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Molecular Docking Studies of Flavonoids from *Andrographis paniculata* as Potential Acetylcholinesterase, Butyrylcholinesterase and Monoamine Oxidase Inhibitors Towards the Treatment of Neurodegenerative Diseases

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Abstract: Neurodegenerative diseases have been characterized by loss of neuron structures as well as their functions. This study was designed to assess molecular docking of flavonoids from *Andrographis paniculata* as potential acetylcholinesterase, butyrylcholinesterase, and monoamine oxidase inhibitors in the treatment of neurodegenerative diseases. Eight identified possible inhibitors of acetylcholinesterase, butyrylcholinesterase, and monoamine oxidase from *Andrographis paniculata* were retrieved from the PubChem database. The molecular docking, ADMET, and Lipinski's rule of five were examined using different bioinformatic tools. It was shown that only rutin has the highest binding affinity (-12.6 kcal/mol) than the standard used. ADMET results demonstrated that all the eight compounds are druggable candidates except rutin. Also, only tangeritin has a blood-brain barrier (BBB) permeation potential. Hence, it can be deduced that all flavonoid compounds from *Andrographis paniculata* are orally druggable, which can make them useful in the treatment of neurodegenerative diseases better than donepezil.

Keywords: *Andrographis paniculata;* flavonoid; molecular docking; Lipinski's rule of five; neurodegenerative diseases.

1. Introduction

Monteiro *et al.* [1] documented that neurodegenerative diseases (NDDs) ascend due to progressive loss of both neuron structures and functions, leading to weakness of the muscle and decline of the body's physiological roles. This development prone mature cells that can be no longer capable of undergoing mitosis to cell death, causing apoptosis as well as oxidative stress [2]. According to Ajiboye *et al.* [3], the NDDs include Alzheimer's disease, Parkinson's disease, Huntington's disease, schizophrenia, amyotrophic lateral sclerosis, seizure disorders, amongst others. The NDDs are the major health complications distressing the lives of mainly aged globally [4]. It has been acknowledged that Alzheimer's disease is the most prevalent

form of a neurological condition, described by steady memory loss, cognitive dysfunctions, behavioral imbalance, etc. [5,6].

Notably, the most common form of Alzheimer's disease is dementia, and this affects more than 50 million people globally [7]. Currently, there are several drugs used in the management of NDDs, but they are characterized by different negative health effects [8]. In this regard, scientists have been focusing on plants as an alternative means of treatment/management of NDDs, due to their phytochemical endowment. Phytochemicals have been reported as a varied class of naturally arising bioactive compounds in plants. This includes flavonoids, phenols, alkaloids, terpenoids, etc., and they are known with different biochemical and molecular properties [1,9]. Also, phytochemicals are favorable candidates for different uncontrolled disorders, including modulation of numerous signal pathways, helping as an antioxidant, anti-inflammatory mediators, anti-cancer as well as anti- neurodegenerative diseases among others [10].

In this regard, different medicinal plants have been reported, and an example is *Andrographis Paniculata*, which belongs to a family of Acanthaceae. This plant has been reported to contain different flavonoid compounds that may be responsible for its medicinal usage locally. The plant is endowed with a series of flavonoid phytochemicals such as epicatechin, apigenin, luteolin, rutin, tangeritin, hesperetin, taxifolin, eriodictyol, etc. [11]. Therefore, this study aims to access the most druggable phytochemicals among these flavonoid compounds that could be helpful in the treatment of neurodegenerative diseases using *in silico* approach.

2. Materials and Methods

2.1. Protein preparation.

The crystal structures of AChE, BChE, and monoamine oxidase (with PDB IDs 1QTI, 1P0P, and 2Z5Y, respectively) were retrieved from the protein databank (www.rcsb.org). All the crystal structures were organized individually by eliminating the current ligands and water molecules, although lost hydrogen atoms were supplemented via the Autodock v4.2 program, Scripps Research Institute. Subsequently, non-polar hydrogens were combined, whereas polar hydrogen was added to each enzyme. The process was recurrent for each protein and then saved into dockable pdbqt format in preparation for molecular docking.

2.2. Ligand preparation.

The SDF structures of donepezil (standard inhibitor), as well as eight other ligands, were retrieved from the PubChem database (www.pubchem.ncbi.nlm.nih.gov). The compounds were transformed into mol2 chemical format using an Open babel, as documented by O'Boyle *et al*. [12]. Polar hydrogens were added while non-polar hydrogens were combined with the carbons, and the internal degrees of freedom and torsions were set. The protein and ligand molecules were thereafter transformed to the dockable pdbqt format using Autodock tools.

2.3. Molecular docking.

According to Trott and Olson [13], the docking of the ligands to various targets protein and evaluation of binding affinities was determined via AutodockVina. Pdbqt format of the

receptors, as well as those of the ligands, was dragged into their respective columns, and the software was run. A cluster analysis based on Root Mean Square Deviation (RMSD) values, regarding the starting geometry, was then performed, and the lowest energy conformation of the more populated cluster was measured as the most trustable solution. The binding affinities of compounds for the three protein targets were recorded. The compounds were then classified by their affinity scores. For comparison of *in silico* performance, the molecular interactions between the receptors and compounds with a binding affinity equal to or greater than standard inhibitors were viewed with Discovery Studio Visualizer, BIOVIA, 2016.

2.4. ADME studies.

The eight flavonoids from *Andrographis paniculata* were subjected to Absorption, Distribution, and Metabolism (ADME) studies to determine the drug-likeness of the compounds. ADME studies were determined by the Swiss online ADME web tool [14,15] to assess the drug-likeness of the chosen compounds. A graph of WLOGP against TPSA was plotted with the aid of GraphPad Prism 6 software (GraphPad Software, California, USA) to determine the blood-brain barrier (BBB) properties of the as described by Ishola and Adewole [16].

3. Results and Discussion

Results obtained from molecular docking of ligands to AChE revealed rutin had a higher binding affinity (-12.6 kcal/mol) for AChE compared to donepezil (-12.5 kcal/mol), a standard inhibitor of AChE (Table 1). Closely the following rutin is apigenin, taxifolin, epicatechin, and tangeritin with a binding affinity of -11.1, -11.0, -10.8, and -10.8 kcal/mol respectively for AChE. As observed for AChE, rutin also shows the most negative binding affinity (-12.2 kcal/mol) for BChE compared to donepezil's -10.6 kcal/mol (Table 1). However, tangeritin and taxifolin matched donepezil's binding affinity score of – 10.6 kcal/mol for BChE. For monoamine oxidase, rutin was the most outstanding ligand (-12.0 kcal/mol0 surpassing donepezil's affinity score of -11.5 kcal/mol. Out of the remaining ligands, only taxifolin (-11.0 kcal/mol) was closer to donepezil in its affinity for monoamine oxidase.

Table 1. Binding affinity of flavonoids from *Andrographis paniculata* for acetylcholinesterase, butyrylcholinesterase, and monoamine oxidase.

		Binding Affinity (Kcal/mol)		
S/N	Compounds	AChE	BChE	Monoamine Oxidase
S	Donepezil	-12.5	-10.6	-11.5
1	Apigenin	-11.1	-9.5	-9.9
2	Epicatechin	-10.8	-10.4	-10.2
3	Eriodictyol	-10.4	-10.2	-8.6
4	Hesperetin	-10.6	-10.0	-8.8
5	Luteolin	-10.6	-9.9	-10.7
6	Rutin	**-12.6**	**-12.2**	**-12.0**
7	Tangeritin	-10.8	-10.6	-8.2
8	Taxifolin	-11.0	-10.6	-11.0

Donepezil bind to a narrow gorge in AChE consisting of conserved amino acid residues. A π-π stacking was noticed among donepezil and Tyr84 as well as Phe330 in the anionic site of AChE. Also, a π-alkyl interaction was observed with Tyr334 in the peripheral anionic site (PAS) of AChE (Figure 1b). The side chain hydroxyl group in rutin was visualized to be involved in a multiple hydrogen bond formation with Ser286 and Arg289 in addition to two π-π stacking with Tyr70 and Trp279 (Figure 1d). Interaction between donepezil and BChE

revealed mainly hydrophobic interaction with conserved amino acid residues in BChE binding site. A π-π stacking was between donepezil, and active site residue (Tyr82) followed a π-anion interaction with Asp70 as well as a carbon-hydrogen bond with Ser72 (Figure 2b).

Rutin formed a π-anion bond with Asp70 in the PAS site of BChE. Another important residue, i.e., Tyr332 of the PAS site, was in multiple hydrogen and π-π stacking with rutin, whereas Asn68 was involved in hydrogen bond formation with one of the hydroxyl groups in rutin (Figure 2d). Hydrophobic interaction was predominant in the binding of donepezil to monoamine oxidase. Notably, a π-π stacking was revealed between donepezil and catalytic residue Tyr444 in the active gorge of monoamine oxidase. Arg51 was associated with both π-cation and π-alkyl formation with donepezil in addition to carbon-hydrogen bonds with Asn181, Tyr407, and Tyr444. (Figure 3b). No fewer than five hydrogen bonds were formed between Arg76, Glu477, His488, and Ile486 of monoamine oxidase and rutin with Lys440 involved in multiple π-cation interactions with the heterocyclic ring of rutin (Figure 3d).

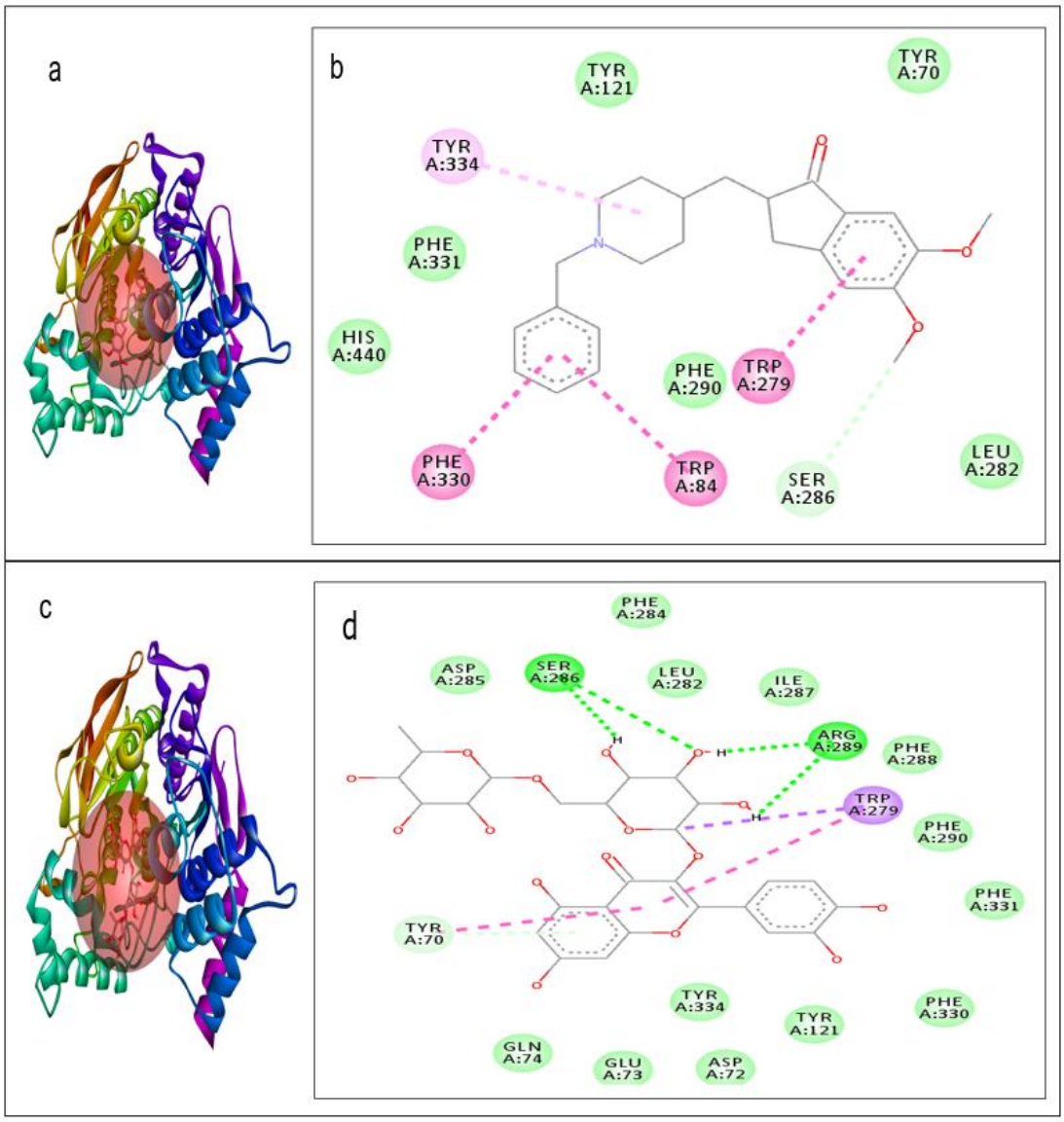

Figure 1. Binding profile of acetylcholinesterase inhibitors, (a) donepezil binding site (b) interaction between donepezil and amino acid residues in acetylcholinesterase (c) rutin binding site (d) interaction between rutin and amino acid residues in acetylcholinesterase. The green dotted line represents a hydrogen bond. The deep pink dotted line represents π-π stacking. The faint pink dotted line represents π-alkyl interaction; purple dotted lines represent a π-sigma bond.

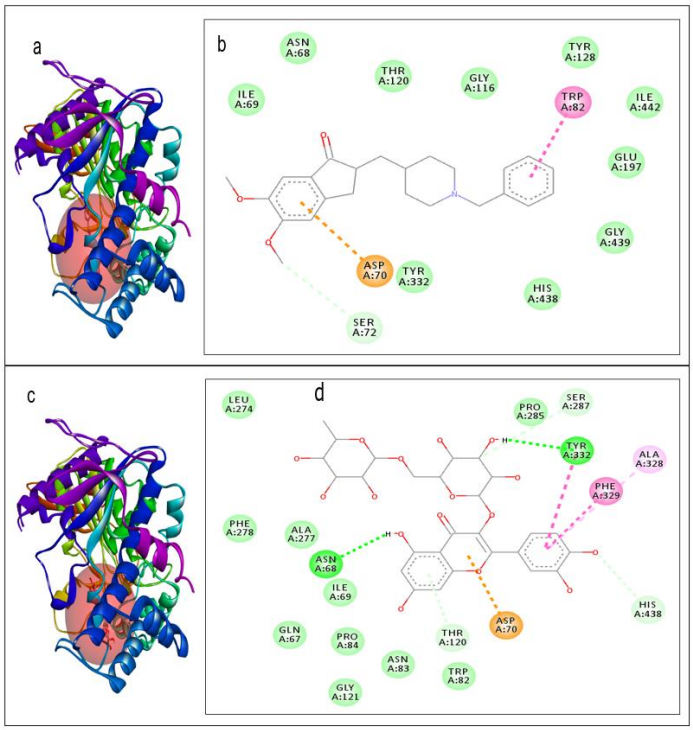

Figure 2. Binding profile of butyrylcholinesterase inhibitors, (a) donepezil binding site (b) interaction between donepezil and amino acid residues in butyrylcholinesterase (c) rutin binding site (d) interaction between rutin and amino acid residues in butyrylcholinesterase. The green dotted line represents hydrogen bond, the deep pink dotted line represents π-π stacking, the faint pink dotted line represents π-alkyl interaction, the faint green dotted line represents a carbon-hydrogen bond, orange dotted line represents π-anion interaction.

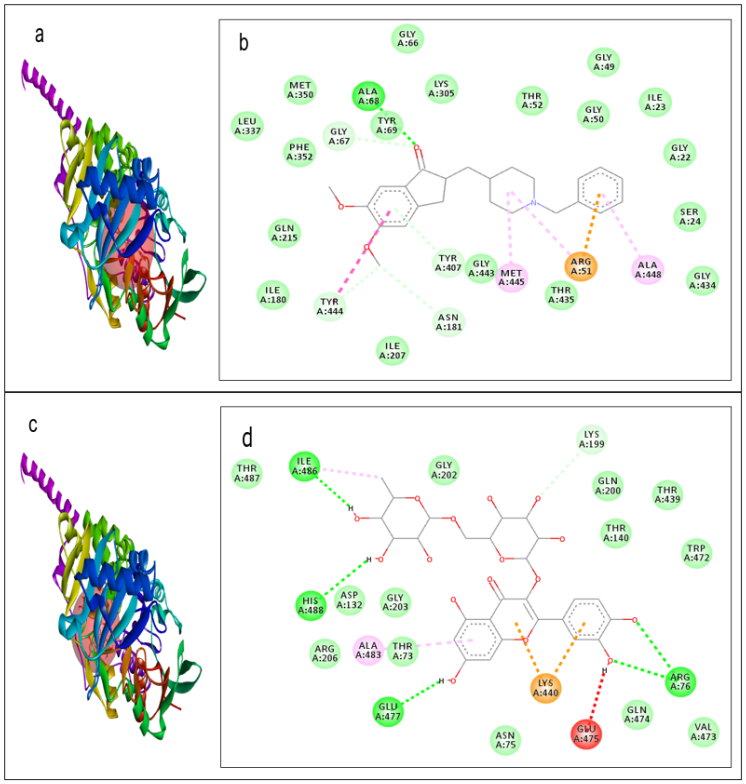

Figure 3. Binding profile of monoamine oxidase inhibitors, (a) donepezil binding site (b) interaction between donepezil and amino acid residues in monoamine oxidase (c) rutin binding site (d) interaction between rutin and amino acid residues in monoamine oxidase. The green dotted line represents hydrogen bond, the faint pink dotted line represents π-alkyl interaction, the faint green dotted line represents a carbon-hydrogen bond, orange dotted line represents π-anion interaction.

The obtained results from the ADME study of the eight flavonoids under study revealed that all but one of the compounds are probable oral drug candidates. Except for rutin, other compounds had a molecular weight less than 500 Daltons, less than 10 hydrogen bond acceptors, and less than 5 hydrogen bond donors. Also, MLogP (octanol/water partition coefficient) was less than 5. Rutin, however, violated the Lipinski's rule of 5 by having a molecular weight (610.52) greater than 500 Daltons, 16 hydrogen bond acceptors (greater than the accepted 10), 10 hydrogen bond donors (greater than the stipulated 5) (Table 2). Of all these compounds, only tangeritin fall within the acceptable range for a blood-brain barrier (BBB) permeate compound by having a TPSA < 79 Å**2** and WLogP less than 6 (Table 2). This shows in an egg yolk like model where 7 non-permeants fall outside the sphere with rutin (the only permeant found within the sphere (Figure 4)

Table 2. Physicochemical properties of flavonoids from *Andrographis paniculata*.

S/N	Compounds	MW	H-bond acceptor	H-bond donor	MLogP	Lipinski's violations	TPSA (Å^2)	WLogP	BBB Permeation
1	Apigenin	270.24	5	3	0.52	0	90.9	2.58	No
2	Epicatechin	290.27	6	5	0.24	0	110.38	1.22	No
3	Eriodictyol	288.25	6	4	0.16	0	107.22	1.89	No
4	Hesperetin	302.28	6	3	0.41	0	96.22	2.19	No
5	Luteolin	286.24	6	4	-0.03	0	111.13	2.28	No
6	Rutin	610.52	16	10	-3.89	3	269.43	-1.68	No
7	Tangeritin	372.37	7	0	0.63	0	76.36	3.5	Yes
8	Taxifolin	304.25	7	5	-0.64	0	127.45	0.68	No

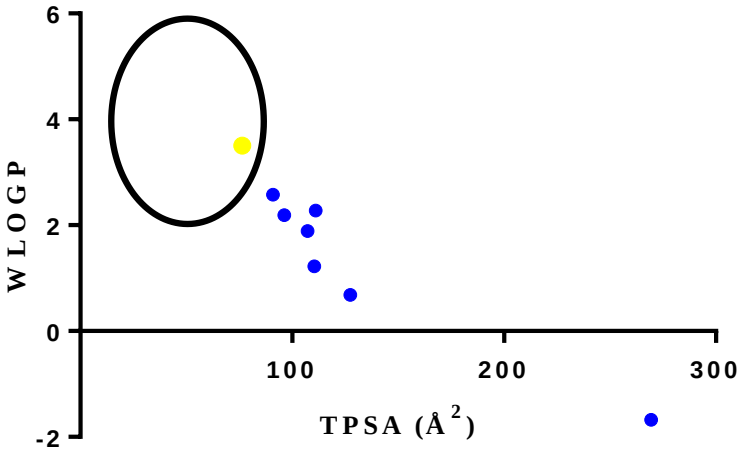

Figure 4. Blood-brain barrier properties of *Andrographis paniculata* alkaloids. 1 permeant (BBB+, the yellow dot inside the black sphere), 7 nonpermeants (BBB-, blue dots).

According to Jung and Park [17], the latest therapeutic approach to the management of neurodegenerative diseases is by inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzyme activities. Inhibiting these enzymes promotes communication amongst nerve endings and enhance their activities in the cholinergic pathways in the brain, thus improving the symptoms of various neurodegenerative diseases. It is well documented that AChE promotes aggregation of Aβ peptide and formation of Aβ–AChE complex at the synaptic region of the hippocampus leading to neuronal degeneration [17,19]. BChEs are assumed to perform a crucial role at the beginning of neurodegenerative diseases due to its major role in the transformation of harmless amyloid plaques to pathogenic structures existing in dementia and neurodegenerative diseases [20]. Therefore, the ability of rutin, taxifolin, and tangeritin to bind effectively to the two cholinesterases could be pivotal in the treatment of neurodegenerative diseases.

Monoamine oxidases (MAOs) are involved in the oxidative deamination of endogenous monoamine neurotransmitters as well as exogenous monoamine, such as tyramine. MAOs catalyze the breakdown of amine neurotransmitters and hence are considered as attractive drug targets in the therapy of neurological disorders [21]. Inhibition of MAO activity in the brain upsurges the synaptic level of the neurotransmitters serotonin, norepinephrine, and dopamine and the so-called ‘‘trace amines’’ such as β-phenylethylamine, tryptamine, and tyramine, these have been reported in the etiology of various psychiatric and neurologic disorders [22-24]. The ability of rutin to inhibit monoamine oxidase more than standard drug i.e., donepezil, suggests a positive neuromodulatory effect that can be worked on to achieve positive results in the treatments of neurodegenerative diseases.

Lipinski rule-of-five explained the relationship between pharmacokinetics and physicochemical parameters [25]. Lipinski highlighted that, normally, an orally active drug must not violate more than one of some criteria such as not greater than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms), not greater than 10 hydrogen bond acceptors (nitrogen or oxygen atoms), a molecular mass less than 500 Daltons and an octanol-water partition coefficient log P not greater than 5 [26, 27]. Except for rutin, all flavonoids considered in this study have their physicochemical properties within the acceptable range of oral drug candidates with no violation.

BBB (blood-brain barrier) disturbance has been noticed in other forms of neurological diseases, including amyotrophic lateral sclerosis (ALS), epilepsy, oedema, brain traumas, and Parkinson’s disease [28]. Therefore, the ability to cross the BBB is a vital reflection in the development of CNS-acting therapeutics. Reasonably polar (TPSA < 79 Å2) and relatively lipophilic (WLOGP from 0.4 to 6.0) compounds have a high probability of accessing the central nervous system (CNS) [15]. Thus, out of the *Andrographis paniculata* derived flavonoids used in this study, only tangeritin falls within the range of compounds that can transverse the BBB. The BBB is an essential cellular barrier that strictly controls the microenvironment of the CNS to allow for adequate neuronal function [29, 30]. Tangeritin with a reasonable binding affinity for AChE and BChE and its BBB crossing ability could prove significant in the treatment of neurodegenerative diseases. However, rutin displayed the most remarkable binding affinity but may not be able to transverse the BBB probably because of its low lipid solubility. Therefore, the use of this drug as a neurotherapeutic agent may be achieved through the use of selective vasoactive compounds like bradykinin to enhance brain permeability. Also, an alternative route of administration, such as the intranasal route, could be exploited. This would ensure that the drug bypasses the BBB and enters the brain through the olfactory route.

4. Conclusions

Inhibition of cholinesterase and monoamine oxidase activities are effective strategies employed in the treatment of neurodegenerative diseases. All *Andrographis paniculata* derived flavonoids used in this study are orally druggable except for rutin. Taxifolin and tangeritin showed a reasonable binding affinity for cholinesterases, while rutin was the most outstanding ligand for cholinesterases and monoamine oxidase. However, only tangeritin possesses the ability to cross the blood-brain barrier. Thus study emphasized flavonoids that could be examined using different experimental models to establish their anti-neurodegenerative activities.

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Conflicts of Interest

The authors declare no conflict of interest.

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