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Theoretical Investigation of Natural and Synthetic Cholinesterase Inhibitors for Alzheimer's Disease Treatment

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ABSTRACT

In Alzheimer's disease (AD), acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) represent important enzymatic targets, with inhibition achieved using either natural products or synthetic compounds. Passiflora incarnata provides natural bioactive molecules, mainly flavonoids (apigenin, luteolin, myricetin, orientin, quercetin, kaempferol, vitexin, isovitexin, isoorientin) and alkaloids (harman, harmine, harmol, harmaline, harmalol, 8-hydroxyharmine, harmine N-oxide). Prominent examples of synthetic inhibitors employed in clinical practice include donepezil, rivastigmine, galantamine, and tacrine.

To advance the design of next-generation inhibitors, molecular docking simulations were employed to screen for ligands with optimal interaction energies and to elucidate their binding affinities for each target enzyme. The analysis of natural products highlighted flavonoids as the most promising class, with isovitexin and orientin revealing the most robust binding profiles for AChE and BuChE. In parallel, donepezil demonstrated the highest affinity among the synthetic comparators.

These data illuminate the therapeutic viability of diverse chemical scaffolds in mitigating AD-associated enzyme activity, offering a valuable foundation for the development of optimized pharmacological treatments.

Keywords: *Acetylcholinesterase (AChE); Butyrylcholinesterase (BuChE); Passiflora incarnata; Flavonoids; ligand–protein interactions; binding affinity.*

1. INTRODUCTION

The emergence of multiple cognitive deficits is a defining characteristic of Alzheimer's disease (AD). A universal finding in patients with a probable diagnosis is early-onset memory impairment, which frequently co-occurs with attentional disturbances, difficulties in acquiring new information, and language deficits [1].

AD is the most common neurodegenerative disease, accounting for approximately 70% of reported cases of dementia [2]. The incidence and prevalence of AD increase with age, and other risk factors include a family history of dementia, genetic predisposition, female sex, head trauma, vascular disease, low educational level, and various environmental factors [2]. The formation of insoluble extracellular amyloid plaques due to the accumulation of amyloid β peptide is one of the key pathological features observed in the brains of patients with AD [3,4]. Several hypotheses have been proposed to explain AD, but none of them can provide the exact cause of the disease [5]. Among these, the cholinergic hypothesis, which involves the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), is the most prominent in the context of AD treatment [6]. AChE and BuChE inhibitors have become important tools in the management of AD. Although the effects of these agents appear mainly to be symptomatic, they may also exert potential neuroprotective effects. Currently, four cholinesterase inhibitors—tacrine, donepezil, galantamine, and rivastigmine—have been approved by the FDA for the symptomatic treatment of AD [6].

Plant extracts and their constituents are important natural sources of antioxidants. The antioxidant activity of many plant extracts is primarily attributed to secondary metabolites, especially phenolic compounds such as flavonoids, alkaloids, and tannins. The strong antioxidant capacity of flavonoids is considered one of their most relevant biological properties and is thought to underlie many of their physiological effects in the body [7]. Numerous experimental and theoretical studies have reported the neuroprotective effects of flavonoids [8-13].

Passiflora incarnata L. (Passifloraceae), commonly known as maypop or passionflower, is a medicinal plant that has long been used worldwide as an anxiolytic and sedative [14]. It is native to the tropical regions of the Americas, and its aerial parts have traditionally been employed, particularly in the United States, for the treatment of anxiety, nervousness, and neuralgia [15]. Flavonoids from Passiflora species are frequently described as antioxidant and neuroprotective agents in the pharmacological literature, which is consistent with this description.

The main constituents of P.incarnata leaves are flavonoids (approximately 0.25%), including vitexin, isovitexin, orientin, isoorientin, apigenin, and kaempferol. In addition to flavonoids, various indole alkaloids based on a β-carboline ring system, such as harman, harmine, harmalol, and harmaline, are also present. Other phytoconstituents identified in P. incarnata include carbohydrates, essential oils, amino acids, and the cyanogenic glycoside gynocardin [16]. The use of P. incarnata in individuals with chronic insomnia may exert therapeutic effects in the management of sleep disorders, memory impairment, and degenerative brain diseases. Passiflora preparations may thus be beneficial in the treatment of insomnia through their sedative properties, facilitating sleep onset in patients experiencing difficulty sleeping [17]. Flavonoids and related constituents from Passiflora species are consistently reported as antioxidant and neuroactive compounds in pharmacological studies.

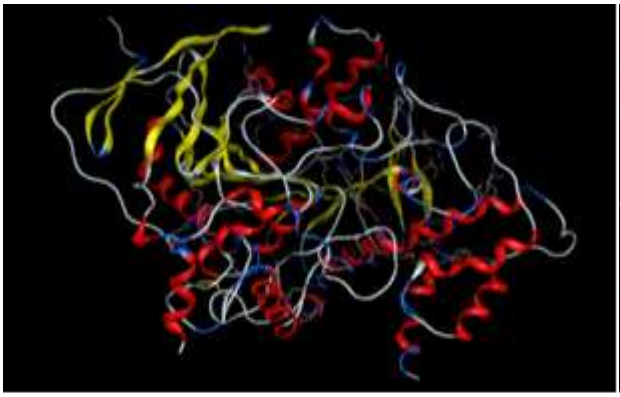
The present study was therefore designed to evaluate the inhibitory activity of two enzymes implicated in Alzheimer's disease, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), using two series of inhibitors: natural compounds from Passiflora incarnata, mainly flavonoids and alkaloids, and synthetic drugs (donepezil, galantamine, rivastigmine, and tacrine). Molecular docking was employed to investigate the formation of enzyme–inhibitor complexes and to characterize the interactions of both natural and synthetic ligands with the active sites of these enzymes.

2. MATERIALS AND METHODS

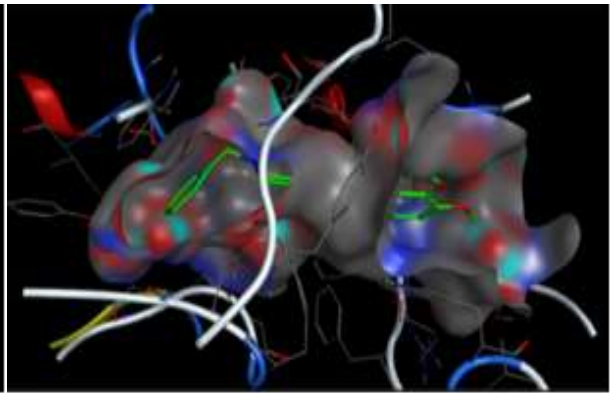
2.2. Preparation of enzymes

The PDB structures used, i.e. AChE (7E3H), BuChE (7QBQ), were obtained from the RCSB Protein Data Bank (www.rcsb.org) [18].

In Figure 1, each enzyme active site together with its co-crystallised ligand is shown.



Simplified model of AChE



AChE Active Site

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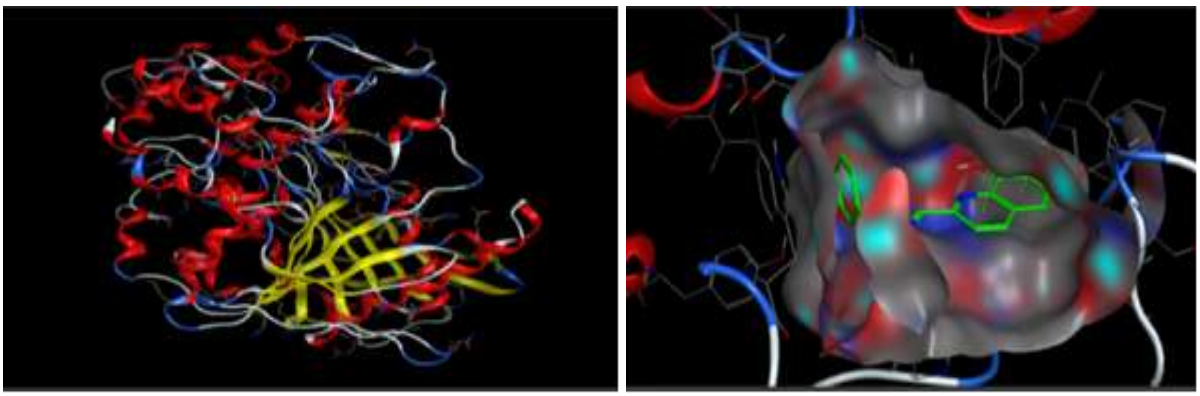


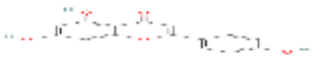
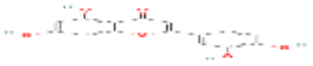
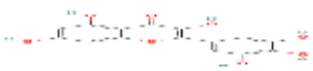
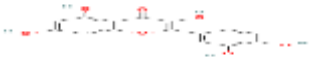
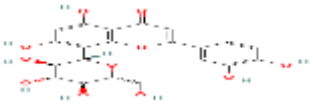
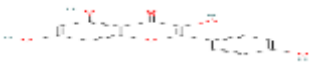
Simplified model of BuChE BuChE Active Site

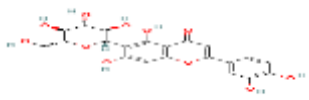
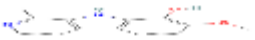
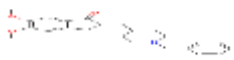
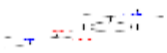
Figure 1. Simplified models and isolated active sites of the AChE and BuChE enzymes

2.2. Preparation of ligands

The structures obtained were optimized at the density functional theory (DFT) level using the hybrid functional B3LYP (Becke three-parameter exchange; Lee–Yang–Parr correlation) with the 6-31G* basis set in Gaussian 05 [19]. According to recent studies, the natural (flavonoid and alkaloid) and synthetic inhibitors considered for each enzyme in this work were identified, and their molecular structures together with their physicochemical properties are presented in Tables 1,2.

Table 1. Natural (flavonoid and alkaloid) and synthetic inhibitors evaluated for AChE and BuChE

Ligand	IUPAC name	Structure	PubChem CID
Flavonoids inhibitors			
Apigenin	5,7-dihydroxy-2-(4-hydroxyphenyl)chromen-4-on		5280443
Luteolin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4 one		5280445
Myricetin	3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one		5281672
Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one		5280343
Orientin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one		5281675
Kaempferol	3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one		5280863
Isovitexin	5,7-dihydroxy-2-(4-hydroxyphenyl)-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one		162350
Vitexin	5,7-dihydroxy-2-(4-hydroxyphenyl)-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one		5280441

Isoorientin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one		11477
Alkaloids inhibitors			
Harman	1-methyl-9H-pyrido[3,4-b]indole		5281404
Harmol	1-methyl-2,9-dihydropyrido[3,4-b]indol-7-one		68094
Harmine	7-methoxy-1-methyl-9H-pyrido[3,4-b]indole		5280953
Harmaline	7-methoxy-1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indole		3564
Harmalol	1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indol-7-ol1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indol-7-ol		3565
Harmin N-oxide	2-hydroxy-7-methoxy-1-methylpyrido[3,4-b]indole		85853001
8-hydroxy harmine	7-methoxy-1-methyl-9H-pyrido[3,4-b]indol-8-ol		129845702
Harmaline-on	7-methoxy-4,9-dihydro-3H-pyrido[3,4-b]indole-1-carbaldehyde		137209017
Synthetic polyphenols inhibitors of AChE and BuChE			
Donepezil	2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one		3152
Galantamine	(1S,12S,14R)-9-methoxy-4-methyl-11-oxa-4-azatetracyclo[8.6.1.01,12.06,17]heptadeca-6(17),7,9,15-tetraen-14-ol		9651
Rivastigmine	[3-[(1S)-1-(dimethylamino)ethyl]phenyl] N-ethyl-N-methylcarbamate		77991
Tacrine	1,2,3,4-tetrahydroacridin-9-amine		1935

The relevant physicochemical descriptors used to assess these compounds are compiled in Table 2.

Table 2. Physicochemical properties of natural and synthetic inhibitors targeting AChE and BuChE

Ligand	Weight	TPSA	Log P	Log P	H-bonds donors	H-bonds acceptors	Toxicity
Physicochemical properties of flavonoids							
Apigenin	270.24	87	2.42	-3.46	3	5	No
Luteolin	286.24	107	2.13	-3.10	4	6	No

Myricetin	218.23	148	1.72	-2.41	6	8	No
Quercetin	302.23	127	2.01	-2.71	5	7	No
Orientin	448.4	197	-0.26	-2.56	8	11	No
Kaempférol	286.24	107	2.31	-3.14	4	6	No
Isovitexin	432.4	66.8	2.71	-3.82	2	4	No
Vitexin	432.4	177	0.03	-2.92	7	10	No
Isoorientin	448.4	197	-0.26	-2.56	8	11	No
Physicochemical properties of alkaloids							
Harman	182.22	28.7	3.02	-2.58	1	1	Yes
Harmol	198.22	41.1	1.26	-2.42	2	3	No
Harmine	212.25	37.9	3.03	-2.63	1	2	Yes
Harmaline	214.26	37.4	2.54	-2.47	1	2	No
Harmalol	200.24	48.4	2.24	-2.06	2	2	No
HarmineN-oxide	228.25	37.3	2.29	-2.57	1	3	Yes
8-hydroxy harmine	228.25	58.1	2.74	-2.27	2	3	Yes
Harmaline-on	228.25	54.4	1.72	2.43	1	3	No
Physicochemical properties of synthetic Inhibitors of AChE and BuChE							
Donepezil	379.5	38.8	4.63	-4.23	0	4	No
Galantamine	287.35	41.9	2.12	-2.29	1	4	No
Rivastigmine	250.34	32.8	2.86	-1.99	0	3	No
Tacrine	198.26	38.9	2.70	-2.78	1	2	Yes

[a]Weight: Molecular weight (10^{-27} kg/mol); [b]TPSA: Polar surface area ($10^{-20}m^2$); [c]logP: Octanol-water partition coefficient; [d]logS:aqueous solubility; [e]H- bonds donors: Number of H- bonds donors; [f]H- bonds acceptors: Number of H- bonds acceptors.

Lipinski's rule of five [20], a valuable tool for selecting suitable candidates by predicting drug-like properties, was also evaluated for all ligands. Geometry optimization was performed using the MMFF94x force field [21], as implemented in MOE, and the semiempirical Hamiltonian AM1 [22]. The docking results were subsequently refined using the force-field energy.

2.3. Docking and Building Complexes

The next step consists of positioning the ligands in the enzyme active site. For this, we used the Molecular Docking Module in the MOE software. Once the ligand-receptor complex is formed, the most stable conformation is adopted and will show the lowest energy.

3. RESULTS AND DISCUSSION

The molecular docking results and interactions for the two best natural inhibitors and the best synthetic inhibitor are presented in Tables 3.

Compound	**Enzyme ; energy (kJ/mol)**	
	AChE	**BuChE**
Native ligand	-36.4245	-29.7060
Flavonoids		
Apigenin	-25.7103	-27.4396
luteolin	-27.5386	-27.8158
Myricetin	-28.1293	-25.3111
Quercetin	-28.2032	-27.9056

Orientin	-32.1182	**-29.5057**
Kaempferol	-27.0901	-24.0375
Isovitexin	**-33.4830**	-29.3222
Vitexin	-30.1294	-27.8195
Isoorientin	-32.0263	-29.2223
Alkaloids		
Harman	-20.9572	-20.8005
Harmol	-22.5247	-23.1877
Harmine	-24.4312	-25.1209
Harmaline	-23.8414	-26.7281
Harmalol	-22.3232	-24.6686
Harmine-N-oxide	-25.0490	-24.6114
8-hydroxy harmine	-23.9083	-24.5813
Harmalin-on	-25.1514	-25.8403
Synthetic Inhibitors of AChE and BuChE		
Donepezil	**-34.3566**	**-29.7060**
Galantamine	-27.2377	-28.4908
Rivastigmine	-26.4272	-23.6245
Tacrine	-22.5293	-26.2031

The corresponding ligand–enzyme interaction patterns are comprehensively summarized and discussed in Table 4.

Table 4. Interaction patterns of natural and synthetic ligands with AChE and BuChE amino acid residues

Compound	Ligand	Receptor	Interaction	Distance (nm)	E (kJ/mol)
Interactions of the best natural ligands with AChE amino acid residues					
Isovitexin	O5 8 6-ring	O TRP 86 6-ring TYR 341	(A) H-donor (A) pi-pi	0.275 0.361	-10.45 -0.00
Orientin	O4 6 6-ring	OE1 GLU 202 CB TRP 86	(A) H-donor (A) pi-H	0.288 0.416	-5.02 -3.76
Interactions of the best natural ligands with BuChE amino acid residues					
Orientin	O2 2 O9 13 6-ring	O PRO 285 NE2 HIS 438 CE2 PHE 329	(A) H-donor (A) H-acceptor (A) pi-H	0.291 0.333 0.386	-10.03 -5.43 -2.93
Isovitexin	O3 4 6-ring	OE1 GLU 197 CA PRO 285	(A) H-donor (A) pi-H	0.331 0.407	-3.76 -4.60
Interactions of the best synthetic ligand with AChE amino acid residues					
Donepezil	O1 1 N4 4 C6 7 6-ring	N ARG 296 OD2 ASP 74 6-ring TYR 341	(A) H-acceptor (A) ionic (A) pi-pi (A) pi-H	0.318 0.376 0.399 0.368	-3.34 -4.60 -3.76 -3.34

		CB TRP 86			
Interactions of the best synthetic ligand with BuChE amino acid residues					
Donepezil	N4 4 C6 7 C8 9	6-ring TYR 332 6-ring TYR 332 6-ring TYR 332	(A) cation-pi (A) H-pi (A) H-pi	0.454 0.430 0.407	-2.51 -2.51 -4.18

The ligand interactions were visualized using an improved 2D depiction layout algorithm, with protein residues arranged around the ligand to indicate spatial proximity. Residues are labeled with their three-letter amino acid code and sequence number [20,21]. In systems containing multiple chains, positions are prefixed by the corresponding letter. Interactions between 2.5 10^{-10} m and 3.1 10^{-10}m are considered strong, while those between 3.1 10^{-10} m and 3.55 10^{-10} m are moderate. Interactions greater than 3.55 10^{-10} m are considered weak [22].

3.1. Interaction to Acetylcholinesterase

3.1.1. Natural Compounds

These results show that Isovitexin and Orientin, two flavonoids, exhibited the lowest binding energy values (-33.4830 and -32.1182 kJ/mol, respectively). This suggests they are the most potent natural inhibitors and form the most stable complexes.

The complex formed by Isovitexin (the top-ranked natural inhibitor) (Figure 2) interacts with residues TRP 86 (A) (H-donor) and TYR 341 (A) (pi-pi interaction).

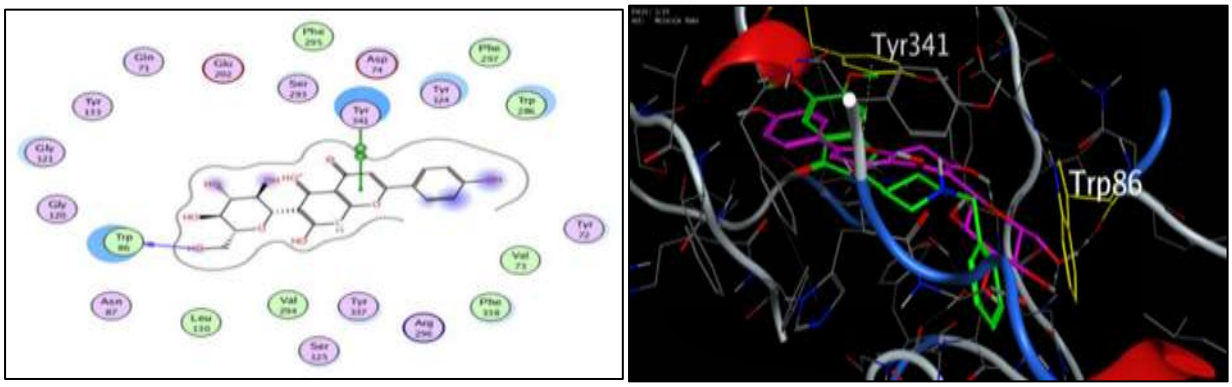


Figure 2. Interaction diagrams (AChE - Isovitexin) complex

These interactions occur at distances of 2.75 10^{-10} m (strong) and 3.61 10^{-10} m (weak), with energies of -2.5 and 0.0 kcal/mol, respectively.

The complex formed by Orientin (the second most stable natural inhibitor) (Figure 3) interacts with residues GLU 202 (A) (H-donor) and TRP 86 (A) (pi-pi interaction).

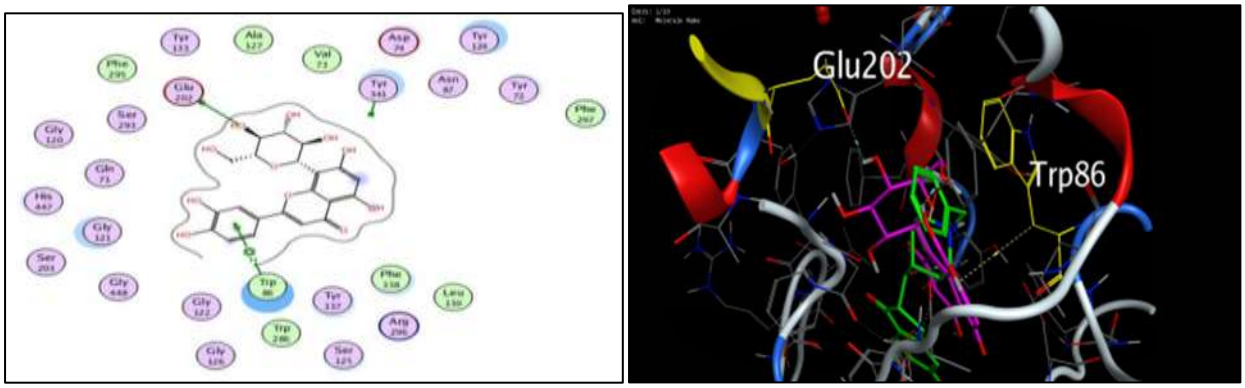


Figure 3. Interaction diagrams (AChE - Orientin) complex

These interactions occur at distances of 2.88 10^{-10} m (strong) and 4.16 10^{-10} m (weak), with energies of -1.2 and -0.9 kcal/mol, respectively. The involvement of TYR 341 suggests that Orientin has a significant binding affinity for acetylcholinesterase [23].

3.1.2. Synthetic Compounds

These results indicate that Donepezil exhibits the lowest binding energy (−34.3566 kJ/mol), suggesting it is the most effective synthetic inhibitor and forms the most stable complex.

The complex (Figure 4) formed by Donepezil interacts with several amino acid residues: ARG 296 (A) via an H-acceptor bond, ASP 74 (A) via ionic interaction, TYR 341 (A) via pi-pi stacking, and TRP 86 (A) via a pi-H interaction.

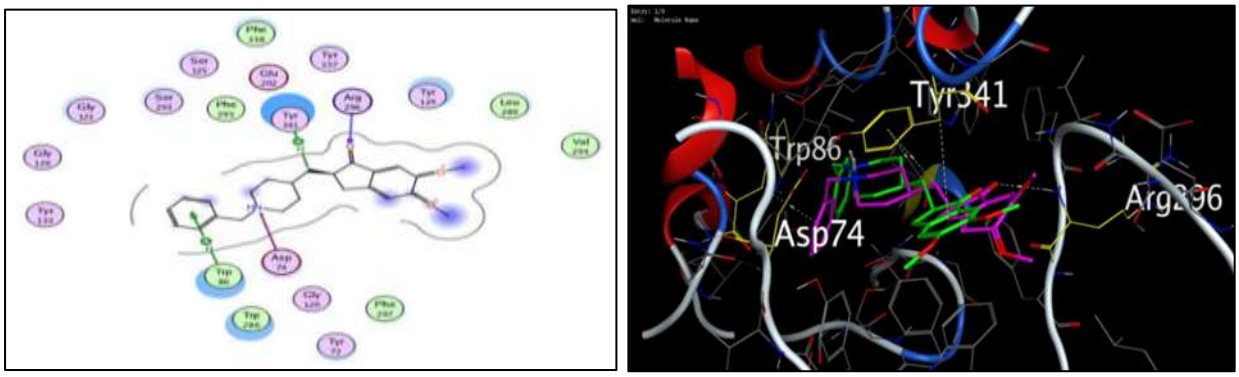


Figure 4. Interaction diagrams (AChE - Donepezil) complex

The respective distances for these interactions are 3.18, 3.76, 3.99, and 3.68 10^{-10} m, with interaction energies ranging between −4.60 and −3.34 kJ/mol [23].

3.2. Interaction to Butyrylcholinesterase

3.2.1. Natural Compounds

These results indicate that Orientin and Isovitexin, two flavonoids, exhibit the lowest binding energy values (−29.5057 kJ/mol and −29.3222 kJ/mol, respectively). This suggests they are likely the most effective natural inhibitors and form the most stable complexes.

The complex (Figure 5) formed by Orientin (the most effective natural inhibitor and most stable complex) interacts with amino acid residues PRO 385 (A) via an H-donor bond, HIS 438 (A) via an H-acceptor bond, and PHE 329 (A) via a pi-H interaction.

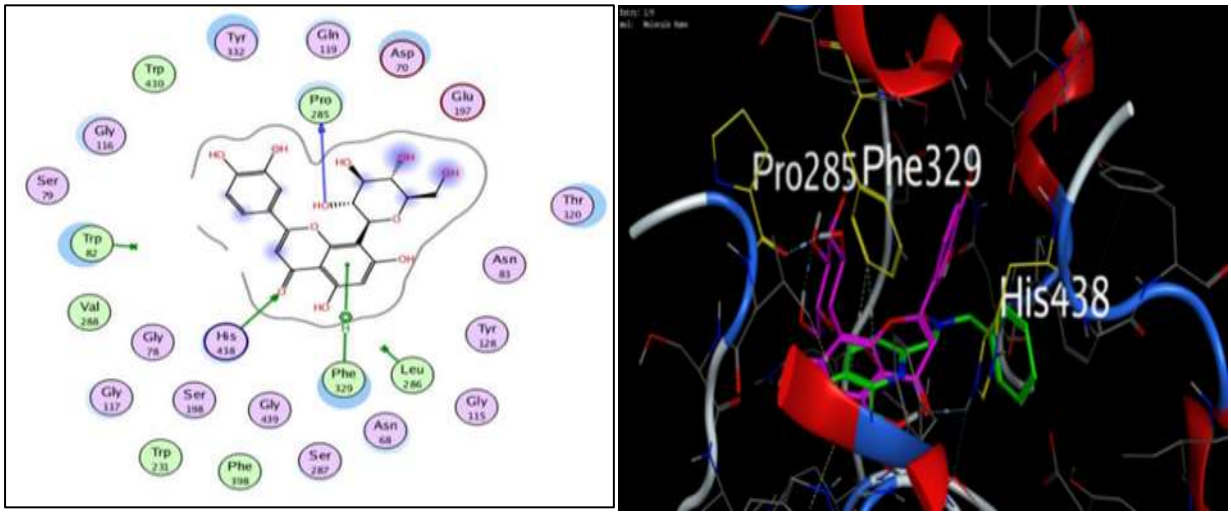


Figure 5. Interaction diagrams (BuChE - Orientin) complex

These interactions occur at distances of 2.91 10^{-10} m, 3.33 10^{-10} m, and 3.86 10^{-10} m, respectively (corresponding to strong, average, and weak interactions), with energies of −10.03, −5.43, and −2.93 kJ/mol. Additionally, the presence of electrostatic forces involving LEU 286 and TRP 82 suggests that Orientin possesses significant binding affinity for butyrylcholinesterase [23].

The complex (Figure 6) formed by Isovitexin (the second most effective natural inhibitor and second most stable complex) interacts with amino acid residues GLU 197 (A) via an H-donor bond and PRO 285 (A) via a pi-H interaction.

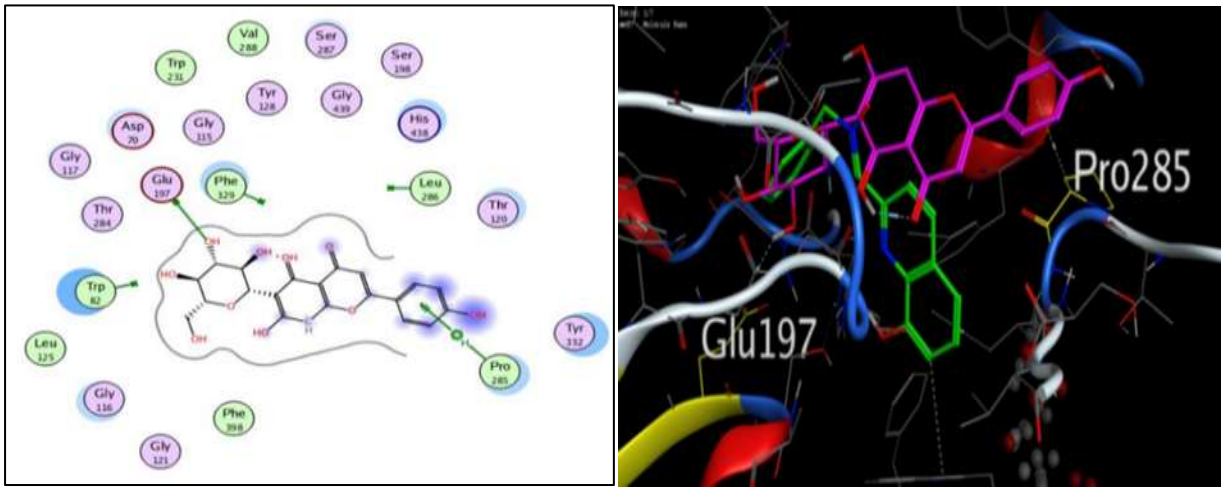


Figure 6. Interaction diagrams (BuChE - Isovitexin) complex

These interactions occur at distances of 3.33 10^{-10} m and 4.07 10^{-10} m, respectively (corresponding to average and weak interactions), with energies of −4.60 and −3.76 kJ/mol. The existence of three electrostatic forces involving LEU 286, PHE 329, and TRP 82 further suggests that Isovitexin has a significant binding affinity for butyrylcholinesterase [23].

3.2.2. Synthetic Compounds

These results indicate that Donepezil exhibits the lowest binding energy value (−29.7060 kJ/mol), suggesting it is likely the most effective synthetic inhibitor and forms the most stable complex.

The complex (Figure 7) formed by Donepezil interacts with the amino acid residue TYR 332 (A) via a cation-pi interaction and two H-pi interactions.

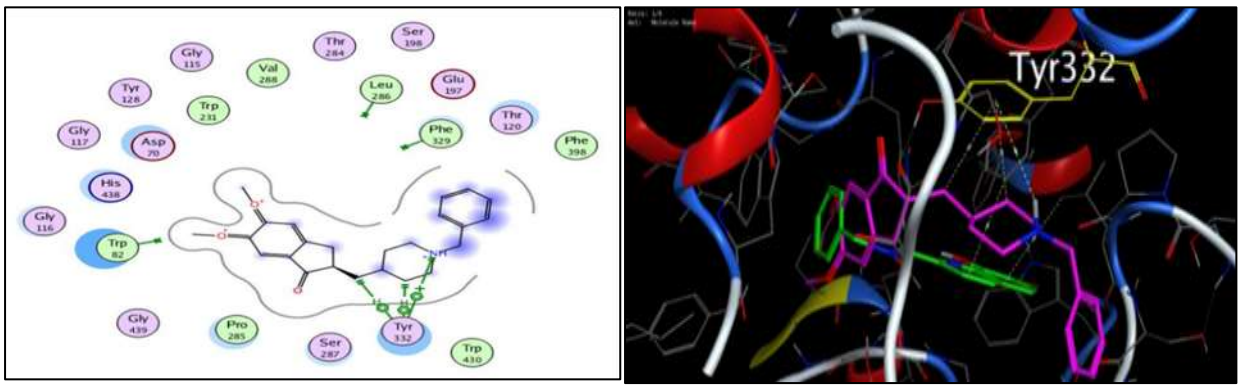


Figure 7. Interaction diagrams (BuChE -Donepezil) complex

These interactions occur at distances of 4.54 10^{-10} m, 4.30 10^{-10} m, and 4.07 10^{-10} m, respectively (weak interactions), with energies of −4.18, −2.51, and −2.51 kJ/mol . Additionally, the existence of electrostatic interactions involving residues LEU 286, PHE 329, and TRP 82 suggests that Donepezil possesses significant binding affinity for butyrylcholinesterase [23].
The graphical legend for the 2D interactions is shown is given in Figure 8.

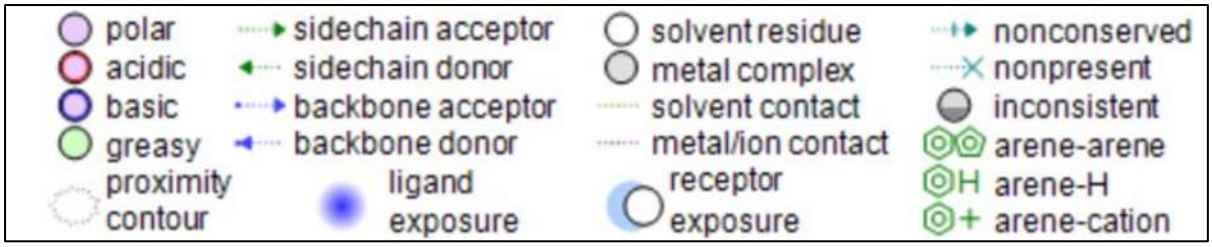


Figure 8. 2D graphical legend

4. CONCLUSION

The work presented in this study focuses on the use of molecular docking to calculate various parameters (score, energy) in order to better understand the inhibition mechanism of a specific neurodegenerative disorder: Alzheimer's disease.
The docking results revealed that flavonoids exhibited the highest affinity for the enzymes (lowest binding energy values) and consistent interaction profiles. Isovitexin and Orientin (natural compounds), along with Donepezil (synthetic compound), appear to be the most promising candidates for slowing the progression of Alzheimer's disease (AD) pathology.
The natural compounds comply with Lipinski's rules for oral drug administration [24,25]. Furthermore, a comparison of these inhibitors suggests that natural inhibitors can contribute effectively to the treatment of Alzheimer's disease.
Given the absence of reported side effects of these natural molecules on human health, they warrant more in-depth study to confirm their biological activity and inhibitory efficacy in larger populations. These results are also highly significant for the fields of phytotherapy and the prevention of this neurodegenerative disease.

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