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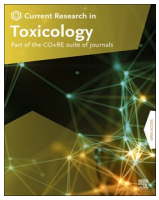

Alzheimer's disease: *In silico* study of rosemary diterpenes activities

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ABSTRACT

The global surge in Alzheimer's disease poses a significant public health concern. In response, we study the efficacy of carnosic acid and related abietane-type diterpenes extracted from rosemary as acetylcholinesterase (AChE) inhibitors. Our analyses, using in silico techniques, encompassed all the compounds within this extract. Through molecular docking, we explored how these compounds interact with the active site of the AChE protein. The docking scores, ranging from −5.560 Kcal/mol to −7.270 Kcal/mol, indicate robust binding affinities. Assessment of the ADME/T (Adsorption, Distribution, Metabolism, Excretion, and Toxicity) properties and pharmacokinetics of these compounds reveal favorable profiles for all the tested substances. These encouraging results suggest the potential of these compounds as candidates for further development to prevent and/or treat Alzheimer's disease. Among these compounds, we find rosmanol as the most likely candidate for further research and clinical trials to validate their efficacy.

1. Introduction

The neurodegenerative Alzheimer's disease (AD) leads to the gradual loss of brain neurons (Knopman et al., 2021). Characterized by the deposition of β-amyloid proteins (amyloid-β plaques) and the dysfunction of the essential neuronal tau protein (Chen et al., 2017; Citron, 2004), AD primarily affects women (Stanciu et al., 2020). AD progresses with accumulation of acetylcholinesterase (AChE). AChE hydrolyzes the neurotransmitter acetylcholine (ACh), terminating its action at a significant rate. This leads to the dysfunction of cholinergic neurotransmission, the loss of ACh receptors, phenotypic changes, and neuronal death (Martinez and Castro, 2006; Cousin et al., 2005). AChE exists in various forms, including monomeric (AChE-R), dimeric (AChE-E), and tetrameric (AChE-S) (Hebert et al., 2003). Current therapeutic strategies focus on drugs refining and inhibiting AChE, showing promise in managing the disease (Stanciu et al., 2020). Chelators have also emerged as potential therapeutic agents to inhibit Aβ aggregation and combat Alzheimer's disease (Massoulie, 2002; Zheng et al., 2010; Bolognin et al., 2009). Studies have identified M30 [5-(N-methyl-N-propargyl-aminomethyl) quinoline-8-yl dimethyl carbamate] chelators capable of reducing senile plaques and alleviating oxidative stress. Metals, particularly zinc, copper, and iron, also play a crucial role in the field of neuroscience, especially concerning Alzheimer's disease, where they can influence the disease's pathology (Amit et al., 2008; Barnham and Bush, 2008; Das et al., 2021).

Numerous medicinal, spice, and aromatic plants exhibit remarkable biological properties. Among these, rosemary, thriving abundantly in Mediterranean climates (Hussain et al., 2022; Filiptsova et al., 2017), stands out as a versatile herb attributed with preventing "brain weakness". Regarded as "the herb of remembrance" (Dehghan et al., 2022), studies have reported positive impact on memory in both humans and animals from inhalation of rosemary aroma (whether from burning rosemary or heated essential oils extracted from rosemary) (Dehghan et al., 2022; Petiwala et al., 2013; Habtemariam, 2016). In addition to its cosmetics applications, it has known anti-inflammatory (González-Trujano et al., 2007; Altinier et al., 2007), anti-cancer (Allegra et al., 2020; Yesil-Celiktas et al., 2010), antioxidant (Yesil-Celiktas et al., 2010; Pérez et al., 2007), and antithrombotic (Memariani et al., 2018) properties.

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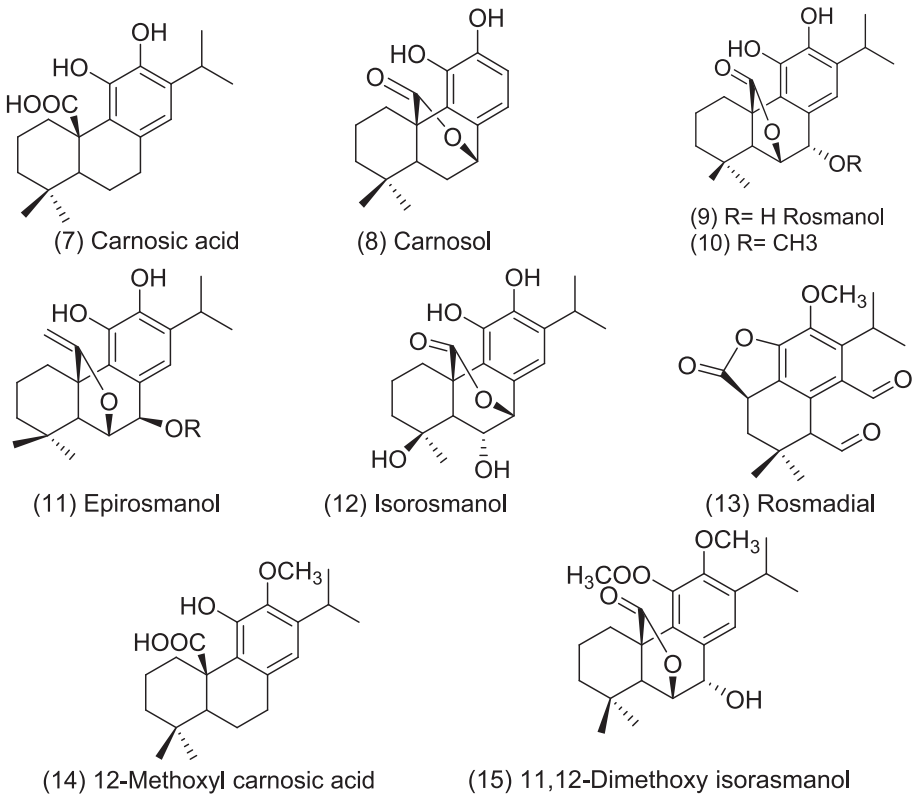

Fig. 1. Carnosic acid and related abietane-type diterpenes of rosemary.

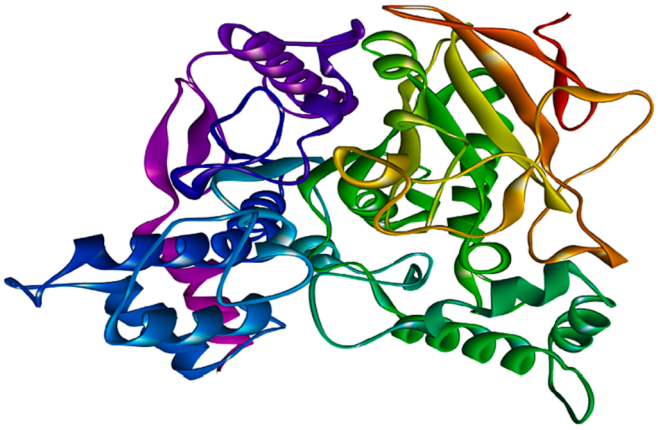

Fig. 2. The three-dimensional structure of the AChE (PDB: 1C2B) protein.

Table 1
Lipinski's rule of five for compounds of Carnosic acid and related abietane-type diterpenes found in rosemary.

Compound N°	Molecular Weight	Donor HB	Acceptor HB	QPlogPo/w	Rule of five
7	332.46	3	3.5	3.766	0
8	330.42	2	4.5	2.956	0
9	346.42	3	6.2	2.071	0
10	360.44	2	6.2	2.835	0
11	346.42	3	6.2	2.071	0
12	364.42	3	6.2	2.049	0
13	344.40	1	7.25	1.761	0
14	346.46	2	3.5	4.552	0
15	390.47	1	7.9	2.706	0

The diverse chemical composition of rosemary includes phenolic acids (Goetz, 2009); carnosic acid, and carnosol. These are prominent diterpenes within the Lamiaceae family known for their potent antioxidant and anti-inflammatory activities (Yesil-Celiktas et al., 2010). Abietane, notably a distinct type of diterpene characterized as a six-ring tricyclic compound, holds significant relevance in the biological context (Brückner et al., 2014; Brückner et al., 2014).

Here, we present results of our comprehensive analyses, using in silico techniques (using the Schrödinger suite of programs (Schrödinger Suite of Programs, 2023), on the efficacy of carnosic acid and related abietane-type diterpenes extracted from rosemary as AChE inhibitors. In the following, we discuss the molecular interactions (e.g., binding affinity and stability when interacting with AChE) and pharmacological profiles (ADME/T properties, viz., Absorption, Distribution, Metabolism, Excretion, and Toxicity (Cherriet et al., 2023) of these compounds to gain insights into their pharmacokinetics and better understand their potential as therapeutic agents.

2. Materials and methods

2.1. Ligands and protein preparations, ADME/T and molecular docking studies

To prepare the ligands (carnosic acid and related related abietane-type diterpenes found in rosemary, cf., Fig. 1) for ADME/T and molecular docking studies, we took the initial three-dimensional (3D) structures from the PubChem database (Database, 2023) (cf., carsonic acid: PubChem CID 66126; carsonol: 442009; rosmanol: 13966122; epirosmanol: 23243694; isorosmanol: 13820511; rosmadial: 15801061, 12-Methoxycarnosic acid: 133554352; 11,12-Dimethoxy isorosmanol: 143790721). Similarly, for the AChE, we took the initial three-dimensional (3D) structure from the Protein Data Bank (PDB) (Bank, 2023) (cf., PDB: 1C2B, Fig. 2). Ligands and protein structure preparation involved 3D and geometric optimizations, ligand energy minimization,

Table 2
ADME analysis of in silico potential compounds of Carnosic acid and related abietane-type diterpenes found in rosemary.

Compound N°	SASA	FOSA	FISA	PISA	Volume	QPPCaco	QPlogBB	HOA
7	568.2	428.9	115.6	23.62	1051.2	201.0	−0.673	3
8	558.0	422.3	110.9	24.70	1024.7	878.0	−0.571	3
9	563.3	396.9	143.6	22.55	1044.8	870.1	−0.902	3
10	591.5	461.2	110.2	19.99	1104.5	891.7	−0.641	3
11	563.1	396.9	143.6	22.55	1044.8	430.3	−0.902	3
12	559.6	394.5	143.9	21.18	1041.1	427.5	−0.895	3
13	602.3	469.6	11.3	21.38	1112.7	231.5	−0.677	3
14	582.8	487.8	77.1	17.83	1100.7	465.3	−0.335	3
15	601.1	496.4	97.4	7.29	1171.2	1179.3	−0.551	3

SASA: Solvent Accessible Surface Area. Range: (: 300.0–1000.0).
FOSA: Hydrophobic Component of SASA. Range: (0.0–750.0).
FISA: Hydrophilic Component of SASA. Range: (7.0–330.0).
PISA: Pi Component of SASA. Range: (0.0–450.0).
Volume: Total solvent-accessible volume in cubic angstroms. Range: (500.0 – 2000.0).
QPPCaco: Predicted apparent Caco-2 cell permeability in nm/sec. Range: (<25 poor, >500 great).
QPlogBB: Predicted brain/blood partition coefficient. Range: (−3.0 – 1.2).
HOA: Predicted qualitative human oral absorption. Range: (1, 2, or 3 for low, medium, or high).

Table 3
Summary of the molecular docking studies in (Kcal/mol) of selected componds against AChE using SP docking.

N°	Compound Name	Dock Score	Contributing Binding Residues
7	Carnosic acid	−5.560	TRP72,ASP74,TYR124,PHE338,TYR341, TYR337,PHE297,PHE295,TYR341, ILE294,SER29.
8	Carnosol	−6.142	PHE295,ARG296,TYR341,PHE297, GLY342,TRP286,PHE338,TYR337, TYR124,ILE294,LEU289,SER293, GLN291,GLU292.
9	Rosmanol (R = H)	−6.383	LEU289,GLY342,SER293,ILE294, ARG296,TYR341,PHE295,PHE297, TYR337,TYR124,PHE338,ASP74,TYR72, TRP286,LEU289.
10	Rosmanol (R = CH_3)	−7.270	TRP286,ASP74,TYR341,TYR72,PHE297, TYR124,PHE338,ILE294,SER293, GLU292,GLN292,LEU289.
11	epirosmanol	−7.130	SER293,ILE294,GLU292,GLN291, LEU289,HIS287,TRP289,ASP74,TYR72, TYR124,PHE297,TYR341.
12	isorosmanol	−6.464	SER293,ILE294,ARG296,TYR124, PHE295,TYR337,PHE297,PHE338, TRP286,TYR341,GLY342,GLU292, LEU289.
14	12-Methoxyl carnosic acid	−5.735	TYR337,ASP74,TYR72,TRP286,TYR341, SER293,ILE294,PHE297,PHE298, PHE338,ARG296,GLY122,TYR124.
15	11,12-Dimethoxy isorosmanol	−6.071	TYR341,TYR337,PHE338,PHE295, ILE294,LEU289,ARG296,SER293, TRP286,GLY342,LEU76,THR75,TYR72, ASP74.

and energy minimization using the OPLS_2005 force field, and limiting the root-mean-square deviation (RMSD) of atomic positions to 0.3 Å. We removed non-necessary water molecules from, added hydrogen atoms added to AChE before the docking assay. Similarly, we generated the ionization states of the ligands at pH7.0 ± 2.0. We then identify and discuss some noteworthy physicochemical characteristics, e.g., elasticity, molecular weight/size, hydrophobicity, bioavailability, permeability, and polar solubility, based on Lipinski's Rule of Five (Lipinski et al., 1997).

3. Results and discussion

3.1. ADME/T properties

Table 1 shows that, in general, carnosic acid and related abietane-type dipertenes extracted from rosemary showed good results/compliance with Lipinski's Rule of Five (Lipinski et al., 1997) (Molecular Weight < 500 Da, # of hydrogen bond donors: Donor HB < 5, # of hydrogen bond acceptors: Acceptor HB < 10, and predicted octanol–water partition coefficient: QPlogPo/w < 5), without any observed violations (Diass et al., 2023; Boumezzourh et al., 2023; Dash et al., 2015; Khan et al., 2009; Fajriyah et al., 2023; Faris et al., 2023; Zhang and Wilkinson, 2007; Merzouki et al., 2023). Similarly, Table 2 shows that, in general, all compounds exhibit ADME/T properties/pharmacokinetic descriptor values falling within the range of recommended values (values in parentheses at the bottom of the Table 2), with no observable violations in terms of drug characteristics. In addition, all compounds show high predicted qualitative human oral absorption. QPPCaco (predicted apparent Caco-2 cell permeability) values greater than 500 nm/sec indicate excellent permeability. All compounds also show QPlogBB (predicted brain/blood partition coefficient) values within the acceptable range of −3.0 to + 1.2. All the compounds considered exhibited drug-like characteristics as AChE inhibitors.

3.2. Molecular docking studies

Table 3 shows the results of the molecular docking studies on selected rosemary extracts on AChE (PDB: 1C2B). The negative docking scores indicate that all the rosemary extracts considered bind favourably to AChE, with rosmanol having the best dock score of −7.270 kcal/mol. Rosmanol firmly binds to the AChE active site through two conventional hydrogen bonds with SER293 and seven alkyl interactions with TRP286, TYR341, TYR72, and TYR124, as well as two other bonds pi-sigma and pi-pi-stacked with TRP286, and other van der Waals type interactions with ASP74, PHE297, PHE338, ILE294, GLN291, LEU289, and GLU292, respectively (cf., Fig. 3).

These results suggest the merit of conducting additional clinical and laboratory investigations, to further establish the therapeutic potential of the compounds derived from *Rosmarinus officinalis* essential oil for the prevention and/or treatment of Alzheimer's disease.

4. Conclusion

At present, there is still no known (well-established) means of prevention and/or cure for Alzheimer's disease. Our study harnessed computational techniques, offering the advantage of reduced time and cost compared to experimental approaches, to conduct evaluations scrutinizing the ADME/T properties of rosemary extracts (carnosic acid and related abietane-type diterpenes). We found that these rosemary extracts possess promising pharmacological attributes, marking them as potential candidates for Alzheimer's disease treatment. Furthermore,

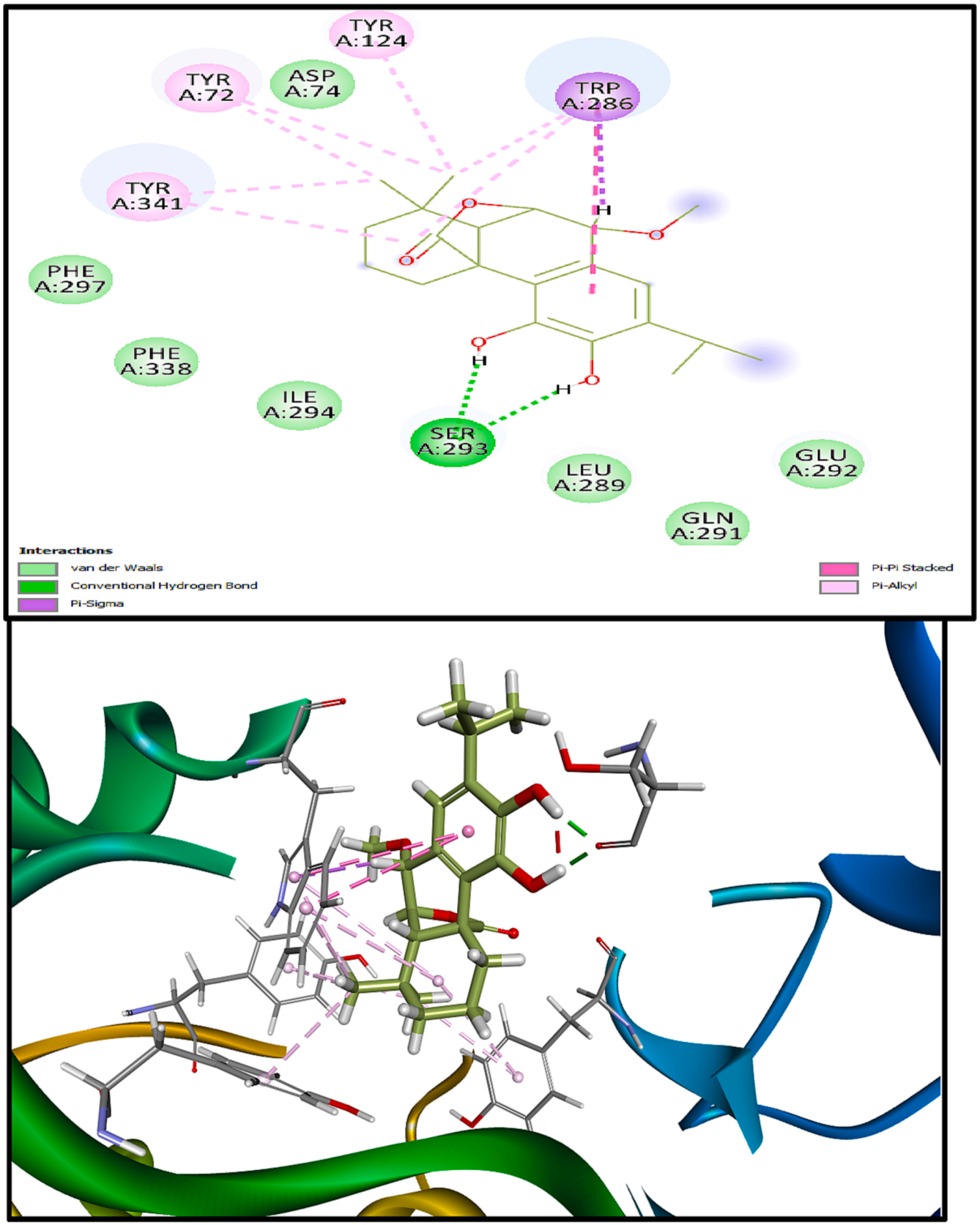

Fig. 3. Intermolecular interactions 2D and 3D between AChE with Rosmanol (R = CH3).

these compounds exhibited low risk and toxicity. Based on our findings, we have deduced that the studied compounds can effectively inhibit acetylcholinesterase (AChE) by forming strong bonds with the active site of the protein. Among the rosemary extracts considered, rosmanol exhibited the most promising Dock Score of −7.270 kcal/mol, indicating a strong affinity for the active site. Nonetheless, further clinical and laboratory investigations on rosemary extracts, esp., in vitro tests and development of new research methods, are imperative to substantiate their therapeutic potential against Alzheimer's disease.

CRediT authorship contribution statement

Zakariae Abbaoui: Investigation. **Mohammed Merzouki:** Investigation. **Imane Oualdi:** Investigation, Supervision. **Abdelhamid Bitari:** Review & Editing. **Abdelouhed Oussaid:** Methodology, Data curation. **Rachid Touzani:** Conceptualization, Validation. **Belkheir Hammouti:** Supervision, Resources. **Wilson Agerico Dino:** Supervision, Writing, Funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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