

Research Article

In -Vivo Neuropharmacological and *In-Silico* Study with GABA & 5-HT to Discover Potent Anxiolytic Compound from *Clerodendrum viscosum* Vent. (Family: *Verbenaceae*)

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Abstract

There is a raising focus on significance of the medicinal plants in addition to traditional plants healthiness systems in resolving the healthcare crisis of the globe. In this research work *in-vivo* neuropharmacological study which performed by open field and hole cross test with albino mice shows that the methanolic extract of *Clerodendrum viscosum* has moderate Central Nervous System (CNS) depressant activity. It also increases significantly Phenobarbital (45 mg/kg) induced onset of sleeping time and duration of sleeping time in mice for *Clerodendrum viscosum* is 12.88 mins, 11.4 mins and 104.2, 135.8 mins for 250 mg and 500 mg dose respectively. The effect of *Clerodendrum viscosum* extract on Aminophylline (280mg/kg) induced convulsion in mice has raised the threshold of seizure and exerted a statistically significant dose dependent delay on the onset of clonic and tonic convulsion for 250 mg and 500mg is 14.04, 39.824 and 14.6, 48.74 respectively when compared to control and in case of standard drug; diazepam (2mg/kg), the effect is minimal than the control. From *In-silico* pharmacological study it has been observed that the anxiolytic activity of *Clerodendrum viscosum* may be due to Scutellarin and Xylitol which has been found from their gliding energy with Gamma-Aminobutyric Acid (GABA) (PDB id: 4COF) -50.78, -27.211 respectively and due to Scutellarin, Xylitol and 3-Deoxy-d-mannonic lactone with 5-HT (PDB id: 4IAR) the gliding energy is -49.52, -25.185, -29.397 respectively which predicts that

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these compound may have potential anxiolytic activity. Taken all together, the present study demonstrates that methanolic extracts of *Clerodendrum viscosum* shows significant Central Nervous System (CNS) depressant activity as well as anxiolytic activity which is comparable to standard (Diazepam). From *In-Silico* Pharmacological study it is observed that the anxiolytic activity of *Clerodendrum viscosum* may be due to Scutellarin, Xylitol and 3-deoxy d-mannonic lactone either alone or synergistic effect of two or more compound interactions. So, for the molecular interaction analysis such as Scutellarin and Xylitol. Molecular docking with GABA glide score was presented as a method in this research.

Keywords: *Clerodendrum viscosum*; GABA (PDB id: 4COF); 5-HT (PDB id: 4IAR); Neuropharmacology.

Introduction

The plant that have therapeutic actions or wield beneficial pharmacological outcomes on animal bodies are usually assigned as “Medicinal Plants”. While there is no perceptible morphological property in medicinal plants producing with them, so far, they have several special qualities that create them medicinally so important. Over the last few decades, use of herbal drugs has been emphasized due to their easy availability, therapeutic potential, least side effects and minimum cost. At present nearly 80% of the world population relies on plant-based drugs for their health care need. Presently, phytoconstituents are playing pivotal role for development of novel compounds, which might be crucial for maintaining a healthy society [1]. The human civilization has been maintaining an intimate relationship with the plants from time immemorial. They depend on plants and other natural sources for their well-being and survival. Various plants still available in the nature are yet to be explored for their medicinal potential [2]. Uses of computational chemistry to discover, enhance, or study drugs and related biologically active molecules. The most fundamental goal is to predict whether a given molecule will bind to a target and if so, how strongly. Molecular mechanics or molecular dynamics are most often used to predict the conformation of the small molecule and to model conformational changes in the biological target that may occur when the small molecule binds to it [3].

Materials and Methods

Collection and preparation of leaf extract

The plant leaves *Clerodendrum viscosum* were collected at their fully mature form, from Foy’z lake hill tracts, Chittagong, Bangladesh. The plant samples were identified by Dr. Sheik Baktier, Chittagong University, Bangladesh. Leaves of *Clerodendrum viscosum* were carefully separated, cleaned, shade dried, mechanically ground and coarsely powdered. About 100 gm of air-dried powdered material was extracted with 98.5% methanol in a Soxhlet extractor for 30 hours. It was concentrated to dryness under reduced pressure and controlled temperature (40-50°C) using rotary evaporator. The methanolic extract yielded a green Sticky mass weighing 100 gm. The methanolic extract was concentrated by vacuum distillation to

dryness; the yield obtained was 12.5% w/w with respect to dried leaf. The collected leaf extract was stored in a desiccator. The aim of the present study is to find out if the extract had any effect on central nervous system. In addition, this study performed to discover potent anxiolytic compound from *Clerodendrum viscosum*.

Drugs and chemicals

All the chemicals and solvents used in this study were of analytical grade and standards drug diazepam were obtained from Square Pharmaceuticals Ltd.

Experimental animal

Young Swiss albino mice of either sex, weighing between 20-25 gm, were collected from Animal Research Branch of BCSIR. Animals were maintained under standard environmental conditions [(27.0 ± 1.0) °C, relative humidity (55-65) % and 12 h light/12 h dark cycle] and free access to feed and water ad libitum. Prior to experimentation, the animals were acclimatized to laboratory condition for one week. All protocols for animal experiment were approved by the Institutional Ethics Committee [4].

In vivo neuropharmacological study

Neuropharmacology is the study of how drugs affect cellular function in the nervous system, and the neural mechanisms through which they influence behavior. For the neuropharmacology tests it takes four different studies. They are (1) Open field method, (2) Hole cross method, (3) Prolongation Effect on Phenobarbital Induced Sleeping Time in Mice, (4) Aminophylline Induced Convulsion in Mice.

Open field test

In open field test, the animals were divided into control, positive control, and test groups containing five mice each. The test groups received extracts (100, 200 mg/kg) body weight orally whereas the control group received saline water. Like hole cross test, animals in positive control group received diazepam (1 mg/kg). The floor of an open field of half square meter was divided into a series of squares each alternatively colored black and white. The apparatus had a wall of 40 cm height. The number of squares visited by the animals was counted for 3 min at 0, 30, 60, 90, and 120 min after oral administration of the test drugs and the standard [5].

Hole-cross test

A wood partition was fixed in the middle of a cage having a size of 30 × 20 × 14 cm. A hole of 3 cm diameter was made at a height of 7.5 cm in the Centre of the cage. The animals were divided into control, positive control, and test groups containing five mice each. The test groups received extracts at the doses of (100,200 mg/kg) body weight orally whereas the vehicle control and positive control groups received vehicle due to observe variation and the standard drug diazepam (1 mg/kg) respectively. The number of passages of a mouse through the hole from one chamber to other was counted for a period of 3 min at 0, 30, 60, 90 and 120 min after oral administration of the test drugs and the standard [6].

Prolongation effect on phenobarbital induced sleeping time in mice

Eighteen male Swiss albino mice (20-28 g) were randomly divided into 3 groups (n = 6). Group I received phenobarbital (45 mg/

kg b.w; i.p.) and served as phenobarbital control. Group II and III received MECV (250 and 500 mg/kg b.w; i.p.) 30 min prior to the administration of phenobarbital (45 mg/kg b.w; i.p.). The time between the loss of the righting reflex and the regain of this reflex measured as the sleeping time [7].

Aminophylline induced convulsion in mice

Clerodendrum viscosum extract was evaluated for activity against aminophylline – induced convulsion. The adult Swiss albino mice were divided into four groups of six animals each. Group 1 received normal saline. Group 2 received diazepam 2 mg/kg one hour before induction of convulsion. Groups 3 and 4 received *Clerodendrum viscosum* 250 and 500 mg/kg p.o. respectively. The seizure was induced using aminophylline (280 mg/kg) [8].

In silico techniques

In silico techniques are developed particularly as an alternative to animal experimentation. This technique may be better alternatives for the drug and chemical testing, with reduced animal use up to some levels, since with the help of such software programs we can tailor make a new drug for the specific binding site and then in final stage animal testing is done to obtain confirmatory results [9].

Collection and preparation of ligand

The structure of Phyto-constituents of *Clerodendrum viscosum* were collected from (Goutam Ghosh et. al /articles/PMC4285639) related drug molecules from PubChem database was downloaded from (<https://pubchem.ncbi.nlm.nih.gov>). From this database comprise 12 bioactive compounds from *Clerodendrum viscosum*. Their ionization states were generated at pH 7.0±2.0 using default settings of Epik2.2 in Schrödinger Suite v11.2 Up to 32 possible stereoisomers per ligand was retained. This collected structures (ligands) prepared for further analysis [10,11].

Selection of desired ligand

The drug-like activity of the ligand molecules was categorized using ADME properties by QikProp module of Schrodinger Suit v11.2. The selected properties are known to influence metabolism, cell permeation, and bioavailability. QikProp generates physically relevant descriptors and uses them to perform ADMET predictions [12].

Preparation of receptor

The Crystal structure of a human gamma-aminobutyric acid receptor, the GABA (A) R-beta3 homopentamer (PDB id: 4COF) and crystal structure of the chimeric protein of 5-HT1B-BRIL in complex with ergotamine (PSI Community Target) (PDB id: 4IAR) downloaded from the protein data bank. Structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v11.2. Reorientation of certain group was optimized at neutral pH. Using force field OPLS_2005, minimization was carried out setting maximum heavy atom RMSD to 0.30 Å. Then the protein structure was prepared by the removal of water atoms and unnecessary residues [13,14].

Molecular docking

The docking has been carried out by the application of Schrödinger software suite. To prepare protein for docking and simulation,

initial step is setup protein grid. This grid represents pre-calculated properties of protein such as assign bond orders, add hydrogen bond, create disulfide bonds and fill missing side chains and loops. The grid is generated to enclose the expected binding region. An energy minimization performed to find out best scoring pose that is geometrically similar to the input pose. The glide or docking scores will be displayed in text document. Thus, the ligand which has the least glide score will be considered to have the best glide score or docked pose [15].

Results and Discussion

Open field method

In the search of *in vivo* neuro pharmacological activity of methanolic extract of *Clerodendrum viscosum* we have started our research with open field test and hole-cross and hole cross test instinctive locomotor effect. The result was presented on table 1. From the result it is significant that increased in dose show slight decreased in locomotor activity of mice, which are evident for depressant activity of the extract.

Minutes	Neuro pharmacological activity test of methanolic extract of leaves of <i>Cl.viscosum</i> by open field and hole-cross method.			
	Control	Diazepam	<i>Cl.viscosum</i> (100mg)	<i>Cl.viscosum</i> (200mg)
Open Field Method				
0	4	2.6	2.8	2.9
30	3.6	2	3.5	2.7
60	3.2	1	2.8	2.6
90	3.8	0.6	2	1.8
120	3.4	0.4	1.8	1.02
Hole-cross Test				
0	96	79	91	71
30	77	56.2	68	42.6
60	69.7	27.8	42.6	35.2
90	56.6	19.2	38.9	29.4
120	54.8	11	35.2	21.8

Table 1: Neuro pharmacological activity test of methanolic extract of leaves of *Cl.viscosum* by open field and hole-cross method.

Hole-cross test

The result was represented in table 1. From the table it was seen that this extract shows moderate neuro pharmacological activity on mice. Overall open field test and hole-cross test results obtained from this study suggested that, the methanolic extract of *Cl. viscosum* has moderate CNS depressant activity on experimental animal models.

Prolongation effect on phenobarbital induced sleeping time in mice

The result from the prolongation effect on phenobarbital induced sleeping time in mice is presented on table 2. The study was undertaken to evaluate the sleep potentiating effect of MECV (250 and 500 mg/kg b.w; i.p.) in mice and the extract significantly increased Phenobarbital (45 mg/kg b.w; i.p.)-induced sleeping time in a dose dependent manner.

Aminophylline induced convulsion in mice

The CNS depressant activity of *Cl.viscosum* leaves extract was confirmed upon on the aminophylline induced convulsion treatment

of the animal with the plant extract in table 3. The result shows that the effect of *Clerodendrum viscosum* extract on aminophylline induced convulsion in mice. The extract (250mg-500mg) raised the threshold of seizure and exerted a statistically significant dose dependent delay on the onset of clonic and tonic convulsion when compared to control and this was short compared to that of the standard drug diazepam (2mg/kg).

Treatment	Dose (mg/kg)	Onset of Sleep in Minutes	Duration of Sleep in Minutes
Phenobarbital 45mg/kg	45	2.5	82
MECV 250mg/kg	250	12.88	104.2
MECV 500mg/kg	500	11.4	135.8

Table 2: Neuro pharmacological activity *Cl.viscosum* leaves extract on phenobarbital induced sleeping time in mice.

Treatment (mg/kg)	Latency of clonic convulsion	Latency of tonic convulsion	Time of death (mins)	Mortality%
Control	6.78	7.84	8.6	100
Diazepam	3.5	49	109.66	100
MECV250mg	14.06	39.82	65.12	100
MECV500mg	14.4	48.74	89.48	100

Table 3: Neuro pharmacological activity *Cl.viscosum* leaves extract on aminophylline induced convulsion in mice.

ADMET and drug linkage properties of selected ligands

In silico ADMET analysis identify favorable compounds to be used as human therapeutic agents and molecular descriptors are the deciding factors of a compounds for pharmacokinetics properties and toxicity All 12 bioactive compounds from *Cl. viscosum* analyzed with ADMET related properties (Table 4), among which were molecular weight, H-bond donor, H-bond acceptor, human oral absorption, CNS, octanol/water partition coefficient and total solvent accessible area were calculated by QikProp program. In the determination of predicted nervous system activity compounds which are in the range between -2 to +2 scales have significant CNS depressant effect.

Molecular docking with GABA

Molecular docking is a combination of both molecular dynamics and molecular docking, predicts accurately receptor natural conformation changes and ligand binding modes. Accordingly, the top 2 were selected for the molecular interaction analysis such as Scutellarin and Xylitol. Molecular docking with GABA glide score presented on table 5.

In order to study the interaction between GABA and the ligand scutellarin (Figure 1) demonstrates a strong favorable bond. Major residues like VAL 50, GLU 52, TYR 143, TYR 220, THR 271 significant H-bonding between them.

Also, ligand Xylitol interaction with GABA (Figure 2) represents strong bond including major residues GLU 52, TYR 143, TYR 220, GLN 185, THR 271 significant H-bonding between them.

Number	Ligand	Molecular weight	H-bond donor	H-bond acceptor	Human Oral Absorption %	CNS	Qlog Po/w	SASA
1	1,3-Methylene-d-arabitol	164.158	3	8.5	70.361	-1	-1.182	316.858
2	Xylitol	152.147	5	8.5	57.384	-2	-1.704	335.374
3	Hispidulin-7-O-glucuronide	300.267	2	4.5	78.033	-2	1.867	521.099
4	Scutellarin	462.366	5	9.5	0	-2	-0.239	659.99
5	5-Hydroxymethylfurfural	126.112	1	4.2	73.882	-1	-0.176	317.742
6	3-Deoxy-d-mannoic lactone	162.142	3	8.1	57.69	-2	-1.532	331.739
7	Orcinol	124.139	2	1.5	84.602	0	0.803	322.449
8	Acetamide	144.13	0	2	69.245	-1	0.127	349.602
9	2,4-Dihydroxy-5,6-dimethylpyrimidine	140.141	2	3.5	71.752	-1	-0.231	320.086
10	Glycerol	92.094	3	5.1	71.327	-1	-0.988	252.307
11	2(1H) Pyrimidinone, 1-methyl-	110.115	0	3.5	83.629	0	-0.166	294.697
12	N hexadecanoic acid	256.428	1	2	88.061	-2	5.252	664.882

Table 4: Details of ligands with ADMET properties.

Name of the compound	Docking score	Glide score	Glide energy
GABA			
Scutellarin	-8.255	-8.259	-50.78
Xylitol	-5.137	-5.137	-27.211
5-HT			
Scutellarin	-9.651	-9.655	-49.562
Xylitol	-5.452	-5.452	-25.185
3-Deoxy-d-mannoic lactone	-5.356	-5.356	-29.397

Table 5: Molecular docking and binding energy analysis with GABA and 5-HT.

Molecular docking with 5-HT

The molecular docking between ligands with 5-HT receptor is representing in table 5. Thus top 3 ligands such as Scutellarin, Xylitol and 3-Deoxy-d-mannoic lactone show significant glide docking scores in the evaluation of potent anxiolytic compound.

In order to study the interaction between 5-HT and the ligand scutellarin (Figure 3) demonstrates a poor bonding in comparison with GABA. Major residues like TYR110, THR355, ASP252, ASP129 binds with H-bond.



Figure 1: Scutellarin_GABA_3D.

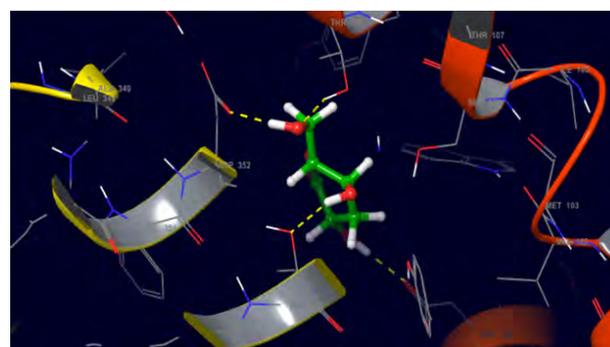


Figure 3: Scutellarin_5-HT_3D.

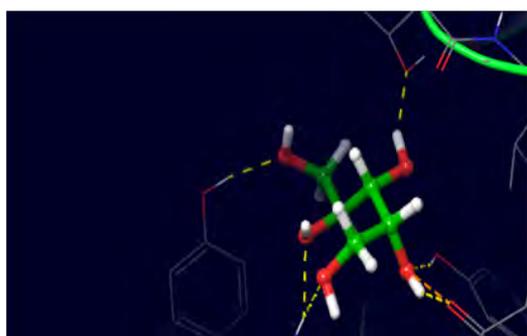


Figure 2: Xylitol_GABA_3D.

Here the interaction between 5-HT and the ligand Xylitol (Figure 4) demonstrates strong favorable bond. Major residues like ASP352, TYR359, TYR110, THR110 ASP129 binds significantly with h-bond.

In other content the interaction between 5-HT and the ligand 3-Deoxy-d-mannoic lactone (Figure 5) demonstrates poor bond. Major residues like ASP129, ASP352, THR271, THR110 binds with H-bond.

Conclusions

In this research study, the result shows that the effect of *Clerodendrum viscosum* extract on aminophylline induced convulsion in mice. the extract(250mg-500mg) raised the threshold of seizure and exerted a statistically significant dose dependent delay on the onset of clonic and tonic convulsion when compared to control and this was short compared to that of the standard drug diazepam (2mg/kg).

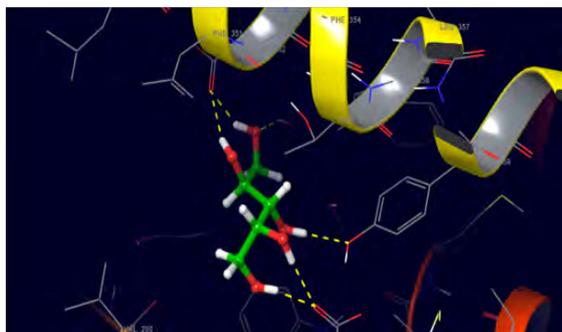


Figure 4: Xylitol_5-HT_3D.

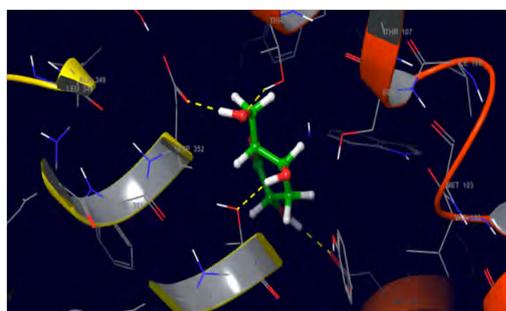


Figure 5: 3-Deoxy-d-mannonic lactone_5-HT_3D.

From above study, *In-Vivo* Neuropharmacological study methanolic extract of *Clerodendrum viscosum* (Family: *Verbenaceae*) shows significant CNS depressant activity as well as anxiolytic activity which is comparable to standard (Diazepam). *In-Silico* Pharmacological study it is observed that the anxiolytic activity of *Clerodendrum viscosum* may be due to Scutellarin has good binding affinity with GABA receptor rather than 5-HT. But Xylitol shows moderate binding affinity with GABA and as well as 5-HT. Here the interaction between 5-HT and the ligand Xylitol demonstrates a strong favorable bond. Major residues like ASP352, TYR359, TYR110, THR110, ASP129 binds significantly with H-bond.

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