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Research Article

Neuroprotective Potentials of *Ageratum conyzoides* Phyto-constituents via Inhibition of Monoamine Oxidase: An *In-silico* Study

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ABSTRACT

A surge of monoamine oxidase (MAO) causes neurodegenerative disorders like depression linked to suicides among youths. The goal of this work was to use a molecular docking technique to predict the neuroprotective potentials of phytoconstituents found in *Ageratum conyzoides* leaves (ACL), a popular folk remedy for neurological disorders. The 23 phytoconstituents previously found in ethanol leaf extract of ACL (ACL1-23) were identified and their 3D structures were either sketched (ACD/ChemSketch) or downloaded from the PubChem website. MAO was the target protein, and phenelzine (PNZ) was the standard inhibitor. The protein structure was obtained from the Protein Data Bank and processed for docking with UCSF Chimera. Before molecular docking with the AutoDock Vina Plugin PyRx, the 23 ACL bioactive compounds were tested for blood-brain barrier (BBB) permeability and other pharmacological characteristics. The protein-ligand interactions were visualized using the Discovery Studio 2020 after docking. The result revealed that all other ACL bioactive compounds were shown to potentially be BBB-permeants with good pharmacological characteristics, except for ACL17 and ACL18 bioactive compounds. Standard inhibitor indicated two binding pockets within the protein, and all BBB-permeants bound to any of the two pockets. The PNZ had docking values of -6.8 and -6.0 kcal/mol at the pockets; whereas the ACL had docking values ranging from -6.7 to -4.6 kcal/mol. ACL similarly interacted with MAO as the PNZ, indicating that they are competitive inhibitors and therapeutics. We reported a step forward in the discovery of greener neuroprotective drugs and their molecular mechanisms to combat neurodegenerative illnesses.

Keywords: *Neuroprotective, Ageratum conyzoides, Phytoconstituent, Molecular docking, Monoamine oxidase*

INTRODUCTION

Neurodegeneration is one of the most significant difficulties in healthcare delivery across the world. The gradual loss of a neuron's structure or function, or "neurodegeneration," causes a neurodegenerative illness. The terrible effects of brain cell miscommunications include neurodegenerative disorders, which cause the death of neurons (Kalia and Lang, 2015). Many different aspects, including mobility, speech, memory, IQ, and a lot more, can be affected by these diseases (Finkbeiner, 2011; Bak and Chandran, 2012). Due to the complexity of these diseases, the etiology of many neurodegenerative disorders is still unknown (Holmes and Amin, 2016). Several exciting research reports published over the last three decades have demonstrated that many antidepressants and antipsychotics have neuroprotective properties (Baker *et al*., 2012; Chen and Nasrallah, 2019; Hunsberger *et al*., 2009; Li and Xu, 2007; Lieberman *et al*., 2008; Song *et al*., 2013).

Monoamine oxidase increase is a characteristic of neurodegenerative pathological disorders noted by researchers (Matveychuk *et al*., 2022). The neurotransmitters norepinephrine, serotonin, and dopamine are eliminated from the brain by a substance called monoamine oxidase (Finberg and Rabey, 2016). The most crucial chemotherapeutic target now is monoamine oxidase inhibition since it prevents neurotransmitter eliminations, increasing the amount of these brain chemicals available to alter the depressive-affected cells and circuits (Aluf *et al*., 2013). Many researchers have focused on the selective irreversible monoamine oxidase-B inhibitors (l-deprenyl and rasagaline) which have shown neuroprotective properties in a variety of in vitro and in vivo models (Pathak *et al*., 2011; Hill *et al*., 2020; Szök *et al*., 2018; Kumar *et al*., 2015).

Interestingly, a significant study has shown that the MAO-Inhibitor (phenelzine: PNZ) has numerous activities that may contribute to neuro-protection/neuro-rescue (Matveychuk *et al.*, 2022). Phenelzine is beneficial in the treatment of all neurodegenerative diseases. Although it is a non-selective irreversible MAO-inhibitor (inhibits both MAO isoforms) marketed as antidepressant, clinical studies have shown that it is also effective in the treatment of anxiety disorders such as panic disorder and social anxiety disorder (Nam *et al*., 2010; Aarre, 2003; Shanahan *et al*., 2019; Williams *et al*., 2020; Zhang and Davidson, 2007). Some dietary restrictions are recommended for patients on PNZ, as with other irreversible non-subtype-selective MAO inhibitors, to avoid a potential hypertensive crisis when certain foods are consumed, although the effects on blood pressure appear to be less serious than previously thought (Matveychuk *et al*., 2022).

PNZ is a complex medicine that targets some enzymes and other variables that have been linked to neuroprotection and the genesis of several mental and neurological illnesses (Brue and Oakland, 2002; Al-Nuaimi *et al*., 2012; Baker *et al*., 2019; Hill *et al*., 2020; Jarrahi *et al*., 2020). Remarkably, Matveychuk *et al*. (2022) effectively reviewed the key aspects that appear to be contributing to the neuroprotective effects of PNZ as the contribution of an active metabolite, inhibition of MAO, inhibition of gamma-aminobutyric acid transaminase (GABA-T), and elevation of brain GABA levels, the elevation of brain levels of the amino acid ornithine and N-acetylamino acids, and sequestration of toxic reactants.

Although MAO inhibitors, particularly phenelzine, would undoubtedly reduce the effect of increased MAO in neurodegenerative diseases, there have been various negative effects described (Matveychuk *et al*., 2022). Serotonin syndrome, significant food interactions leading to high blood pressure and stroke, and a rise in suicidal thoughts are all serious adverse effects. Dizziness, sleepiness, sleeplessness, and nausea are all common adverse effects. Edema, muscular soreness, myoclonus, paraesthesias, sexual dysfunction, and weight gain are all possible side effects of long-term medication (Matveychuk *et al*., 2022). As a result, a greener alternative, such as plant bioactive, is required.

In folk medicine, *Ageratum conyzoides* has been believed to have the ability to heal a variety of ailments including depression (Van-Burden and Robinsin, 1981; Raheela *et al*., 2008; Aja *et al*., 2016; Jasvidianto *et al*., 2020). A gas chromatography-mass spectrometric (GC-MS) study of the leaf ethanol extract revealed the presence of 23 bioactive components, with 5-(1-methylidene)-1,3-methylidenecyclopentane (14.6%), nonane (18.2%), propane-2-ylcyclohexane (8.9%), (1-methylethyl) benzene (9.1%), and hexanoic acid (4.3%) being the most prominent (Aja *et al*., 2016). The presence of these phytoconstituents may be responsible for the plant's diverse therapeutic properties. An *in-silico* technique was used to screen these phytoconstituents for possible MAO inhibitors, which might potentially replace phenelzine and other drugs with underlying toxicity.

MATERIALS AND METHODS

Study design and location

In this study, the tools used were Software: UCSF Chimera, Bovia Discovery Studio 2020, AutoDock Vina Plugin PyRx, ACD/ChemSketch, Ms. Excel; Webserver: PubChem Database (https://pubchem.ncbi.nlm.nih.gov/), Protein Data Bank (https://www.rcsb.org/), Drug.com (https://www.drugs.com/), and admetSAR (http://lmmd.ecust.edu.cn/admetsar2/).

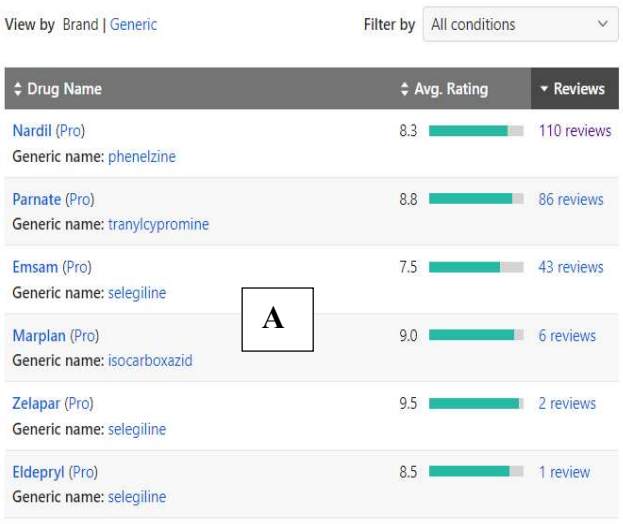
Retrieval of Ligands

According to Aja *et a*l. (2016), the ligands were phytocompounds identified in GC-MS analysis of *Ageratum conyzoides* leaf ethanol extract (Table 1). Furthermore, certain ACL phyto-compounds were collected from the PubChem database using IDs, while those not found in PubChem were drawn using the ACD/ChemSketch program.

Further, the list of standard monoamine oxidase inhibitors was searched on Drug.com using the term *'all conditions'* to filter the available alternatives. Phenelzine (PubChem CID: 3675) was chosen as the standard inhibitor since it scored the highest reviews even though it scored fourth on the average rating (see Figures 1A and 1B). Additionally, as adopted by Aja *et al.* (2021) the standard inhibitor is used to anticipate the precise binding pocket of the protein as well as the validity of molecular docking.

Table 1. Phytochemical Compositions and Gas Chromatography-Mass Spectrometric (GC-MS) Analysis of Ethanol Leaf-Extract of *Ageratum conyzoides* (Aja et al., 2016)

Given ID	PubChem CID	Compound	Molecular Formula	Molecular Weight	Retention Time	Percentage Content (%)	Base Peak
ACL1	Drawn	5-(1-methylidene)-1,3-methylidenecyclopentene	C_6H_8	106	3.508	14.6	91
ACL2	8141	Nonane	C_9H_{20}	128	3.625	18.2	43
ACL3	12763	Propan-2-ylcyclohexane	$C_{10}H_{17}$	106	3.817	14.6	91
ACL4	15600	Decane	$C_{10}H_{22}$	152	4.917	8.9	43
ACL5	7406	(1-methylethyl) benzene	C_9H_{12}	143	5.150	3.2	105
ACL6	Drawn	Nonane	C_9H_{19}	142	6.408	9.1	91
ACL7	Drawn	1-methyl-4-(prop-1-en-2yl) cyclohexa-1,3-diene	$C_{10}H_{16}$	152	6.508	9.1	119
ACL8	Drawn	1-methyl-3(propan-2yl) benzene	$C_{10}H_{14}$	134	7.108	1.4	119
ACL9	13403	1-ethyl-2,4-dimethylbenzene	$C_{10}H_{11}$	132	7.625	4.8	119
ACL10	Drawn	1-methyl-3-(propan-2-yl) benzene	$C_{10}H_{13}$	204	11.4	4.2	41
ACL11	8126	Oct-2-ene	C_8H_{15}	168	13.2	4.3	41
ACL12	356	Octane	C_8H_{17}	142	13.3	2.7	43
ACL13	8900	Heptane	C_7H_{15}	155	14.5	3.1	43
ACL14	8126	Oct-2-ene	C_8H_{15}	168	15.7	4.3	43
ACL15	33744	Non-2-ene	C_9H_{17}	155	19.3	4.3	41
ACL16	8094	Heptanoic acid	$C_7H_{13}O_2$	298	19.6	2.7	41
ACL17	Drawn	Penta-2,4-dienoic acid	$C_5H_6O_2$	264	21.2	4.3	55
ACL18	Drawn	Penta-2,4-dienoic acid	$C_7H_{16}O_2$	228	21.6	4.3	74
ACL19	Drawn	Non-2-ene	C_9H_{17}	196	22.17	4.3	55
ACL20	Drawn	Non-2-ene	C_9H_{17}	125	22.6	3.7	43
ACL21	8094	Heptanoic acid	$C_7H_{13}O_2$	129	24.6	5.5	43
ACL22	8892	Hexanoic acid	$C_6H_{12}O_2$	116	24.8	4.3	43
ACL23	20200	Hex-3-enoic acid	$C_6H_{10}O_2$	133	26.4	4.3	43



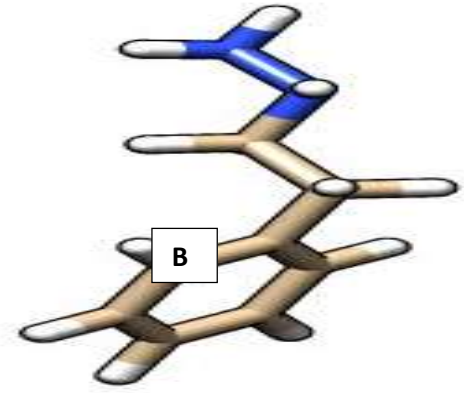
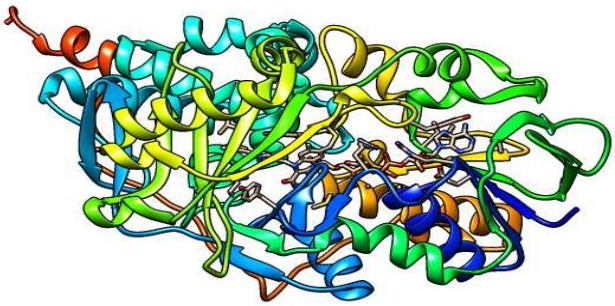


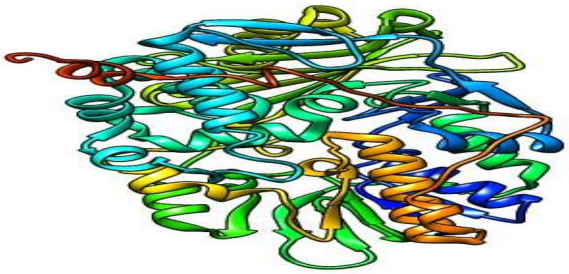
Figure 1. Standard Inhibitor (**A:** List of monoamine oxidase inhibitors from Drug.com) (**B:** Phenelzine, PNZ) (https://www.drugs.com/drug-class/monoamine-oxidase-inhibitors.html)

Retrieval and Preparation of the Target Protein

Human MAO (PDB ID:1GOS) 3D crystal structures (Figure 2) were obtained from the Protein Data Bank (www.rcsb.pdb.com), prepared, and stored in PDB format (Figure 2). In a nutshell, the protein was imported into the UCSF Chimera program workspace and prepared according to the procedure described by Aja *et al.* (2021).



Monoamine Oxidase (PDB ID: 1GOS)



Monoamine Oxidase (Prepared)

Figure 2. The 3D Crystal Structure of Monoamine Oxidase

Prediction of drug-like properties of the *Ageratum conyzoides* bioactive compounds

The admetSAR website was initially used to predict the pharmacological qualities of *Ageratum conyzoides* bioactive compounds based on their physicochemical in terms of Lipinski rule of five and pharmacokinetic properties (Aja *et al*., 2021). Only molecules that could pass across the blood-brain barrier were selected for molecular docking investigations targeting Monoamine Oxidase.

Molecular Docking Studies

The AutoDock Vina plugin PyRx was used to test the compounds for potential inhibitors utilizing multiple ligands docking of the discovered blood-brain barrier permeants among *Ageratum conyzoides* phytocompounds with the standard inhibitor (phenelzine) to the target proteins (MAO). In a nutshell, the prepared MAO was placed into the PyRx and transformed into macromolecules. In the PyRx, the phenelzine and the blood-brain barrier permeants were imported one by one in chemical table format. The ligands were also minimized in the default by adding hydrogen and charge Gastiger and then converted to pdbqt format. All of the ligands and proteins were selected using Vina wizard, and the grid box was configured to superimpose the protein such that it reads Centre (X: 57.2509; Y:144.1355; Z: 34.3662), Dimension (X: 64.9053; Y:77.7086; Z:75:9208), and the research was run at exhaustiveness of 8. Two binding pockets were discovered in the typical inhibitor. The putative inhibitors' docking scores were obtained for the posture in which the upper and lower RMSD were both zero. As possible inhibitors, only ligands that bind to any of the two binding pockets disclosed by the standard inhibitor were chosen. To better comprehend the amino acids, bond distances, and types of bonds engaging at the binding sites, the Discovery Studio 2020 was used to show protein-ligand interactions.

RESULTS

The 3D Crystal structure of the *Ageratum conyzoides* bioactive compounds

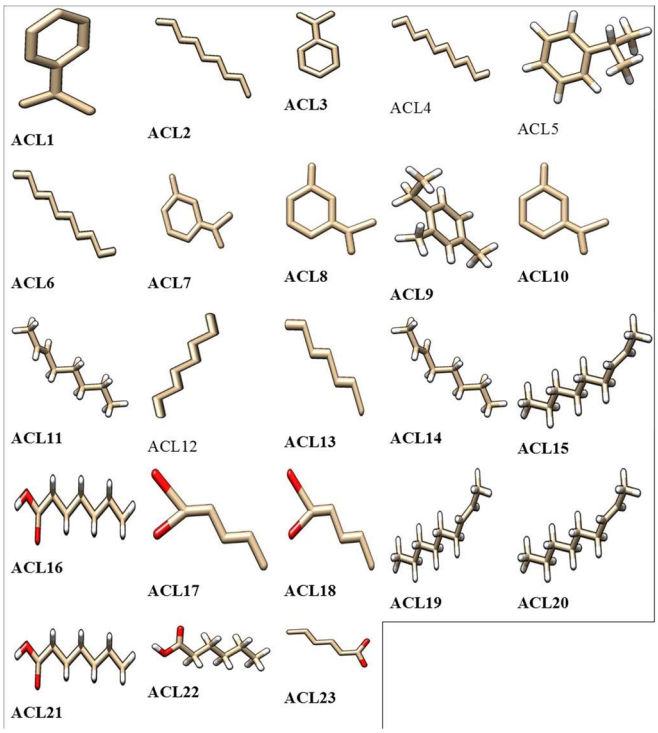


Figure 3. The 3D Crystal Structures of the ACs

Pharmacological properties of the *Ageratum conyzoides* bioactive compound

Table 2. Pharmacokinetics Properties of the *Ageratum conyzoides* Bioactive Compounds (www.admetsar.com)

Given ID	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
ACL1	Low	Yes	No	No	No	No	No	No
ACL2	Low	Yes	No	No	No	No	No	No
ACL3	Low	Yes	No	No	No	No	No	No
ACL4	Low	Yes	No	No	No	No	No	No
ACL5	Low	Yes	No	No	No	No	No	No
ACL6	Low	Yes	No	No	No	No	No	No
ACL7	Low	Yes	No	No	No	No	No	No
ACL8	Low	Yes	No	No	No	No	No	No
ACL9	Low	Yes	No	No	No	No	Yes	No
ACL10	Low	Yes	No	No	No	No	No	No
ACL11	Low	Yes	No	No	No	No	No	No
ACL12	Low	Yes	No	No	No	No	No	No
ACL13	Low	Yes	No	No	No	No	No	No
ACL14	Low	Yes	No	No	No	No	No	No
ACL15	Low	Yes	No	No	No	No	No	No
ACL16	High	Yes	No	No	No	No	No	No
ACL17	High	No	No	No	No	No	No	No
ACL18	High	No	No	No	No	No	No	No
ACL19	Low	Yes	No	No	No	No	No	No
ACL20	Low	Yes	No	No	No	No	No	No
ACL21	High	Yes	No	No	No	No	No	No
ACL22	High	Yes	No	No	No	No	No	No
ACL23	High	Yes	No	No	No	No	No	No

Table 3. Physicochemical Properties of the *Ageratum conyzoides* Bioactive Compounds (www.admetsar.com)

Given ID	MW	#Heavy atoms	#Aromatic heavy atoms	#Rotatable bonds	#H-bond acceptors	#H-bond donors	MR	TPSA	iLogP	Lipinski #violations
ACL1	106.17	8	0	0	0	0	37.03	0	2.16	0
ACL2	128.26	9	0	6	0	0	45.38	0	3.06	1
ACL3	126.24	9	0	1	0	0	43.26	0	2.66	0
ACL4	142.28	10	0	7	0	0	50.18	0	3.29	1
ACL5	120.19	9	6	1	0	0	41.02	0	2.25	1
ACL6	128.26	9	0	6	0	0	45.38	0	3.06	1
ACL7	120.19	9	0	1	0	0	41.84	0	2.37	0
ACL8	120.19	9	6	1	0	0	41.02	0	2.25	1
ACL9	134.22	10	6	1	0	0	46.15	0	2.49	1
ACL10	120.19	9	6	1	0	0	41.02	0	2.25	1
ACL11	112.21	8	0	4	0	0	40.1	0	2.74	0
ACL12	114.23	8	0	5	0	0	40.57	0	2.88	1
ACL13	100.2	7	0	4	0	0	35.76	0	2.65	0
ACL14	112.21	8	0	4	0	0	40.1	0	2.74	0

ACL15	126.24	9	0	5	0	0	44.9	0	3.02	1
ACL16	130.18	9	0	5	2	1	37.53	37.3	1.79	0
ACL17	112.13	8	0	3	2	1	31.37	37.3	1.25	0
ACL18	112.13	8	0	3	2	1	31.37	37.3	1.25	0
ACL19	126.24	9	0	6	0	0	44.9	0	2.96	1
ACL20	126.24	9	0	6	0	0	44.9	0	2.96	1
ACL21	130.18	9	0	5	2	1	37.53	37.3	1.79	0
ACL22	116.16	8	0	4	2	1	32.73	37.3	1.57	0
ACL23	114.14	8	0	3	2	1	32.25	37.3	1.45	0

MW: Molecular weight; H: Hydrogen; MR: Molecular refractivity; TPSA: Topological surface area; iLogP: n-octanol-water partition coefficient.

Binding poses of the Novel inhibitors with the target protein

The PNZ disclosed two binding pockets at RMSD values of 0 and 3 and all BBB permeants were found and bound to one of them at RMSD values of zero, respectively (Figure 4). As a result, they are classified as new monoamine oxidase inhibitors.

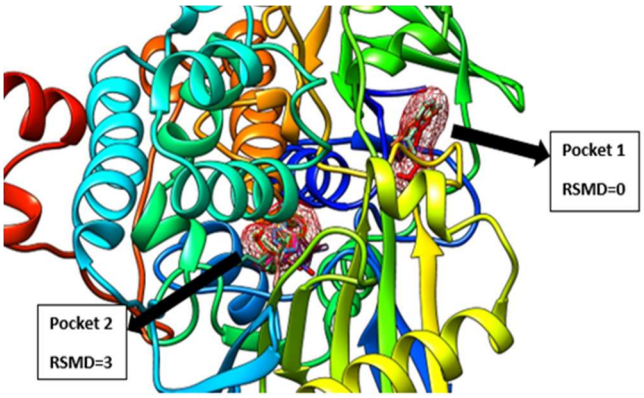


Figure 4. Binding Poses of Novel Inhibitors at the Pockets of MAO

Docking Scores of the Novel inhibitors

The putative inhibitors' binding affinities at the two pockets of monoamine oxidase are listed below (Figures 5A and B).

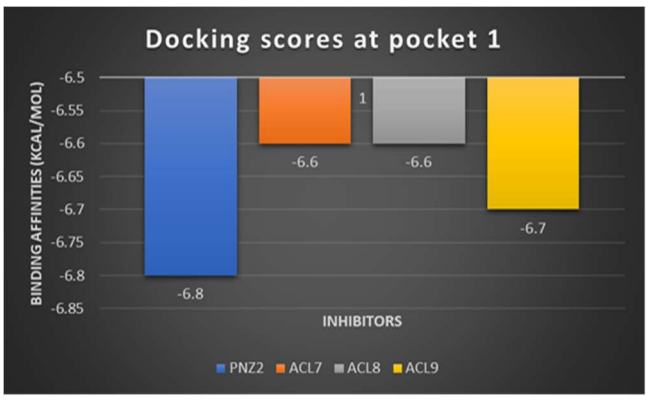


Figure 5A. Binding Affinities of the Pocket 1 Potential Inhibitor

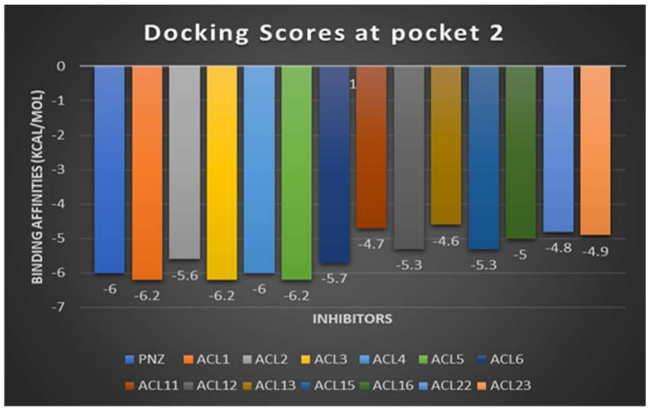
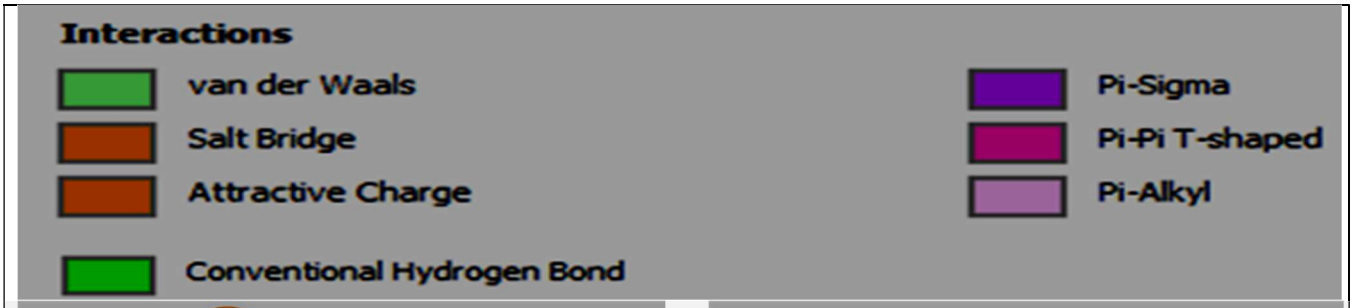
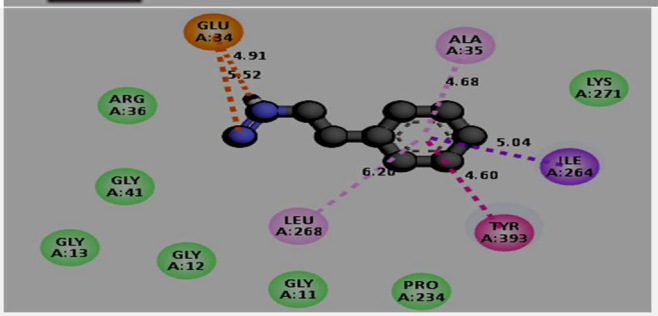


Figure 5B. Binding Affinities of the Pocket 2 Potential Inhibitors

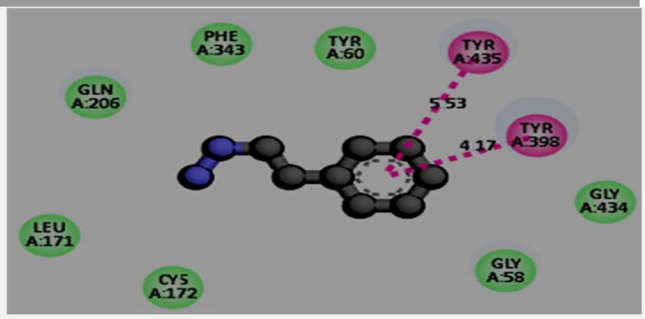
Visualization of the MAO-Inhibitors Interactions

These are the relevant protein-ligand interactions discovered utilizing Discovery Studio 2020's post-docking analysis.

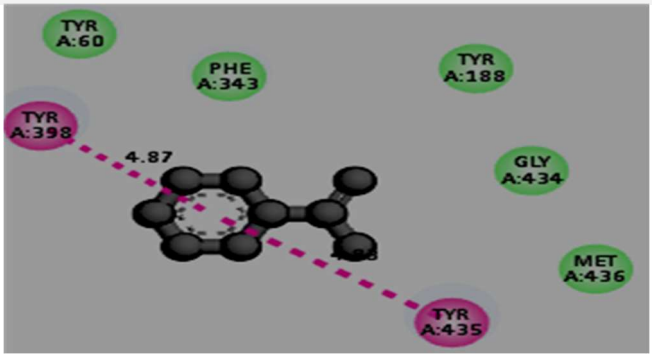




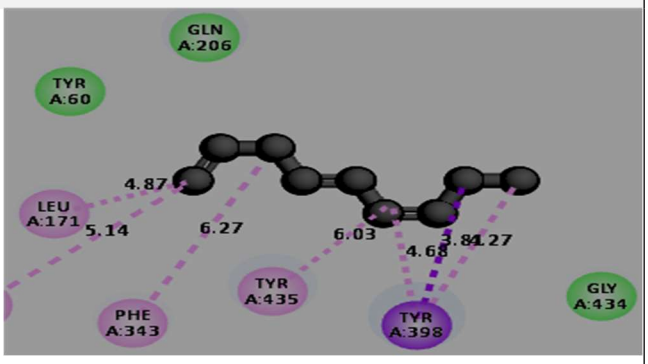
PNZ (Pocket 1)



PNZ (Pocket 2)



ACL1



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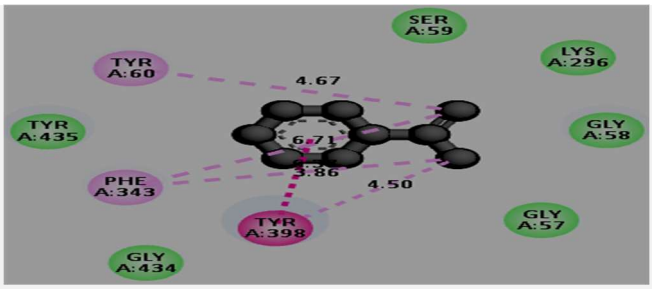
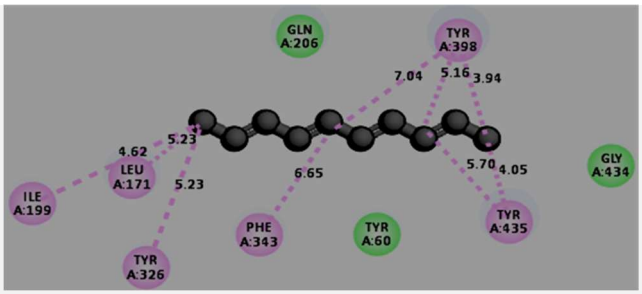
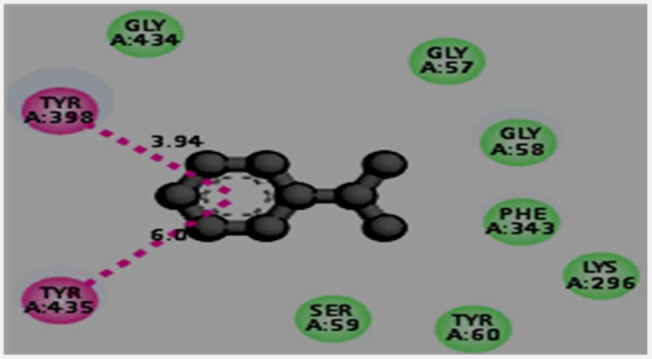


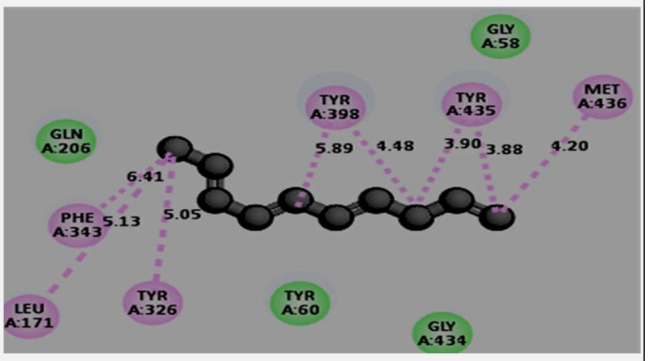
ACL3



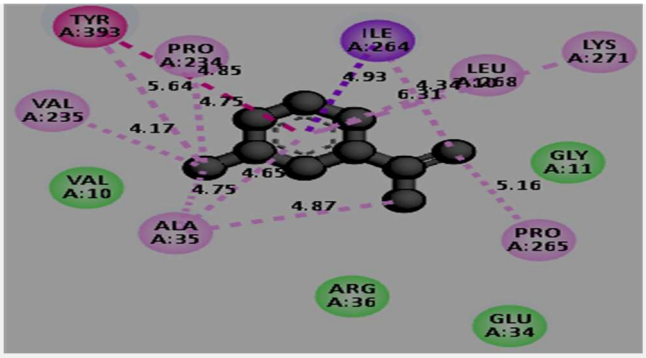
ACL4



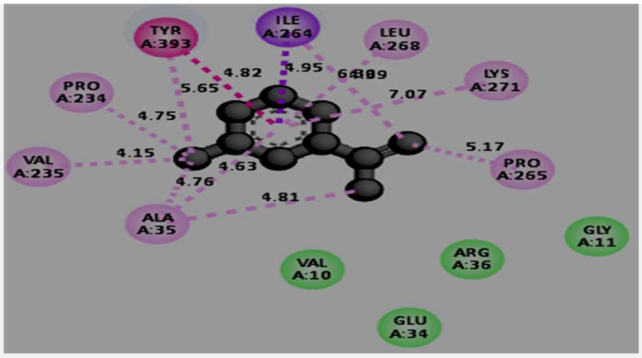
ACL5



ACL6



ACL7



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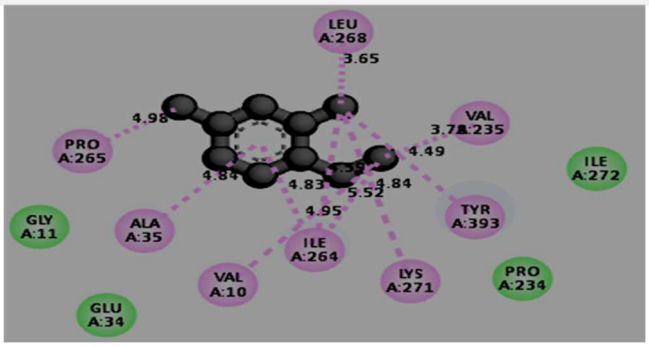

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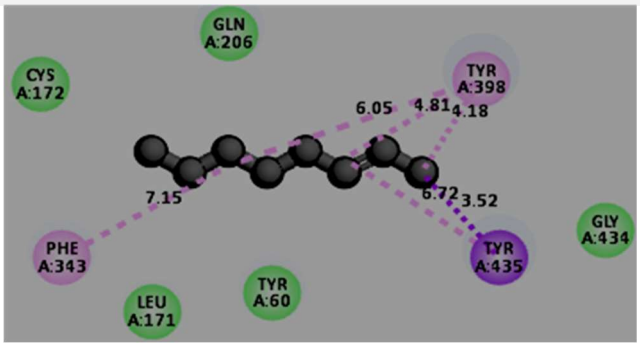

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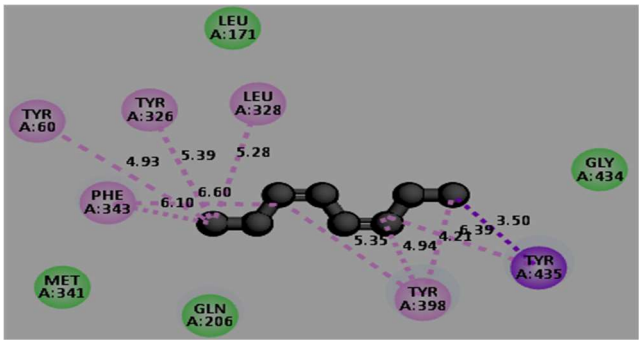

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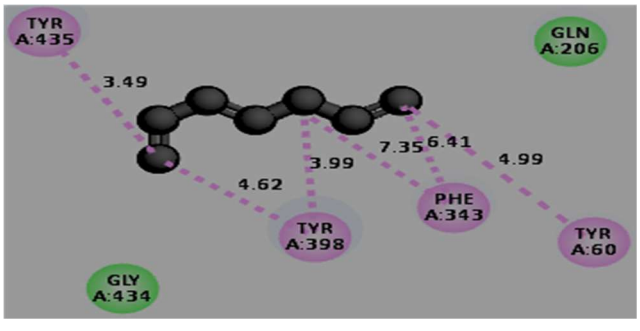

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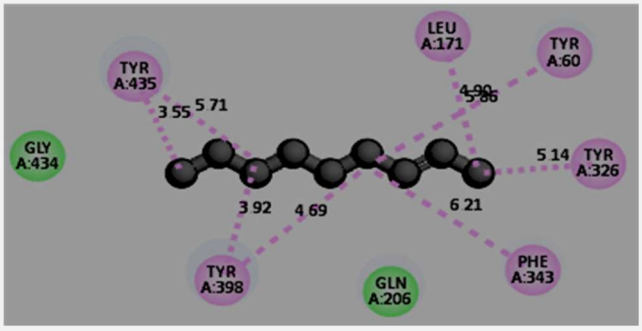

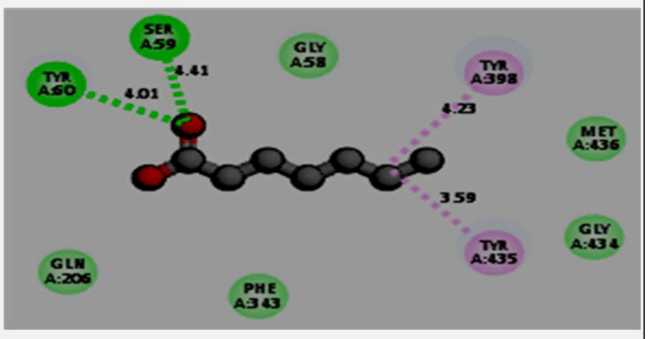

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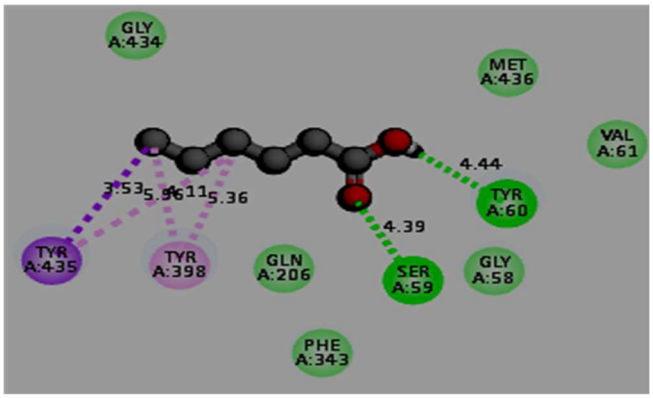
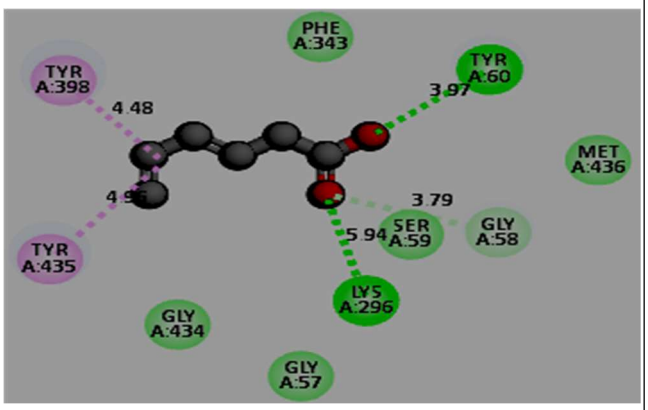


ACL16



ACL22 **ACL23**

DISCUSSION

Neurodegeneration is a process that occurs as a result of neuropathological diseases as well as the aging of the brain. Many synthetic medications in the market today have a long list of negative side effects. Unfortunately, with the global upsurge, the high cost of treatment of neurodegenerative illness has made a lot of people resort to herbal remedies (Jasvidianto *et al.,* 2020; Kolominsky-Rabas *et al.,* 1998). For instance, herbal medicines, whose phytochemical ingredients can have long-term health-promoting or therapeutic properties, have also sparked a lot of attention during the last decade (Kumar and Khanum, 2012; Jasvidianto *et al.,* 2020). Despite their usefulness, however, little or no information on the molecular underpinnings of those herbal medications' pharmacological effects exists. This necessitated the current study, therefore, we used an *in silico* technique to find therapeutic candidates for neuroprotection and analyze their molecular mechanisms of action as well as their pharmacological characteristics.

This study shows that from the list of currently used neuroprotective medications, phenelzine (PNZ) seems to be gaining the most attention, possibly due to its efficacy in all neurodegenerative disorders (Figure 1). Therefore, PNZ was used as the standard inhibitor to get a broader understanding of our test compounds.

In the current investigation, we perceived that the phytocompounds structures, as reported by Aja *et al*. (2016) which were presented in Figure 3 may be the mediators of *Ageratum conyzoides*' various therapeutic potentials documented in traditional medicine. Notably, if a phytocompound has a pharmacological impact, it is termed a drug candidate. In furtherance, the pharmacokinetic parameters of the putative inhibitors are shown in Table 2. The capacity of a drug-like molecule to pass the BBB influences whether it can achieve bioavailability in brain tissues. In this study, except for ACL17 and ACL18, all were shown to be BBB permeants in the current investigation. This means that they can target monoamine oxidase in brain environments. Again, only ACL16 and ACL21-24 have a high gastrointestinal absorption rate, making them suitable for oral administration, whereas the others have a poor absorption rate and must be delivered intravenously. The ACL is well digested by the drug-metabolizing enzymes in the liver (CYP). Others are neither substrates nor inhibitors of P-glycoproteins (P-gp) and cytochrome P-450 (CYP-450) isoforms, except for ACL9, which is a CYP2D6 inhibitor. As a result, the ACLs are efficiently absorbed, distributed, metabolized, and eliminated. Furthermore, when molecules are submerged in a biological system, their physicochemical characteristics reveal their interactions. This is a drug-like indication that is graded using the Lipinski rule of five (RO5). Table 3 shows that among the BBB permeants, ACL3-10, ACL12, ACL15, and AC19-20 violated at least one of the Lipinski RO5, whilst others followed all of the RO5. Those who broke the RO5 may be optimized to make them more drug-like.

PNZ inhibits MAO through two binding pockets at RMSD values of 0 and 3 respectively, as shown in Figure 4. The BBB permeants were classified as pocket 1 or 2 inhibitors based on their competitive binding at the same location as PNZ when their RMSD values equal 0 (a point of maximum stability). The capacity of PNZ to bind in these distinct locations might explain its efficiency under all situations (Drug.com). Various amounts of neuroprotection may be elicited by these alternative binding sites in different degenerative diseases. We suggest, in the current investigations, that ACL can elicit neuroprotection in the same way as PNZ does since they target the same MAO site.

The efficiency of their interactions is also determined by the affinity of a ligand for a protein. The negative value of free energy promotes chemical reactions to be spontaneous. In

addition, the greater the affinity, the bigger the negative value of the free energy. MAO had an equal binding affinity for both the traditional (PNZ) and new inhibitors (ACL), as shown in Figures 5A-B. For the two pockets, PNZ exhibits binding affinities of -6.8 and -6.0 Kcal/mol, respectively, whereas new inhibitors have binding affinities ranging from -6.7 to -4.6 Kcal/mol. These new two pockets inhibitors are potential alternatives to PNZ.

Consistently; the type of bond, the distance between the bonds, and the type of amino acids in the binding pockets were all revealed by visualizing the 2D interactions between protein and ligands (Aja *et al*., 2021). This adds to our understanding of the molecular targets for chemotherapy. The individual interactions between the proteins and the inhibitors were disclosed in Figure 6. Van der Waals, Salt bridges, attractive chargers, conventional hydrogen bonds, and Pi-bonds were detected within the two binding pockets. The modal bonds between the new inhibitors and the MAO are van der Waals, Pi-bonds, and traditional hydrogen bonds. Only PNZ utilized a salt bridge and an attractive charge in pocket 1. The interacting ligands' bond angles within the binding pockets range from 3 to 7 Å. Within the binding pockets, both the PNZ and the ACLs interacted mostly with the same amino acids.

With the exciting observations discussed so far, it is noteworthy that through inhibiting MAO, ACLs similar to PNZ, can raise the brain levels of monoamine neurotransmitters 5-hydroxytryptamine (5-HT, serotonin), noradrenaline, and dopamine, all of which have been linked to depression (Ortiz *et al.,* 1999; Blier, 2016). In this study, the inhibition of MAO which has been linked to some of PNZ's neuroprotective benefits is now being recommended for ACLs. On another note, hydrogen peroxide, an aldehyde from an imine, ammonia from primary amines, or an alkyl-substituted amine are produced via MAO's catalytic cycle meant for secondary and tertiary amines (Doble, 1999; Yang, 2004; Drevets *et al.,* 1999; Yang *et al.,* 2003; Wang *et al.,* 2004; Wood *et al.,* 2007). However, these hydrogen peroxide, ammonia, and some of the aldehyde metabolites produced are potentially neurotoxic but MAO inhibitors limit their synthesis. Also, the synthesis of 3,4-dihydroxyphenylacetaldehyde (DOPAL) from dopamine, 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL) from noradrenaline and adrenaline, and 5-hydroxyindoleacetaldehyde (5-HIAL) from 5-HT arise from the MAO-catalyzed oxidation of catecholamines and 5-HT. These three aldehydes have been implicated in the etiology of Alzheimer's disease (AD) and Parkinson's disease (PD) (Masato *et al.,* 2019) and have been reported to produce toxicity in a variety of in vitro and in vivo experiments (Panneton *et al.,* 2010; Cagle *et al.,* 2019). Therefore, ALC can inhibit these biochemical events and protect against neurodegenerations.

It is notable that PNZ, a prototype inhibitor investigated with ACLs in the current work, is non-isoform specific (Matveychuk *et al.,* 2022), even though, humans' brain activity of MAO with isoform specificity increases with age, according to research findings (Shemyakov, 2001; Volchegorskii *et al.,* 2001; Fowler *et al.,* 2002). The B-isoform (Monoamine oxidase-B) activity rose in Alzheimer's disease patients' brains when compared to age-matched controls, but A-isoform (Monoamine oxidase -A) activity was found to be stable or increased depending on the brain areas studied (Ansari *et al.,* 2002; Jossan *et al.,* 1991; Quartey *et al.,* 2018; Sherif *et al.,* 1992). Because B-isoform is expressed in glial cells, increasing B-isoform activity in aging and Alzheimer's disease might be the result of glial cell expansion caused by age and neurodegeneration (Sowa *et al.,* 2004; Ansari *et al.,* 2002; Tatton *et al.,* 2003). This rise in B-isoform activity has been linked to cholinergic neuron death, cognitive impairment, and the production of amyloid plaques and neurofibrillary tangles (Cai, 2014; Manzoor and Hoda, 2020). The mechanism of action of B-isoforms cholinergic neurons is unknown, however, it might be a result of excess B-isoform causing more hydrogen peroxide, which then leads to the creation of reactive oxygen species such the hydroxyl radical (Riederer *et al.,* 2004; Practico, 2008; Quartey *et al.,* 2018;). In research with a cholinergic neurotoxin in rats, Jossan *et al.* (1989) found that degeneration of cholinergic neurons causes an increase in B-isoform activity in the hippocampus, striatum, and cortex, but not A-isoform activity. These researchers theorized that the rise was related to enhanced gliosis following cholinergic neuronal degeneration and that increased B-isoform activity might indicate cholinergic system degeneration (Yehuda *et al.,* 2002). B-isoform has also been suggested to contribute to neurodegeneration by regulating α-amyloid levels in neurons by activating β-secretase (Jhamandas *et al.,* 2005;). The combination of B-isoform and GABA may also play a role in the cognitive impairment found in Alzheimer's disease. In glia, B-isoform has been shown to catalyze the production of GABA from the polyamine putrescine, with the GABA released mediating tonic inhibition (Ortiz *et al.,* 1999;). In mice models of Alzheimer's disease, the existence of reactive astrocytes near amyloid plaques has been seen, and it has been suggested that abnormal levels of GABA generated by B-isoform activation in such astrocytes impair memory (Hartman *et al.,* 2006; Jo *et al.,* 2014). With the robust evidence on the events which take place in neurodegeneration progressions as a result of a rise in the level of MAO, we reported that ACLs may have comparable pharmacological effects as

phenelzine via inhibitions resulting in neuroprotection against neurodegenerative disorders.

CONCLUSION

The uncontrolled increase of monoamine oxidases is a hallmark of neurodegeneration. The current chemotherapeutic drugs for treating neurodegenerative illnesses that target monoamine oxidase inhibition, notably phenelzine, are difficult to use due to a variety of adverse effects. Herbal products used for the same purpose have obvious potency, but comprehending their molecular mechanism is still in its infancy. *Ageratum conyzoides* contain bioactive, which may explain its widespread use in traditional medicine. According to molecular docking research, the bioactive from *Ageratum conyzoides* permeate BBB and could elicit neuroprotection in the same way as phenelzine does. As a result of the findings of this investigation, novel neuroprotective drugs and their molecular mechanisms against neurodegenerative illnesses have been proposed.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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