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Insilico Studies and Pharmacokinetic Properties of Anti-Alzheirmer's Disease Activities of Phytocompounds Derived from *Lasianthera Africana*

Dearsly, Emmanuel Markus[1]; Eze, Kingsley Chijioke[2,3]; Chukwu, Constance Adaeze[2]; Ofem, Lilian William[2]

[1]Salem University Lokoja, Kogi State, Nigeria

[2]Department of Biochemistry, Faculty of Basic Medical Sciences, University of Calabar Nigeria

[3]Aquatic Bioresources Training Centre, Adiabo, Cross River State.

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Abstract: **Alzheimer's disease (AD) is a devastating mental illness with an irreversible progressive brain disorder that slowly destroys memory skills and learning abilities. No treatments stop or reverse the progression of Alzheimer's disease, though some may temporarily improve symptoms. Hence, the limitations of these treatment methods necessitate the search for an alternative among the herbs available to man. Lasianthera africana locally known as "Editan" in Ibibio and Annang tribes of Southern Nigeria, has pharmacological benefits which includes; possession of analgesic, antipyretic, antimalarial, anti-ulcerogenic, antimicrobial, antidiabetic, anti-inflammatory, antioxidant, hepatoprotective and cardioprotective. Computational methods were used to study the binding interaction of 44 compounds derived from lasianthera africana against four target receptors (butyrylcholinesterase, beta secretase enzyme 1, protein tyrosine phosphate 1B and glycogen synthase kinase-3 beta) out of which, top four compounds (quercetin, epicatechin, oleandrin and quercetin 3-methyl ether) were selected based on their binding affinities. These four compounds in comparison with domepezil (reference drug) were subjected to drug-likeness screening to examine their physiochemical properties and admet analysis to examine their pharmacokinetical properties. These four ligands showed the best pharmacokinetic and physicochemical properties, including good absorption, distribution, metabolism, and excretion (ADMET) and admetSAR toxicity tests. It is demonstrated that quercetin, oleandrin, epicatechin and quercetin-3-methyl ether have promising therapeutic effect on Alzheirmer's disease and Oleandrin exhibited a higher binding affinity and also a lower level of toxicity than the reference drug domepezil.**

Keywords: **Alzheimer's, phytocompounds, Lasianthera-africana, Admet, Domepezil.**

1. INTRODUCTION

Neuro-degenerative diseases represent a major threat to human health. These age- dependent disorders are becoming increasingly prevalent because the elderly population has increased in recent years [1]. Examples of neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia and the spinocerebellar ataxias [2]. As of 2020, there were approximately 50 million people worldwide with Alzheimer's disease [3]. It most often begins in people over 65 years of age, although up to 10% of cases are early-onset affecting those in their 30s to mid-60s. It affects about 6% of people 65 years and older, and women more often than men.

The disease is named after German psychiatrist and pathologist Alois Alzheimer, who first described it in 1906 [4]. Alzheimer's financial burden on society is large, with an estimated global annual cost of US$1 trillion. These diseases are diverse in their pathophysiology – with some causing memory and cognitive impairments and others affecting a person's ability to move, speak and breathe [5] [6] [7]. Alzheimer's disease (AD) is a neurodegenerative disease that usually starts slowly and progressively worsens. It is the cause of 60–70% of cases of dementia [8]. The most common early symptom is difficulty in remembering recent events. As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, self- neglect, and behavioral issues. As a person's condition declines, they often withdraw from family and society [9]. Gradually, bodily functions are lost, ultimately leading to death. There are many environmental and genetic risk factors associated with the development of Alzheimer's disease. The strongest genetic risk factor is from an allele of apolipoprotein E. [10]. Other risk factors include a history of head injury, clinical depression, and high blood pressure. The disease process is largely associated with amyloid plaques, neurofibrillary tangles, and loss of neuronal connections in the brain [11]. Good nutrition, physical activity, and engaging socially are known to be of benefit generally in aging, and these may help in reducing the risk of cognitive decline. There are no medications or supplements that have been shown to decrease risk. No treatments stop or reverse its progression, though some may temporarily improve symptoms [12]. Affected people increasingly rely on others for assistance, often placing a burden on the caregiver. [13]. The pressures can include social, psychological, physical, and economic elements. Exercise programs may be beneficial with respect to activities of daily living and can potentially improve outcomes [14]. No treatments stop or reverse the progression of Alzheimer's disease, though some may temporarily improve symptoms. Hence, the limitations of these treatment methods necessitate the search for an alternative among the herbs available to man. The aim of this study is to assess the anti alzheirmer's disease activities of phytocompounds from Lasianthera africana with target enzymes, Protein tyrosine phosphate 1B (PTB 1B), Butyrylcholinesterase (BChE), Glycogen Synthase Kinas-3 Beta (GSK3B) and Human beta secretase 1 (BACE 1), in Alzeihmer's diesease through molecular docking.

2. MATERIALS AND METHODS

Preparation of Phytocompounds from *lasianthera africana*

An in-house library of 44 compounds from *Lasianthera africana* was prepared by compiling phytochemicals previously reported from this plant through an extensive literature search performed on public databases including: the PubMed, Google Scholar, and Google databases.

Preparation of ligands

45 bioactive phytochemicals in structured Data Format (SDF) were derived from *Lasianthera africana, they* were retrieved from the PubChem database (www.pubchem.ncbi.nlm.nih.gov), PubMed Database [15], the Ligand molecules were further converted to the dockable PDBQT format using AutoDock Tools.

Table I. List of bioactive compounds derived from *lasianthera Africana*

S/N	COMPOUNDS
1.	Camphene
2.	2-hydroxybutanedioic acid
3.	2-hydroxypropane-1,2,3-tricarboxylic acid
4.	2-oxopropanoic acid
5.	2-pentylnon-2-enal
6.	2-tert-butylbenzene-1,4-diol
7.	3,4,5-trihydroxybenzoic acid
8.	4-(hydroxyiminomethyl)phenol
9.	4-phenylchromen-2-one
10.	5,7-dihydroxy-3-(4-hydroxypheny l)chromen-4-one
11.	8-methyl-8-azabicyclo[3.2.1]octane
12.	Acetic acid
13.	Acridine

14.	B-Carotene
15.	benzoic acid
16.	Butyric Acid
17.	Chlorogenicacid
18.	Coniferol
19.	Desulphosinigrin
20.	Dexpropranolol
21.	dihydrocaffeic acid
22.	Enalapril
23.	Epicatechin
24.	Furosemide
25.	Hexadecanoic acid
26.	Isocaryophyllene
27.	Isoorientin
28.	Isoquinoline
29.	Glutamic acid
30.	Linoleic acid
31.	Lisinopril Dihydrate
32.	octadeca-9,12,15-trienoic acid
33.	Oleandrin
34.	Phytyl acetate
35.	quercetin 3-methyl ether
36.	Quercetin
37.	Quinoline
38.	Rutin Hydrate
39.	Shikimic acid
40.	Squalene
41.	Succinic Acid
42.	Valeric acid
43.	Pyrazoles
44.	Epicaptoril

Preparation of protein

The crystal protein structures and their co-crystallized compounds as presented in Table II were retrieved from the Protein Data Bank [16]. From the retrieved structures, the native ligands were extracted, and water molecules removed using Discovery studio program.

Table II. Target proteins in alzheimer's disease

S/N	PROTEIN	PDB NUMBER	RESIDUES	CO-CRYSTALLINE COMPOUNDS
1	Protein Tyrosine phosphate 1B (PTB 1B)	2CM7	ARG 24	Isothiazolidinone
			ALA 27	
			SER 28	
			ASP 29	
			PHE 30	
			PRO 31	
			CYS 32	
			ALA 35	
			LYS 36	
			PHE 52	

			TRP 86	
			GLU 202	
			VAL 211	
			ILE 219	
			LEU 233	
			ARG 257	
			MET 258	
			GLY 259	
2	Butyrylcholinesterase (BChE)	6ESJ	ASP 70	Propidium
			TRP 82	
			GLY 117	
			SER 198	
			TRP 231	
			LEU 282	
			VAL 288	
			GLU 325	
			TYR 332	
			HIS 438	
3	Human Beta secretase 1 (BACE 1)	5I3V	ILE 110	Aminoquinoline
			ILE 126	
			ASN 233	
			SER 10	
			GLY 11	
			GLN 12	
			GLY 13	
			LEU 30	
			ASP 32	
			GLY 34	
			SER 35	
			VAL 69	
			PRO 70	
			TRY 71	
			THR 72	
			GLN 73	
			PHE 108	
			ILE 110	
			ASP 228	
4	Glycogen Synthase Kinas-3 Beta (GSK3B)	4ACH	ARG 92	Protium
			LYS 94	
			ARG 96	
			ASP 105	
			LEU 128	
			TYR 216	

Druglikeness screening

The selected compounds that were having higher binding affinity with target proteins in Alzheirmer's disease were subjected to various drug-likeness filtering analysis. The drug-likeness analysis which includes Lipinski, Veber, Ghose, Egan and Muegge were performed on the SwissADME [17] webserver.

The drug-likeness properties of the compound were screened using the Lipinski's rule (molecular mass (MM) less than 500 Da, no more than 5 hydrogen bond donors (HBD), no more than 10 hydrogen bond acceptors (HBA), and partition coefficient (log p).

ADMET (absorption, distribution, metabolism, excretion and toxicity) analysis

The compounds with the highest binding interaction with target proteins where subjected to ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) analysis to study and analyze the **Absorption** – (How much of the phytocompound can be absorbed and how quickly), **Distribution**- (where is the phytocompound distributed within the body and what is the rate and extent of the distribution), **Metabolism**- (How fast can the phytocompound be metabolized, what is the mechanism of action and what metabolite is formed and is it active or toxic) **Elimination**- (How is the phytocompound excreted and how quickly) (**Toxicity**-Does this phytocompounds have a toxic effect to body systems or organs).

3. RESULTS AND DISCUSSION

Alzheimer's disease (AD) is an aggressive form of dementia, manifesting in memory, language and behavioral deficits [18]. The future of treatment of Alzheimer's disease lies in targeting important enzyme with medicinal plants and phytochemicals with acclaimed anti-alzheimer's activity [19]. Butyrylcholine, a choline-based ester that can function as a neurotransmitter is similar to acetylcholine, with activation of some of the same receptors as acetylcholine. Butyrylcholine is rapidly destroyed by the enzyme Butyrylcholinesterase and thus is effective only briefly. Inhibitors of the enzyme (drugs known as butylincholinesterases) prolong the lifetime of butyrylcholine [20]. Individuals with Alzheimer's disease have the presence of β-amyloid plaques and neurofibrillary tangles (NFT) which destroys the butyrlcholine in the brain that has to deal with memory and learning at the hippocampus in the brain [21]. The main target of this *in silico* analysis is to identify phytoconstituents in *lasianthera africana* that can inhibit the activities of butyrylcholinesterase in the brain in comparism with Domepezil (reference drug).

To investigate the *in silico* interaction of phytocompounds from *lasianthera africana* with important drug target in alzheimer's disease, an in-house library of the phytochemicals was created. Compilation of phytoconstituent of l*asianthera africana* leaf was made and a total number of 60 compounds were recorded.

The molecular docking was carried out on the 60 phytocompounds with prepared protein and amino acid residues. The docking scores was recorded to pick the top phytocompounds that interacted most with the drug target. During molecular docking, 8 exhaustiveness was used to get the best docking scores as shown in table III.

Interaction analysis was carried out using Discovery studio to identify the type of bonds existing between the enzyme-ligand reaction and bond distances as shown in Table VI. From interactions carried out, top four compounds with high binding affinity were recorded as shown in table VI.

Molecular docking results

The results of molecular docking against the selected enzymes in Alzheirmer's disease are shown in table 4.1 as represented by the docking scores. The docking scores of the compounds range from -10.3 to -3.1 for BChE, -8.5 to -3.1 for GSK-3B, -10.3 to -4.1 for BACE-1 and -8.3 to -3.9 for PTB-1B.

Table III. Docking score of phytochemicals from *Lasianthera africana* with target enzymes.

S/N	COMPOUNDS	BChE	GSK-3B	BACE-1	PTB -1B
1.	Camphene	-5.9	-4.8	-5.0	-4.7
2.	2-hydroxybutanedioic acid	-4.7	-4.8	-4.8	-4.5
3.	2-hydroxypropane-1,2,3-tricarboxylic acid	-5.5	-4.9	-4.9	-4.8
4.	2-oxopropanoic acid	-3.9	-3.9	-4.1	-4.2
5.	2-pentylnon-2-enal	-5.9	-4.6	-5.4	-5.0
6.	2-tert-butylbenzene-1,4-diol	-6.2	-5.1	-6.3	-6.0
7.	3,4,5-trihydroxybenzoic acid	-6.6	-5.7	-5.6	-5.7
8.	4-(hydroxyiminomethyl)phenol	-5.9	-5.1	-5.6	-6.0

9.	4-phenylchromen-2-one	-8.7	-7.2	-8.3	-6.7
10.	5,7-dihydroxy-3-(4-hydroxypheny l)chromen-4-one	-8.9	-7.2	-9.0	-7.0
11.	8-methyl-8-azabicyclo[3.2.1]octane	-5.2	-4.0	-4.5	-4.1
12.	Acetic acid	-3.1	-3.1	-3.4	-3.7
13.	Acridine	-8.2	-6.3	-7.2	-7.0
14.	B-Carotene	-8.5	-8.2	-8.1	-7.3
15.	benzoic acid	-5.9	-4.9	-5.9	-5.2
16.	Butyric Acid	-4.2	-3.8	-3.9	-4.8
17.	Chlorogenicacid	-8.2	-7.3	-7.9	-6.5
18.	Coniferol	-6.6	-5.4	-6.1	-6.5
19.	Desulphosinigrin	-6.9	-5.9	-5.7	-5.6
20.	Dexpropranolol	-7.7	-5.8	-7.2	-5.9
21.	dihydrocaffeic acid	-6.7	-6.0	-6.5	-7.2
22.	Enalapril	-8.2	-6.3	-7.5	-6.1
23.	Epicatechin	-8.8	-7.4	-8.4	-7.0
24.	Furosemide	-7.5	-6.3	-7.2	
25.	Hexadecanoic acid	-5.2	-4.2	-5.0	-3.6
26.	Isocaryophyllene	-7.3	-6.2	-6.8	-6.3
27.	Isoorientin	-9.3	-7.7	-8.9	-8.3
28.	Isoquinoline	-6.3	-5.2	-6.1	-5.3
29.	Glutamic acid	-5.0	-4.5	-4.7	-5.4
30.	Linoleic acid	-5.8	-5.2	-5.6	-5.0
31.	Lisinopril Dihydrate	-7.7	-6.4	-7.6	-5.5
32.	octadeca-9,12,15-trienoic acid	-6.0	-4.9	-5.6	-5.1
33.	Oleandrin	-10.3	-8.5	-10.1	-8.0
34.	Phytyl acetate	-5.9	-5.0	-6.0	-4.6
35.	quercetin 3-methyl ether	-8.8	-7.3	-8.7	-6.9
36.	Quercetin	-9.2	-8.0	-8.8	-7.9
37.	Quinoline	-6.4	-5.1	-5.9	-6.4
38.	Rutin Hydrate	-10.0	-8.7	-10.3	-7.8
39.	Shikimic acid	-6.0	-5.0	-5.1	-5.4
40.	Squalene	-7.3	-5.5	-7.1	-4.4
41.	Succinic Acid	-4.6	-4.0	-4.7	-5.3
42.	Valeric acid	-4.5	-3.9	-4.2	-5.1
43.	Pyrazoles	-7.7	-5.6	-4.2	-6.3
44.	Epicaptoril	-5.7	-5.0	-4.8	-4.8

NB: BChE- Butylincholinesterase**, GSK-3B-** Glycogen Synthase Kinas-3 Beta **BACE1-** Human Beta secretase 1, **PTB 1B** -Protein Tyrosine phosphate 1B

Table IV. The Grid Box information of the Target Enzymes

DIMENSIONS	BChE	GSK-3BETA	BACE1	PTB-1B
CENTER_X	26.04	27.66	62.57	5.90
CENTER_Y	29.64	36.24	47.26	2.37
CENTER_Z	43.33	46.84	0.03	5.47
DIMENSION_X	83.08	83.08	76.94	68.55
DIMENSION_Y	82.82	73.03	73.85	61.74
DIMENSION_Z	69.15	68.01	56.74	69.15

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Vol. 11, Issue 5, pp: (58-73), Month: September - October 2024, Available at: www.noveltyjournals.com

Table V. Docking score of selected ligands with high binding affinity, co-crystallized compounds and Drugs used in treatment of AD.

S/N	COMPOUNDS	PTB-1B	GSK-3B	BACE-1	BChE
1	Oleandrin	-6.7	-8.1	-10.2	-9.8
2	Rutin hydrate	-6.5	-8.5	-10.4	-10.0
3	Quercetin	-8.0	-7.4	-8.7	-9.2
4	Isoorientin	-8.3	-7.6	-8.9	-9.3
5	3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one	-7.6	-7.0	-8.5	-9.1
6	3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl) chromen-4-one	-6.8	-7.1	-8.8	-9.4
7	2-(hydroxymethyl)anthracene-9,10-dione	-7.8	-7.4	-8.0	-8.4
8	B-Carotene				
9	quercetin 3-methyl ether	-7.5	-6.9	-8.7	-9.1
10	Epicatchin	-8.0	-7.3	-8.8	-8.8
11	7-hydroxy-3-(4-hydroxyphenyl)chromen-4-one	-7.7	-6.9	-8.7	-8.9
CO-CRYSTALLINE COMPOUNDS					
1	Propidium				-9.4
2	Protium		8.3		
3	Aminoquinoline			-6.4	
4	Isothiazolidinone	-9.9			
DRUGS USED IN TREATING AD					
1	Domepezil	-7.2	-8.2	-8.1	-9.5
2	Rivastigmine	-5.6	-5.3	-6.6	-7.2
3	Memantine	-4.8	-5.7	-6.0	-6.4

Interaction of Bche protein with top ligands

Table VI. Table of interaction of top ligands and (BChE) protein

Compounds	Hydrogen bond interaction (Bond Distance A)		Hydrophobic interaction		Other interaction
	Numbers	Residues	Numbers	Residue	
Oleandrin	4	SER 72 (2.69) **TRP 82 (3.03)** **HIS 438 (2.98)** **TRP 82 (2.30)**	1	**TRP 82 (3.89)**	
Quercetin	3	GLY 116 (2.95) LEU 286 (2.02) **HIS 438 (3.12)**	7	**TRP 82 (5.07)** **TRP 231 (5.47)** PHE 329 (4.93) **HIS 438 (4.50)** GLY 116 (5.05) **GLY 117 (5.05)**	
Quercetin 3-methyl ether	3	THR 120 (2.18) ALA 328 (2.51) GLY 197 (2.34)	2	TRP 430 (5.97) ALA 328 (4.32)	
Epicatchin	2	**SER 198 (2.39)** LEU 286 (2.70)	8	**TRP 82 (5.44)** TRP 231 (5.39/ 5.17) HIS (5.36) PHE 329 (5.02) **HIS 438 (5.26)** GLY 116 (5.04) LEU 286 (5.12)	
Domepezil	1	**HIS 438 (3.43)**	5	**TRP 82 (4.06)** **TYR 332 (5.21/ 4.09)** ALA 328 (4.11) PHE 329 (5.09)	

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Interaction of top ligands and BChE

The complex shown in figure 1 shows the interaction of donepezil with BChE protein, it shows the 2-D and 3-D interaction of donepezil-BChE with His 447 with bond distance of 3.43. His438 an important amino acid in BChE and a nucleophile. It also shows interaction of Donepezil-BChE where a ketone group on the pyrol ring on donepezil conducted conventional hydrogen bond with amino acid His438 which acts as a nucleophile. The hydrogen bond of His438 to donepezil interprets that His438 is bonded tightly to donepezil. The hydrogen bond indicates that when donepezil interacts with BChE, the nucleophile will not be easily broken off the drug target and will keep the active site of BChE occupied from further hydrolysis of Ach in patients with Alzheimer's disease

The complex as shown in Figure 2 shows the interaction of oleandrin with butyrylcholinesterase. It shows the 2-D and 3D representation of oleandrin-BChE with important amino acid His438 with bond distance 2.98. The ketone group on the benzyl ring on oleandrin conducted conventional hydrogen bond with Amino acid His438 (a nucleophile). The hydrogen bond of His438 to oleandrin is tightly bonded and allows oleandrin to bind to the active site of BChE to prevent further hydrolysis of Bch in AD patients.

The complex as shown in Figure 3 shows the interaction of quercetin with butyrylcholinesterase. It shows the 2-D representation of quercetin-BChE with important amino acid His438 which has a conventional hydrogen bond with a bond distance of 3.13 and an electrostatic bond with a bond distance of 4.50. The hydrogen bond of His438 to quercetin is tightly bonded.

Figure 4 shows the interaction of epicatchin with butyrylcholinesterase. It shows the 2-D and 3D representation of epicatchin-BChE with important amino acid His438 with bond distance 5.26. Epicatchin conducted a hydrophobic bond with Amino acid His438 (a nucleophile). The hydrophobic bond of His438 to epicatchin is tightly bonded and allows epicatchin to bind to the active site of BChE to prevent further hydrolysis of Bch in AD patients.

The (2D) and (3D) schematic interaction of ligands and target protein

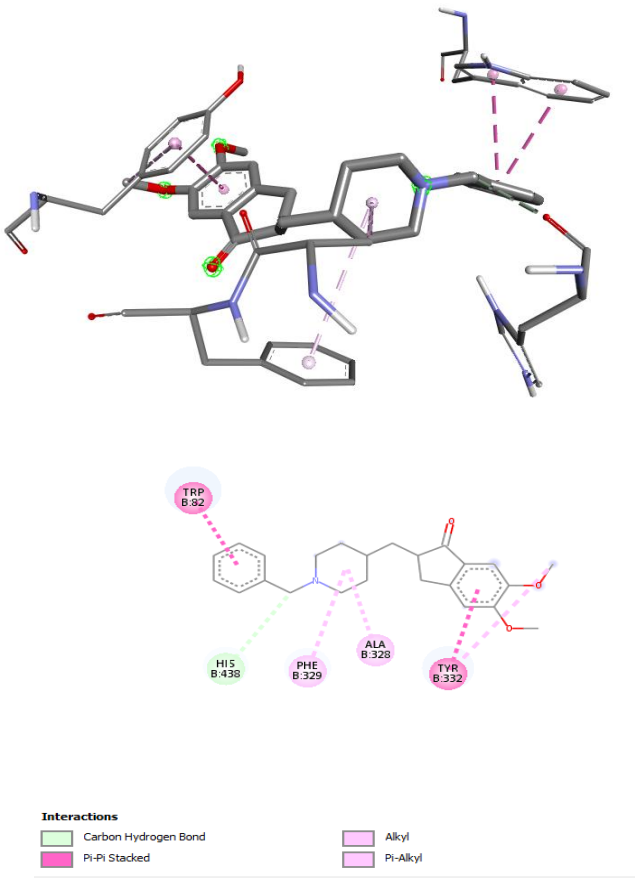

Figure 1. BChE-Domepezil interaction: (3D) and (2D) surface view

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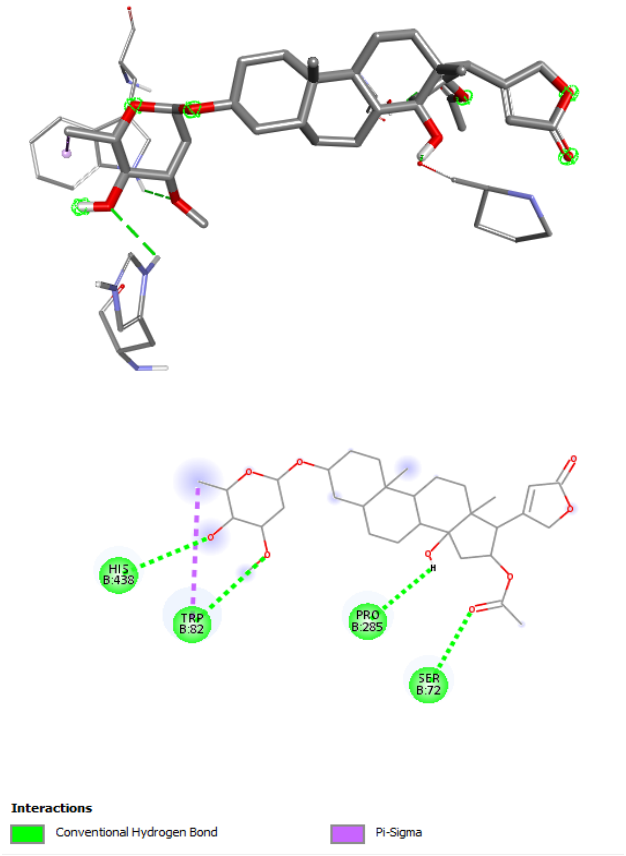

Figure 2. BChE-Oleandrin interaction: (3D) and (2D) surface view

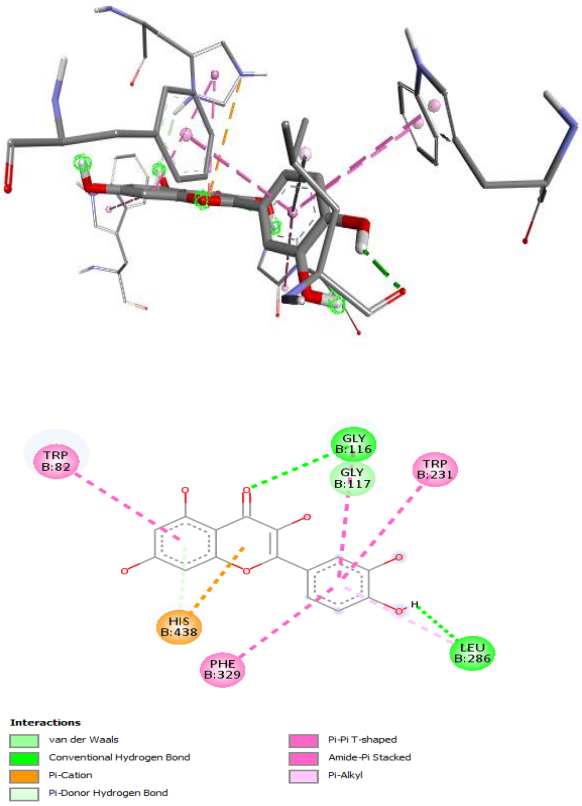

Figure 3. BChE-Quercetin interaction: (3D) and (2D) surface view

International Journal of Novel Research in Life Sciences
Vol. 11, Issue 5, pp: (58-73), Month: September - October 2024, Available at: www.noveltyjournals.com

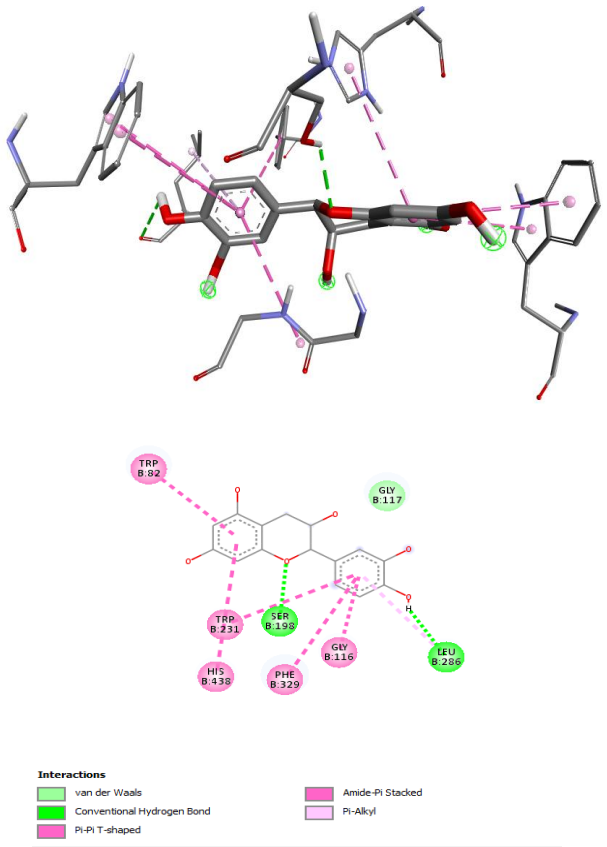

Figure 4. BChE-Epicatchin interaction: (3D) and (2D) surface view

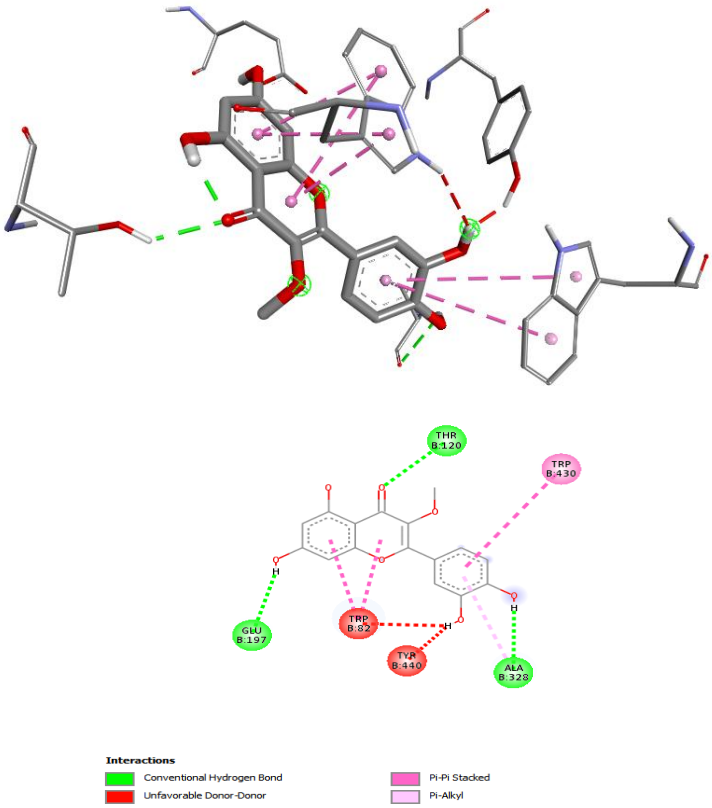

Figure 5. BChE-quercetin-3-methyl ether interaction: (3D) and (2D) surface view

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DRUG-LIKENESS ANALYSIS

Drug-likeness test was carried out. Lipinski rule of five, which involves:≤ 500 Da molecular weight (MM) , ≤ 5 hydrogen bond donors (HBD), ≤ 10 hydrogen bond acceptors (HBA), partition coefficient (logP) score was applied to screen the top four phytocompounds derived with high binding interaction as shown in Table 4.5 All 4 phytocompounds passed the drug-likeness filtering. This test was carried out to ensure that the phytocompounds possess drug-like properties; physiochemical properties. generally, a drug should not be too heavy that is why the molecular weight of drugs should be ≤500 molecular weight. A drug should have ≤5 hydrogen bond donors so it won't attack the biomolecules in the body and ≤10 hydrogen bond acceptors so it can be metabolized by the body.

Compounds with fewer (and preferably no) violations of these rules are considered drug-like and are more likely to be orally available. It was observed from the results that 4 of the top compounds (quercetin, epicatechin, oleandrin and quercetin-3-methyl ether) obeyed these rules as shown in (Table VII). The results therefore proves that the compounds possessed drug-like features, to be considered for future drug developments.

Table VII. Druglikeness results of top compounds that exhibited high binding interaction with BChE target protein

Compounds	Lipinski	Ghose	Veber	Egan	Muegge	Remark
Oleandrin	Yes	No	Yes	Yes	Yes	Passed
Quercetin	Yes	Yes	Yes	Yes	Yes	Passed
Quercetin 3-methyl ether	Yes	Yes	Yes	Yes	Yes	Passed
Epicatechin	Yes	Yes	Yes	Yes	Yes	Passed
Memantine	Yes	Yes	Yes	Yes	No	Passed

Admet analysis of top compounds

With top 4 compounds selected, ADMET (Absorption, distribution, metabolism, excretion and toxicity) analysis was then carried out to determine the behavior of the phytocompounds in a biological system.

Distribution and permeability prediction

Blood brain barrier Penetration

Drugs that act in the CNS need to cross the blood–brain barrier (BBB) to reach their molecular target. Predicting BBB penetration means predicting whether compounds pass across the blood-brain barrier. This is crucial in pharmaceutical sphere because CNS-active compounds must pass across it and CNS-inactive compounds mustn't pass across it in order to avoid of CNS side effects [22].

The results has proven that all 4 compounds have the ability to penetrate through the blood brain barrier and reach their target.

Human Intestinal Absorption

Predicting human intestinal absorption of drugs is very important for identify potential drug candidate. ADMET analysis can predict percent human intestinal absorption (%HIA). Human intestinal absorption data are the sum of bioavailability and absorption evaluated from ratio of excretion or cumulative excretion in urine , bile and feces [23]

The result revealed that all 4 compounds possesses high human intestinal absorption properties.

Prediction of Pgp-inhibitors

The P-glycoprotein, also known as MDR1, is a membrane protein member of the ATP-binding cassette (ABC) transporters superfamily. It is the most promiscuous efflux transporter, among the 4 compounds, oleandrin inhibits the p-glycoprotein which might lead to a certain of toxicity in the body, while the 3 other compounds are not inhibitors of p-glycoprotein.

Prediction of primary metabolism

Human cytochrome P450 3A4 (CYP3A4), an important enzyme mainly in the liver and responsible for the metabolism of more than 80% of medicines. This enzyme contains heme, and it catalyzes mainly 40-45% of phase 1 metabolic reactions such as hydroxylation, oxidation, and dealkylation [24]

All the top 4 compounds showed non or moderate inhibitory activity on the CYP P450 enzyme.

Ames toxicity test

The Ames test is an assay to determine the ability of a chemical or drug to induce mutations in DNA. It can be presented by " AMES toxic " or " Non AMES toxic " indicating a yes or no relationship for the predicted property [25]

All 4 compounds exhibited non AMES toxic property.

Carcinogenicity

Carcinogenicity refers to the ability of a substance to cause cancer. Any chemical, biomolecule or radionuclide that is directly involved in causing cancer can be considered as a carcinogen [26]

The principal objective of carcinogenicity studies is to identify the carcinogenic potential of medicinal products, as part of the assessment of risk for drug discovery.

All compounds exhibited non carcinogenic properties, which means they don't have the potential of inducing cancerous cells when used as drug leads.

Clearance and excretion

Clearance is the ability of the body to clear a drug from the plasma and from all other tissues while Drug excretion is the removal of drugs from the body, either as a metabolite or unchanged drug [27]. There are many different routes of excretion, including urine, bile, sweat, saliva, tears, milk, and stool [28]. But the most important excretory organs are the kidney and liver [29]. From the results obtained, all 4 compounds exhibited good clearance and excretion properties [30].

Comparison between quercetin, epicatechin, oleandrin, quercetin-3-methyl ether (the best hit) and domepezil (reference drug).

It is observed that oleandrin have higher binding affinity than domepezil. It can be seen that all the four compounds have not violated the Lipinski's rule of five, therefore are said to be orally bioavailable with good bioavailability scores. Their human intestinal absorption value indicates that they can be absorbed within the intestine. They were also found to be well distributed within the brain and the central nervous system. Domepezil is an inhibitor of the p-glycoprotein but only oleandrin among the four compounds were seen to inhibit the p-glycoprotein.

Domepezil was seen to have a high potential of inducing liver injury but among the four compounds, only oleandrin was seen to have the potential of inducing liver injury. and none of the compounds showed mutagenic effect which gave a negative result to the AMES toxicity test.

Table VIII. ADMET result of domepezil (reference drug)

PROPERTY	MODEL NAME	PREDICTED VALUE
ABSORPTION	Water solubility	-4.30 (mol/L)
	Human intestinal absorption	High
	P-glycoprotein inhibitors	Yes
DISTRIBUTION	VDss (Human)	1.589 (L/kg)
	BBB permeability	Yes
METABOLISM	CYP 1A2 Inhibitor	No
	CYP2C19 Inhibitor	No
	CYP2C9 inhibitor	No
	CYP2D6 inhibitor	Yes
	CYP3A4 inhibitor	No
EXCRETION	Total Clearance	10.635 (mL/min/kg)
TOXICITY	AMES Toxicity	Non toxic
	Human hepatoxicity	Yes
	Carcinogenicity	Non carcinogenic

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Table IX. ADMET result of quercetin

PROPERTY	MODEL NAME	PREDICTED VALUE
ABSORPTION	Water solubility	-3.16 (mol/L)
	Human intestinal absorption	High
	P-glycoprotein inhibitors	No
DISTRIBUTION	VDss (Human)	0.579 (L/kg)
	BBB permeability	Yes
METABOLISM	CYP 1A2 Inhibitor	Yes
	CYP2C19 Inhibitor	No
	CYP2C9 inhibitor	No
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	No
EXCRETION	Total Clearance	8.284 (mL/min/kg)
TOXICITY	AMES Toxicity	Non toxic
	Human hepatoxicity	Yes
	Carcinogenicity	Non carcinogenic

Table X. ADMET result of epicatechin

PROPERTY	MODEL NAME	PREDICTED VALUE
ABSORPTION	Water solubility	-2.99 (mol/L)
	Human intestinal absorption	High
	P-glycoprotein inhibitors	No
DISTRIBUTION	VDss (Human)	0.661 (L/kg)
	BBB permeability	Yes
METABOLISM	CYP 1A2 Inhibitor	No
	CYP2C19 Inhibitor	No
	CYP2C9 inhibitor	No
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	No
EXCRETION	Total Clearance	17.911 (mL/min/kg)
TOXICITY	AMES Toxicity	Non toxic
	Human hepatoxicity	No
	Carcinogenicity	Non carcinogenic

Table XI. ADMET result of oleandrin

PROPERTY	MODEL NAME	PREDICTED VALUE
ABSORPTION	Water solubility	-4.342 (mol/L)
	Human intestinal absorption	High
	P-glycoprotein inhibitors	Yes
DISTRIBUTION	VDss (Human)	1.516 (L/kg)

	BBB permeability	Yes
METABOLISM	CYP 1A2 Inhibitor	No
	CYP2C19 Inhibitor	No
	CYP2C9 inhibitor	No
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	No
EXCRETION	Total Clearance	6.09 (mL/min/kg)
TOXICITY	AMES Toxicity	Non toxic
	Human hepatoxicity	No
	Carcinogenicity	Non carcinogenic

Table XII. ADMET analysis result of quercetin-3-methyl ether

PROPERTY	MODEL NAME	PREDICTED VALUE
ABSORPTION	Water solubility	-3.642 (mol/L)
	Human intestinal absorption	High
	P-glycoprotein inhibitors	No
DISTRIBUTION	VDss (Human)	0.683 (L/kg)
	BBB permeability	Yes
METABOLISM	CYP 1A2 Inhibitor	Yes
	CYP2C19 Inhibitor	No
	CYP2C9 inhibitor	No
	CYP2D6 inhibitor	No
	CYP2D6 substrate	No
	CYP3A4 inhibitor	No
EXCRETION	Total Clearance	8.978 (mL/min/kg)
TOXICITY	AMES Toxicity	Non toxic
	Human hepatoxicity	No
	Carcinogenicity	Non carcinogenic

4. CONCLUSION

Alzheimer's disease (AD) is a devastating mental illness with an irreversible progressive brain disorder that slowly destroys memory skills and learning abilities. No treatments stop or reverse the progression of Alzheimer's disease, though some may temporarily improve symptoms. Hence, the limitations of these treatment methods necessitate the search for an alternative among the herbs available to man. Lasianthera africana locally known as "Editan" in Ibibio and Annang tribes of Southern Nigeria, has pharmacological benefits which includes; possession of analgesic, antipyretic, antimalarial, anti-ulcerogenic, antimicrobial, antidiabetic, antiinflammatory, antioxidant, hepatoprotective and cardioprotective. Computational methods were used to study the binding interaction of 35 compounds derived from lasianthera africana against four target receptors (butyrylcholinesterase, beta secretase enzyme 1, protein tyrosine phosphate 1B and glycogen synthase kinase-3 beta) out of which, top four compounds (quercetin, epicatechin, oleandrin and quercetin 3-methyl ether) were selected based on their high binding affinities with the target proteins. These four compounds in camparison with domepezil (reference drug) were subjected to drug-likeness screening to examine their physiochemical properties and admet analysis to examine their pharmacokinetical properties. These four ligands showed the best pharmacokinetic and physicochemical properties, including good absorption, distribution, metabolism, and

excretion (ADMET) and admetSAR toxicity tests. It is demonstrated that quercetin, oleandrin, epicatechin and quercetin-3-methyl ether have promising therapeutic effect on Alzheimer's disease and oleandrin having a higher binding affinity also exhibited a lower level of toxicity than the reference drug domepezil

REFERENCES

[1] Heemels, M. T. (2016). Neurodegenerative diseases. *Nature*, 539(7628), 179-180. DOI: 10.1038/539179a

[2] Kumar, V., Abbas, A. K., & Aster, J. C. (2017). The central nervous system. In *Robbins & Cotran Pathologic Basis of Disease* (10th ed., pp. 1271-1342). Elsevier.

[3] Breijyeh, Z., & Karaman, R. (2020). Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules*, 25(24), 5789. DOI: 10.3390/molecules25245789

[4] Alzheimer's Association. (2023). *2023 Alzheimer's disease facts and figures. Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *19*(4), 657-738. https://doi.org/10.1002/alz.13016

[5] Abeliovich, A., & Gitler, A. D. (2016). Defects in trafficking bridge Parkinson's disease pathology and genetics. *Nature*, 539(7628), 207-216.DOI: 10.1038/nature20414

[6] Canter, R. G., Penney, J., & Tsai, L. H. (2016). The road to restoring neural circuits for the treatment of Alzheimer's disease. *Nature*, 539(7628), 187-196.DOI: 10.1038/nature20412

[7] Taylor, D. H., Jr., Sloan, F. A., & Doraiswamy, P. M. (2016). The high cost of Alzheimer's disease. *Nature Reviews Neurology*, 12(11), 602-603.DOI: 10.1038/nrneurol.2016.162

[8] Aminoff, M. J., Boller, F., Swaab, D. F., Romanovsky, A. A., Garami, A., Imeri, L., ... & Steiner, A. A. (2018). Thermoregulation: from basic neuroscience to clinical neurology. In *Progress in Brain Research* (Vol. 156). Elsevier.
DOI: 10.1016/bs.pbr.2018.03.004

[9] Prince, M., Wimo, A., Guerchet, M., Ali, G. C., Wu, Y. T., & Prina, M. (2015). *World Alzheimer Report 2015: The global impact of dementia*. Alzheimer's Disease International (ADI). https://www.alzint.org/resource/world-alzheimer-report-2015/

[10] Holtzman, A., Buys, J., Du, L., Forbes, M., & Choi, Y. (2019). The curious case of neural text degeneration. *arXiv preprint arXiv:1904.09751*.Available at: https://arxiv.org/abs/1904.09751

[11] Querfurth, H. W., & LaFerla, F. M. (2010). Alzheimer's disease. *The New England Journal of Medicine*, *362*(4), 329-344. https://doi.org/10.1056/NEJMra0909142

[12] Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., ... & Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, *396*(10248), 413-446. https://doi.org/10.1016/S0140-6736(20)30367-6

[13] Barnes, K., Marateo, R. C., & Ferris, S. P. (2007). Teaching and learning with the net generation. *Innovate: Journal of Online Education*, 3(4). Available at: http://nsuworks.nova.edu/innovate/vol3/iss4/1

[14] Forbes, D., Forbes, S. C., Blake, C. M., Thiessen, E. J., & Forbes, S. (2015). Exercise programs for people with dementia. *Cochrane Database of Systematic Reviews*, *2015*(4), CD006489. https://doi.org/10.1002/14651858.CD006489.pub4

[15] National Center for Biotechnology Information (NCBI). (2024). PubMed. National Library of Medicine (US). Available at: https://pubmed.ncbi.nlm.nih.gov/

[16] RCSB Protein Data Bank. (2024). Structure of amyloid-beta peptide (PDB ID: 1IYT). Retrieved from https://www.rcsb.org

[17] Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, 7, 42717. DOI: 10.1038/srep42717 Available at: http://www.swissadme.ch/index.php

[18] Santana, I., Farinha, F., Freitas, S., Rodrigues, V., & Carvalho, Á. (2015). The epidemiology of dementia and Alzheimer disease in Portugal: Estimations of prevalence and treatment costs. *Acta Médica Portuguesa*, 28(2), 182-188. DOI: 10.20344/amp.5634

[19] Ayaz, M., Sadiq, A., Junaid, M., Ullah, F., Subhan, F., & Ahmed, J. (2017). Neuroprotective and anti-aging potentials of essential oils from aromatic and medicinal plants. *Frontiers in Aging Neuroscience, 9*, 168. https://doi.org/ 10.3389/fnagi.2017.00168

[20] Lane, R. M., & He, Y. (2013). Butyrylcholinesterase: Heterogeneity, polymorphisms and potential therapeutic targets in Alzheimer's disease. *Drugs & Aging, 30*(8), 671-681. https://doi.org/10.1007/s40266-013-0091-6

[21] Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*, *8*(6), 595-608. https://doi.org/10.15252/emmm.201606210

[22] Ajay, Bemis, G. W., & Murcko, M. A. (1999). Designing libraries with CNS activity. *Journal of Medicinal Chemistry*, 42(24), 4942-4951.DOI: 10.1021/jm990462o

[23] Zhao, Y. H., Le, J., Abraham, M. H., Hersey, A., Eddershaw, P. J., Luscombe, C. N., ... & Platts, J. A. (2001). Evaluation of human intestinal absorption data and subsequent derivation of a quantitative structure–activity relationship (QSAR) with the Abraham descriptors. *Journal of Pharmaceutical Sciences*, 90(6), 749-784. DOI: 10.1002/jps.1029

[24] Lifongo, L. L., Simoben, C. V., Ntie-Kang, F., Babiaka, S. B., & Mbaze, L. M. A. (2013). A bioactivity versus ethnobotanical survey of medicinal plants from Nigeria, West Africa. *Natural Products and Bioprospecting*, 3(6), 236-253. DOI: 10.1007/s13659-013-0018-4

[25] Cheng, F., Li, W., Zhou, Y., Shen, J., Wu, Z., Liu, G., ... & Tang, Y. (2012). admetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. *Journal of Chemical Information and Modeling*, 52(11), 3099-3105.DOI: 10.1021/ci300367a

[26] Kilcoyne, A., Ambery, P., & O'Connor, D. (Eds.). (2013). *Pharmaceutical Medicine*. OUP Oxford. ISBN: 978-0199645686 First Edition

[27] Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *The Lancet, 377*(9770), 1019-1031. https://doi.org/10.1016/S0140-6736(10)61349-9

[28] Gauthier, S., & Wimo, A. (2012). *Drug development in Alzheimer's disease*. In *Drug Discovery and Development - Drug Metabolism* (pp. 251-272). Springer. https://doi.org/10.1007/978-3-642-23859-6_15

[29] Lu, C., Liu, H., & Li, Y. (2018). Pharmacokinetics and pharmacodynamics of drugs used in Alzheimer's disease. *Frontiers in Aging Neuroscience, 10*, 357. https://doi.org/10.3389/fnagi.2018.00357

[30] Jansen, W. J., & van der Flier, W. M. (2014). *The role of liver and kidney function in the pharmacokinetics of drugs used for Alzheimer's disease*. In *Alzheimer's Disease Drug Development* (pp. 161-175). Wiley. https://doi.org/ 10.1002/9781118790652.ch13