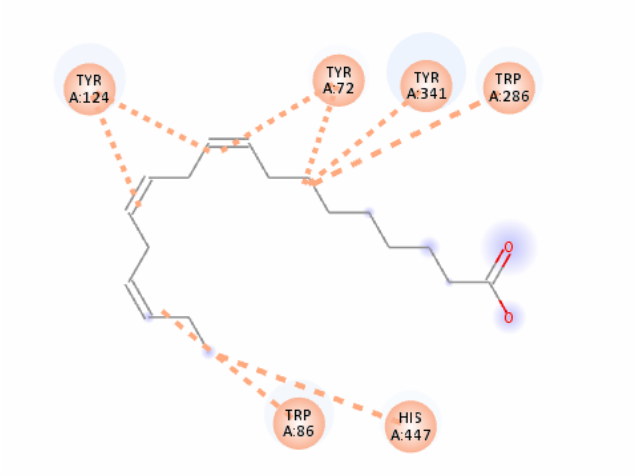

Figure 7. Binding interaction of 9,12,15-octadecatrienoic acid (ZZZ) with acetylcholinesterase enzyme

Table 3: Binding affinity of the compounds

Compounds	Binding Affinity (Kcal/Mol)	Interactions
Vitamin E	-7.97	Hydrogen Bonds: ILE A124, and THR A431 Pi-Sigma: TRP A286 Pi-Alkyl: PHE A331
Phytol	-4.90	Alkyl: LEU A283, PRO A368 and ARG A296
Myo-inositol,4-c-methyl	-5.42	Pi-Donor Hydrogen Bonds: TRP A86, HIS A447 and TYR A337
9,12,15-Octadecatrienoic Acid (Z, Z, Z)	-5.57	**Pi-Alkyl:** TYR A124, TYR A72, TYR A311, TRP A286, TRP A86 and HIS A447
Acetylcholine*	-4.43	**Hydrogen Bonds:** TYR A124 **Attractive charge:** ASP A286

Reference: * = Standard

Discussion

This study investigated the nootropic effect of *Strychnos innocua* ethanol leaf extract in mice using the Y-maze test, a widely used behavioral model for assessing spatial working memory and exploratory behavior. The Y-maze capitalizes on the natural curiosity of rodents to explore novel environments, making it a valuable tool for evaluating interventions that affect cognition (Kraeuter *et al*., 2019). An initial study by the authors on the phytochemical constituents of the extract revealed the presence of alkaloids, flavonoids, glycosides, saponins, tannins, steroids, and phenols (Enegide *et al*., 2025). Alkaloids, flavonoids, and glycosides are known for their neuroprotective and cognitive-enhancing properties (Bellavite 2023). Flavonoids have been shown to improve various aspects of memory, including encoding, consolidation, and retrieval (Spencer, 2009). Glycosides, such as ginsenosides, enhance hippocampal synaptic density and acetylcholine release, whereas alkaloids, such as huperzine A, act as acetylcholinesterase (AChE) inhibitors, boosting cholinergic neurotransmission, which is crucial for memory formation (Li *et al*., 2018). Also, in that study by the authors, the acute oral toxicity of the extract was evaluated and the result showed that the lethal dose of the extract is greater than 5000 mg/kg p.o in mice (Enegide *et al.* 2025). This indicates that the extract is safe in mice at doses up to 5000 mg/kg when administered orally.In this study, the results revealed that the effect of the extract *in vivo* was non-dependent on the dose. Mice treated with 200 mg/kg of the extract showed significantly higher novel arm preference than the control and higher doses, indicating enhanced spatial working memory. This cognitive boost at moderate doses may result from the modulation of neurotransmitters, such as dopamine and serotonin, which are central to novelty-seeking behavior and cognitive flexibility (Baudonnat *et al*., 2011; Izquierdo *et al*., 2017). Dopamine improves working memory and decision-making through its action in the prefrontal cortex (Di Domenico and Mapelli, 2023), whereas serotonin promotes attention to novelty (Meneses, 2015). In contrast, higher doses (400 and 800 mg/kg) reduced the number of novel arm entries, suggesting potential sedative or impairing effects. This trend aligns with the inverted-U hypothesis, which posits that cognitive enhancers exert optimal benefits at moderate doses but become counterproductive at higher doses (Arnsten 2009). Overactivation of cholinergic or dopaminergic pathways at higher doses may lead to receptor desensitization or overstimulation of inhibitory feedback loops (Li *et al*., 2021). PASS online virtual screening, which predicts biological activity based on molecular structure with over 95% accuracy (Filimonov *et al*., 2014), identified four compounds within the extract with high potential for cognitive enhancement, which were among the 40 compounds identified in the GC-MS analysis. These include myo-inositol, 4-C-methyl, Vitamin E, α-linolenic acid (9,12,15-Octadecatrienoic acid) and Phytol. Myo-inositol 4-C-methyl showed strong hydrogen bonding and

hydrophobic interactions with AChE, indicating potential reversible inhibition that could enhance synaptic plasticity and memory. Vitamin E exhibits antioxidant activity and AChE-stabilizing effects, protecting against oxidative stress and preserving cholinergic signaling (Perrig et al., 1997). α-Linolenic acid demonstrated partial AChE inhibition and membrane-stabilizing properties, *supporting neurotransmitter release and cognitive function (Yehuda et al., 2005). Phytol formed stabilizing interactions with A*ChE, suggesting mild inhibition and protective effects on cholinergic neurons (Costa *et al*., 2014).

Conclusion

The results of this study show that the ethanol leaf extract of S. *innocua* enhances cognitive function in mice, likely by modulating cholinergic and monoaminergic neurotransmission. These effects are consistent with *in silico* predictions showing AChE inhibition and other neuroactive interactions by the identified compounds.

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