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Molecular docking and pharmacokinetic and toxicological predictions of natural compounds with anticholinesterasic activity

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Abstract

Alzheimer's disease (AD) is considered the leading and most common age-related dementia, accounting for 50-60% of cases. The most commonly used pharmacotherapeutic approach for the symptomatic control of AD is anticholinesterase drugs, that is, they have an inhibitory activity on the enzyme acetylcholinesterase (AChE), thus increasing the cerebral levels of the neurotransmitter acetylcholine (Ach). For many years, Traditional Chinese Medicine has been cataloging numerous medicinal plants, which present various pharmacological activities, such as anti-Alzheimer's activity. This variety of plants, present compounds that interact with multiple proteins that are involved in several pathways associated with AD. The main objective of this study is an *in silico* study of 14 natural compounds, where the molecular docking and pharmacokinetic and toxicological predictions was carried out. As a first step the following molecules were selected in the literature: 1,8-cineole, bornil acetate, α-pinene, β-pinene, camphor, cariophilene epoxide, physostigmine, galantamine, γ-terpinene, honokiol, huperzine A, licoramine , magnolol and resveratrol, and later designed with the Chemsketch program and the chemical structures optimized with the Hartree-Fock method and the base function 6-31G ** previously validated in the Laboratory of Pharmaceutical and Medicinal Chemistry (PharMedChem) and implemented in the Gaussian program 03. The second step was the molecular docking study carried out with the software GOLD 4.1 where it was possible to study the intermolecular interactions among the selected natural products with the amino acids present in the active site of the AChEenzyme, the connections were largely hydrophobic interactions and hydrogen bonds and all 14 molecules showed interactions with the amino acid residues TRP286, PHE295, TYR341, TYR72 present in the catalytic site of the target enzyme, but only 13 presented three or more interactions, predominantly. In order to predict the pharmacokinetic properties of the selected molecules, the QikProp module of the Schrödinger software was used, which computed some important properties such as: molecular weight, polar surface area (PSA), logP, logBB, percentage of human oral absorption, activity predicted in the central nervous system, apparent permeability in cells and MDCK. As a result, all 14 molecules were found to have satisfactory PSA, LogBB, permeability to Caco-2 and MDCK cells, but only 7 molecules were able to cross the blood-brain barrier. The toxicity profile of the 14 molecules selected was performed by the DEREK program, where a total of 19 structural alerts were verified. The molecules that presented these alerts were: camphor, caryophyllene epoxide, physostigmine, honokiol, magnolol and resveratrol. Based on the results presented by the study, the following compounds were found: α-pinene, β-pinene, galantamine, γ-terpinene and lycoramine presented potential for use in the planning and development of new anti-Alzheimer drug candidates.

Keywords: Alzheimer's disease; molecular docking; natural compounds; pharmacokinetic predictions; toxicological predicions.

INTRODUCTION

- Alzheimer Disease is a progressive neurodegeneration, with marked loss of cognitive functions: memory, concentration and learning.
- Currently, it is considered as the most common senile dementia, and may present in 1% of the population with 65 years old.
- Increasing to 35% in the population with 85 years old.
- It is estimated that 26 milion people sulfer from this type of dementia worldwide.

Source: https://www.dm.com.br/opiniao/2018/03/alzheimer-e-suas-complicacoes.html

(BAGATIN et al., 2013; FERREIRA; MASSANO, 2013)

MAIN SYMPTOMS

IN THE EARLY STAGES OF THE DISEASE

- RECENT MEMORY DEFICIT
- DIFFICULTY OF ATTENTION
- DECREASED VISUOSPATIAL ABILITY

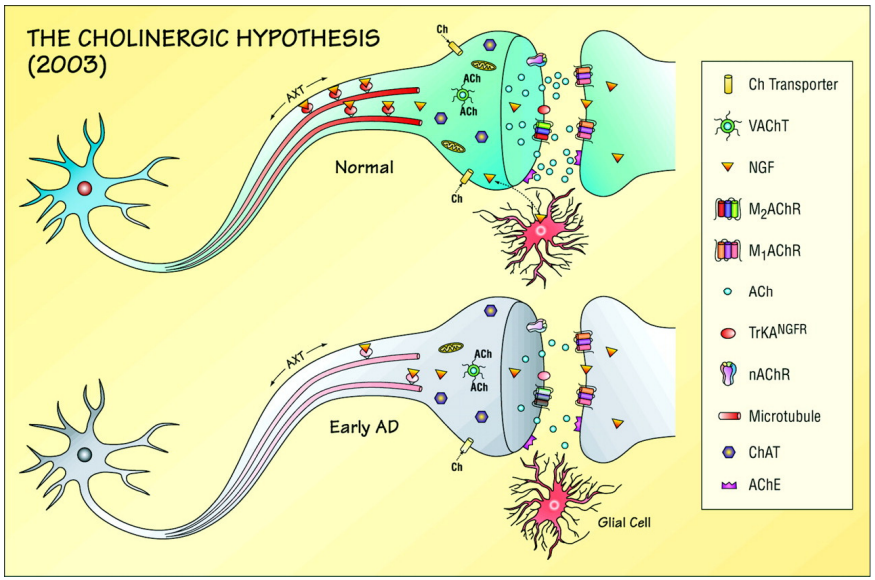
IN THE ADVANCED STAGES

BEHAVIORAL DISORDERS:

- Irritability;
- Aggressiveness;
- Hallucinations;
- Depression.

CHOLINERGIC HYPOTHESIS

- Relates amnesic dysfunction to the variable loss of cholinergic neurons in the basal Meynert nucleus, as well as the decrease in the expression of the enzyme choline acetyltransferase (ChAT) responsible for the production of acetylcholine (DE FALCO et al., 2016).



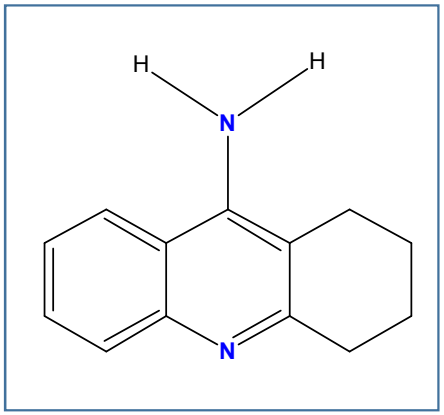
Source: TERRY; BUCCAFUSCO, 2003

ACETYLCHOLINESTERASE INHIBITORS (IAChE)

- The use of IAChE in the treatment of patients with AD has as main function, to increase the cerebral levels of the neurotransmitter acetylcholine (Ach), in this way, optimizes the cholinergic neurotransmission, benefiting the cognitive function of the patient (TALESA, 2001).

- Several IAChE with different chemical structures and mechanisms of inhibition have been used with this purpose being the main responsible for the relative gain of cognitive abilities, on the part of the patient, being clinically demonstrated a real improvement in the attention deficit (TALESA, 2001).

ACETYLCHOLINESTERASE INHIBITORS (IAChE)



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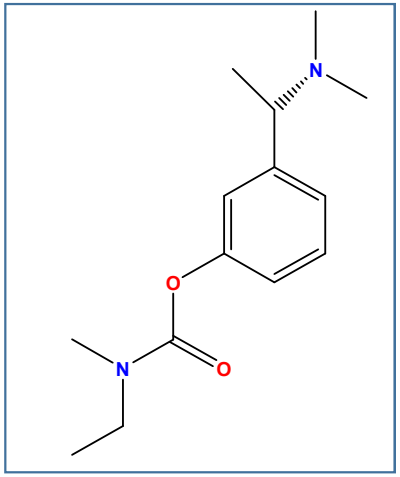

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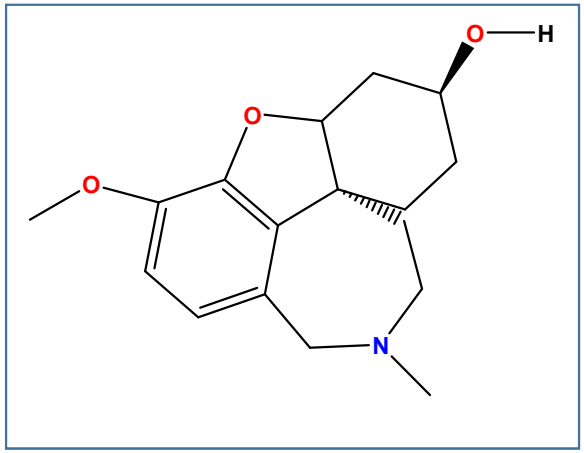

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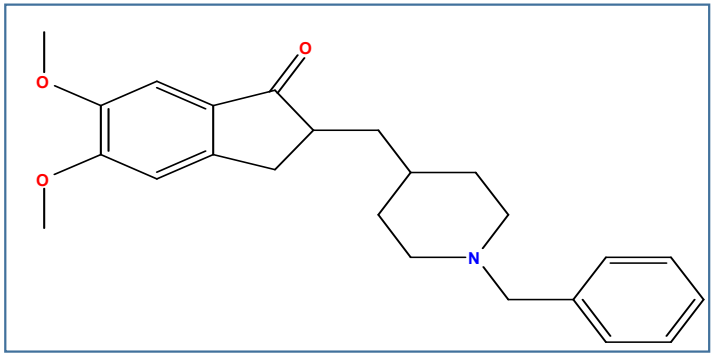
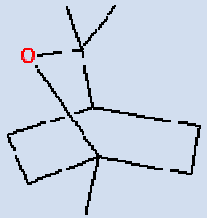
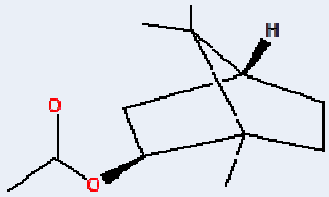
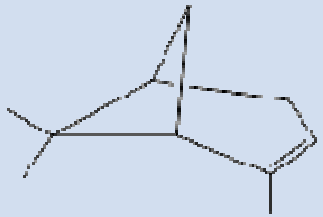
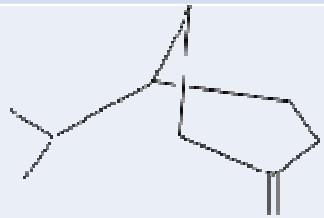


4

1. Tacrine.
2. Rivastigmine;
3. Galantamine;
4. Donepezil

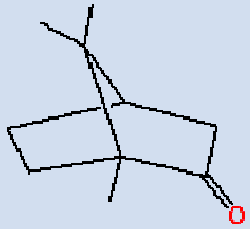
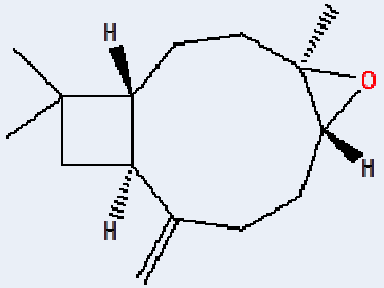
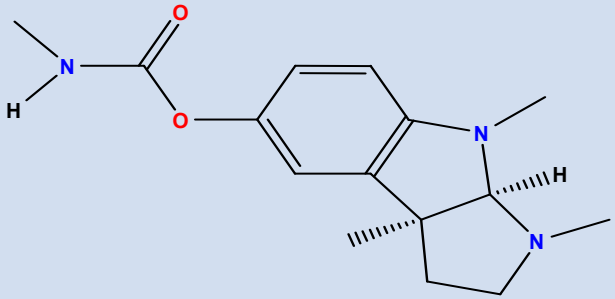
RESULTS AND DISCUSSION

MOLECULES STUDIED

NAME	STRUCTURE
1,8 - cineole	
Acetate bornyl	
α-Pinene	
β-Pinene	

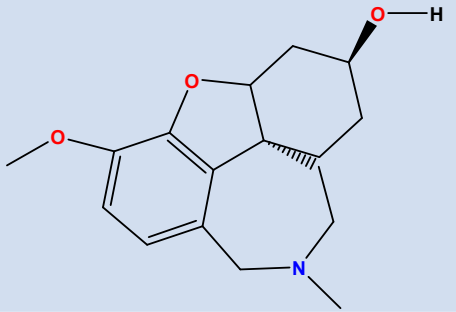
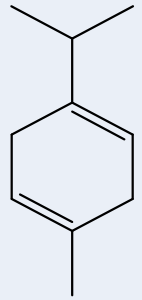
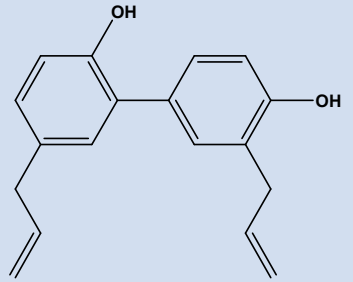
RESULTS AND DISCUSSION

MOLECULES STUDIED

NAME	STRUCTURE
CAMPHOR	
CARYOPHYLLENE EPOXIDE	
PHYSOSTIGMINE	

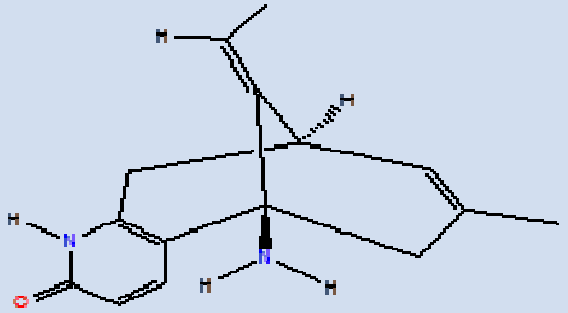
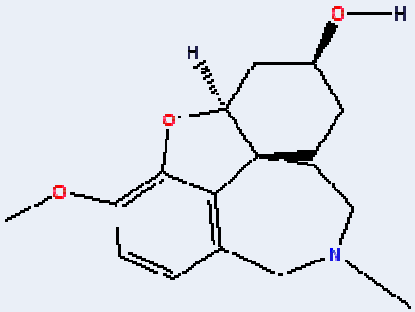
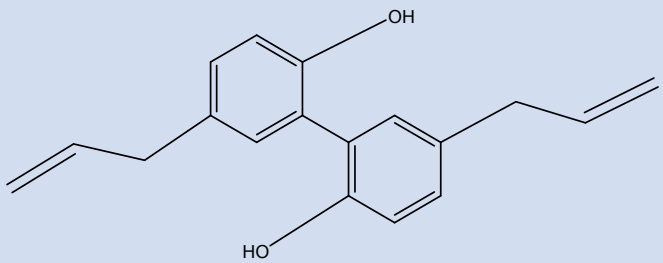
RESULTS AND DISCUSSION

MOLECULES STUDIED

NAME	STRUCTURE
GALANTAMINE	
γ-TERPINENE	
HONOKIOL	

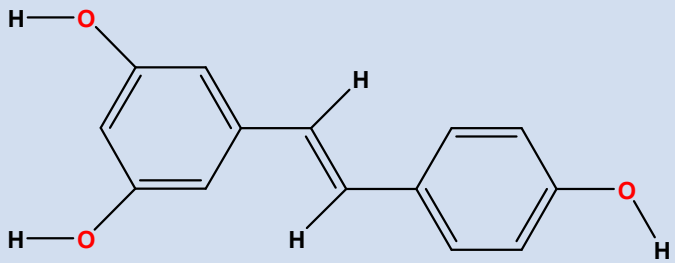
RESULTS AND DISCUSSION

MOLECULES STUDIED

NAME	STRUCTURE
HUPERZINE A	
LYCORAMINE	
MAGNOLOL	

RESULTS AND DISCUSSION

MOLECULES STUDIED

NAME	STRUCTURE
RESVERATROL	

RESULTS AND DISCUSSION

- **MOLECULAR DOCKING**

Molecular docking is an intensive and prominent computational method in the process of drug discovery. The benefit of docking is to identify the mode of binding of the linkers at the binding site of the enzyme or receptor through specific key interactions and to predict the binding affinity between the protein-binding complexes.

MOLECULE	AMINO ACID	INTERACTION	DISTANCE	SCORE
1,8 - cineole	TYR341 TRP286	Hidrofobic π –Alkyl Hidrofobic π –Alkyl	4.72 4.78 4.73 5.17	50.16
Acetate bornyl	PHE295 TRP286 TYR341	Hidrofobic π –Alkyl Hidrofobic π –Alkyl Conventional hydrogen bridge type Hidrofobic π –Alkyl π –Sigma	4.58 5.19 5.37 3.12 4.43 2.23	50.72
α-Pinene	TYR341 TRP286	Hidrofobic π –Alkyl Hidrofobic π -Alkyl	3.58 4.65 5.20 5.34 5.03	43.47

MOLECULE	AMINO ACID	INTERACTION	DISTANCE	SCORE
β-Pinene	TYR341	Hidrofobic π –Alkyl	3.20 4.92 5.00	43.74
	TYR286	Hidrofobic π –Alkyl	4.82 5.33	
Camphor	TRP286	Hidrofobic π –Alkyl	5.03 5.33	43.11
	PHE295	Hidrofobic π –Alkyl	4.48	
	TYR341	Hidrofobic π –Alkyl	4.33 3.65	
		π –Sigma	2.16	

MOLECULE	AMINO ACID	INTERACTION	DISTANCE	SCORE
Caryophyllene Epoxide	TRP286	Hidrofobic π –Alkyl	3.57 4.62 5.02 5.06 5.25 5.31	53.87
		π –Sigma	2.86	
	TYR72	Hidrofobic π –Alkyl	4.11 4.27 4.44	
	TYR341	Hidrofobic π –Alkyl	4.87 4.90	
	PHE295	Conventional hydrogen bridge type	3.03	
Physostigmine	TYR341	Hidrofobic π –π	3.46	71.68
	TYR441	Hidrofobic π –Alkyl	4.28	

MOLECULE	AMINO ACID	INTERACTION	DISTANCE	SCORE
Galantamine	TRP286	Hidrofobic π –Alkyl	4.43 4.90 5.07	59.14
	TYR72	Hidrofobic π –Alkyl	9.92	
	TRP286	Hidrofobic π –π	4.24 3.40	
	TYR72	Hidrofobic π –π	3.66	
γ-Terpineno	TRP286	Hidrofobic π –Alkyl	3.44 3.59 4.38 4.50 4.54 4.94	49.62
	TYR72	Hidrofobic π –Alkyl	3.53 3.92 4.85	

MOLECULE	AMINO ACID	INTERACTION	DISTANCE	SCORE
Honokiol	TRP286	Hidrofobic π –π	4.59 5.60	67.58
	TYR72	Hidrofobic π –π	5.41	
	TYR341	Hidrofobic π –π	5.14	
	TYR341	Hidrofobic π –Alkyl	3.96 5.21	
	TYR72 TRP286 TRP295	Conventional hydrogen bridge type	2.08 3.00 2.77	
Huperzine A	TYR341 TRP286	Hidrofobic π –π Hidrofobic π –Alkyl	4.29 3.38 3.86 4.07 4.57	61.72
	TYR72	Hidrofobic π –Alkyl	3.94 4.57	

MOLECULE	AMINO ACID	INTERACTION	DISTANCE	SCORE
Lycoramine	TYR341	Hidrofobic π –Alkyl	3.85 5.29	59.73
		Hidrofobic π –π	3.78	
	TYR72	Carbonic hydrogen interactions	2.18 2.57	
	TYR341	Carbonic hydrogen interactions	2.82	
Magnolol	TRP286	Hidrofobic π –π	3.62 4.45	74.51
	TYR72	Hidrofobic π –π	3.86	
	TYR341	Hidrofobic π –π	3.92	
	TYR341	Hidrofobic π –Alkyl	4.32	
	TYR72	Hidrofobic π –Alkyl	3.92	
	TRP286	Hidrofobic π –Alkyl	4.94	
Resveratrol	TRP286	Hidrofobic π –π	4.37 4.46 5.38	73.14
	TYR72	Carbonic hydrogen interactions	2.81	
	TRP295	Conventional hydrogen bridge type	3.07	

- In a study conducted by Fang et al. (2014), the interaction of the two compounds analyzed with the amino acid residues of the catalytic site of the enzyme was verified, showing that the two inhibitors presented strong and moderate interactions with residues TYR124, TRP286, GLU292 and TRY341.

- Czarnecka et al. (2017) verified that the synthesized compound presented π-π stacking and cation-π type interactions with residues TRP84 and PHE330 demonstrating inhibitory activity for AChE

PREDICTION OF PHARMACOKINETIC PROPERTIES (ADME) AND TOXICOLOGICAL PROPERTIES (TOX)

- The pharmacokinetic properties and toxicity of the compounds are one of the main reasons for terminating the development of drug candidates (GUPTA; MOHAN, 2014).

- The QikProp module of the Schrödinger software was used to predict the pharmacokinetic properties of the studied molecules.

PHARMACOKINETIC PROPERTIES OF THE STUDIED MOLECULES

	Molecule	Caco-2 (nm/sec)	MDCK (nm/sec)	AIH (%)	LogBB	PSA (Å)
1	1,8 - cineole	9906.04	5899.29	100	0.609	7.489
2	Acetate bornyl	3674.25	2019.43	100	0.194	35.426
3	α-Pinene	9906.04	5899.29	100	0.869	0
4	β-Pinene	9906.04	5899.29	100	0.855	0
5	Camphor	4256.65	2367.55	100	0.28	24.409
6	Caryophyllene Epoxide	9906.04	5899.29	100	0.104	12.535
7	Physostigmine	125.702	64.358	72.014	0.631	57.857
8	Galantamine	864.354	467.521	91.329	0.441	42.446
9	γ-Terpineno	9906.04	5899.29	100	0.863	0
10	Honokiol	1660.18	855.683	100	-0.617	40.258
11	Huperzine A	208.402	100.472	77.232	-0.051	61.667
12	Lycoramine	791.199	424.902	93.187	0.362	42.377
13	Magnolol	1883.22	980.584	100	-0.569	40.438
14	Resveratrol	275.15	122.628	82.038	-1.29	67.309

Source: QikProp, 2018

- All 14 compounds showed high permeability for caco-2 cells with values above 100 nm / sec.
- 10 compounds showed high permeability for MDCK cells and 4 presented intermediate scores.
- As for human intestinal absorption, the compounds: 1, 2, 3, 4, 5, 6, 9, 10 and 13 demonstrated optimal absorption with 100% scores. The compounds: 7, 8, 11, 12 and 14 presented intermediate scores.
- The ability to cross the blood-brain barrier is crucial for compounds with activity in the central nervous system. Seven compounds presented excellent results: 1, 3, 4, 7, 8, 9 and 12. The other seven compounds did not present the ability to cross the BBB.
- All the molecules studied presented PSA results below 90 Å2, demonstrating an optimal ability to permeate cells.

TOXICITY PROFILE

- The toxicity profile of the selected molecules was performed by the program called DEREK, which performs these predictions by verifying the relationship between certain structures present in the molecules (toxicophore) with their probable toxic activity.
- A total of 19 structural alerts were verified. The molecules that presented these alerts were: camphor, caryophyllene epoxide, physostigmine, honokiol, magnolol and resveratrol.
- None of the 14 molecules studied had potential for carcinogenicity and mutagenicity.

TOXICOLOGICAL PROPERTIES OF THE STUDIED MOLECULES

	Molecule	Carcigenocity	Mutagenicity
1	1,8 - cineole	Inactive	Inactive
2	Acetate bornyl	Inactive	Inactive
3	α-Pinene	Inactive	Inactive
4	β-Pinene	Inactive	Inactive
5	Camphor	Inactive	Inactive
6	Caryophyllene Epoxide	Inactive	Inactive
7	Physostigmine	Inactive	Inactive
8	Galantamine	Inactive	Inactive
9	γ-Terpineno	Inactive	Inactive
10	Honokiol	Inactive	Inactive
11	Huperzine A	Inactive	Inactive
12	Lycoramine	Inactive	Inactive
13	Magnolol	Inactive	Inactive
14	Resveratrol	Inactive	Inactive

Source: DEREK, 2018

CONCLUSIONS

- Based on the results presented by the study, the following compounds were found: α-pinene, β-pinene, galantamine, γ-terpinene and lycoramine presented potential for use in the planning and development of new anti-Alzheimer drug candidates.

ACKNOWLEDGMENTS