The 7th International Electronic Conference on Medicinal Chemistry (ECMC 2021)
01–30 NOVEMBER 2021 | ONLINE

Molecular dynamics simulation and free energy calculations of the binding characteristics of multi-target anti-Alzheimer natural compounds isolated from *Psoralea Fructus* to amyloid β-peptide42

Awwad Radwan *, Fares Al-Anazi ,

Kayyali *Scientific Chair for. Pharmaceutical Industry, College of Pharmacy, King Saud University , Riyadh 11451, Saudi Arabia.*

* Corresponding author: aradwan@ksu.edu.sa

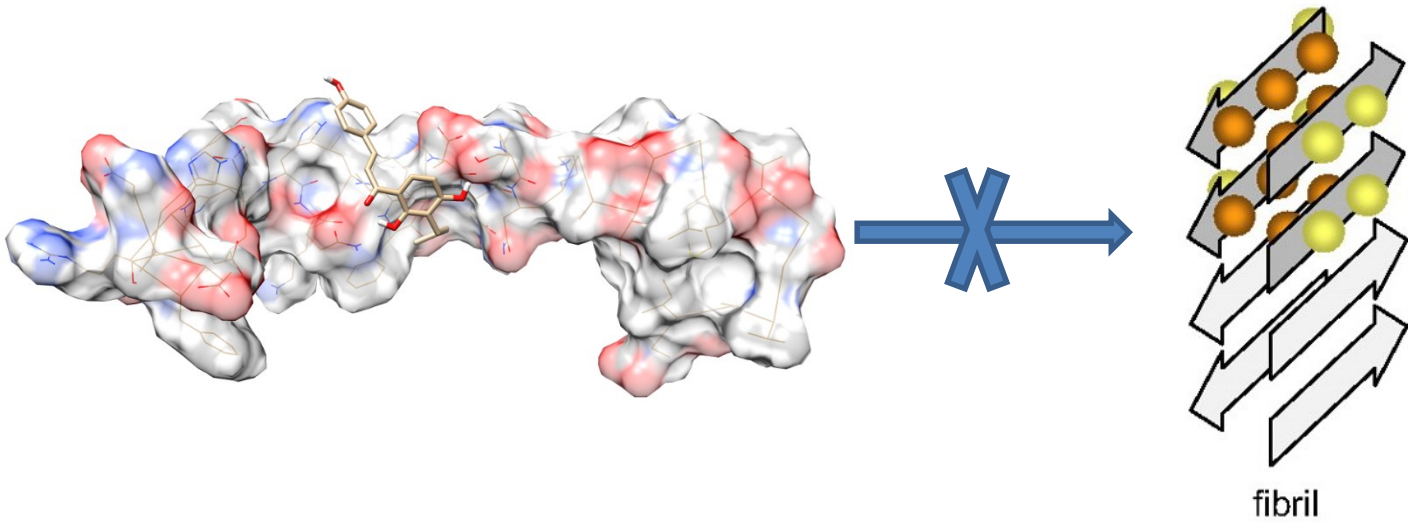
كرسي الكيالي للصناعات الدوائية
Kayyali Chair for Pharmaceutical Industries
Research & Simulations أبحاث ومحاكاة

كلية الصيدلة College of Pharmacy
جامعة الملك سعود King Saud University 1957

Molecular dynamics simulation and free energy calculations of the binding characteristics of multi-target anti-Alzheimer natural compounds isolated from *Psoralea Fructus* to amyloid β-peptide42

Graphical Abstract

A combined molecular modeling study using docking and MD simulations studies performed on anti-Alzheimer natural prenylated compounds as Aβ42 aggregation inhibitors



Abstract: The accumulation of the Amyloid Beta peptide in the brain is an early important incident in the pathogenesis of Alzheimer disease. Recently, four prenylated compounds isolated from *Psoralea Fructus* (PF) and demonstrated some anti-Alzheimer effects both *in vitro* and *in vivo*. These exhibited promising inhibitory effects on Aβ42 aggregation. In this work, a molecular modeling study was performed on the compounds as Aβ42 aggregation inhibitors using docking studies and molecular dynamics (MD) simulations. Molecular mechanics calculation was performed to calculate the binding free energy and to get insight on the binding modes of the ligands and to identify main interacting residues.
Keywords: Alzheimer's disease; Amyloid beta 1-42; MD simulations

Introduction

Alzheimer's disease (AD)	is an aging-associated illness.
	is a neurodegenerative disease
	results in progressive dementia and several cognitive malfunctions.

Introduction

AD progression and development are affected by some factors	*Accumulation of β-amyloid * Aggregation of tau protein * Cholinergic insufficiency
	*Neuro-inflammation, *Oxidative stress *Apoptosis
	*Genes mutation *environmental, psychical and other co-existing health disease factors.

Introduction

AD types

*Familial AD (FAD):

* is an early-onset (40 years old) disease.

*is affected by genetic mutations.

*corresponds to approximately 2% AD cases.

Sporadic AD (SAD): subdivided into:

*Early-onset type, under 65 years of age, (3–5% prevalence).

*Late-onset type above 65 years of age (95–97% prevalence)

Introduction

AD –ve impact on the community

1. Economic impact: Based on the WHO reports:

*The overall forecasted incidence in global people will quadruple in the following decades, achieving 114 million patients by 2050.

* In 2019, the estimated total global societal cost of dementia was US$ 1.3 trillion, and these costs are expected to surpass US$ 2.8 trillion by 2030.

2. Social and health impacts for family carers

*Social impacts may include a reduction in work hours or loss of employment, loss of relationships, time with friends and families and social activities, or the need to relocate or change living arrangements in order to provide care.

*Health impacts include depression, anxiety, stress, physical problems and sleep disruption.

Introduction

Treatment Only symptomatic treatments exist:

1- to counterbalance the neurotransmitter disturbance: cholinesterase inhibitors and memantine.

2- interfere with the pathogenic steps responsible for the clinical symptoms, including the extracellular amyloid β plaques deposition and formation of intracellular neurofibrillary tangle.

3- Other mechanisms are neuroprotective, anti-inflammatory, growth factor promotive, and stem cell therapies.

4- Recent therapies such as neuropsychological outcomes.

Aim of work

Amyloid peptide aggregation is on the AD hypotheses. Although the major constituents of AD-associated amyloid plaques is Aβ1–40, Aβ1–42 peptides are the most toxic species. Aβ oligomer toxicity includes several mechanisms which includes

-adsorption

–insertion

-aggregation

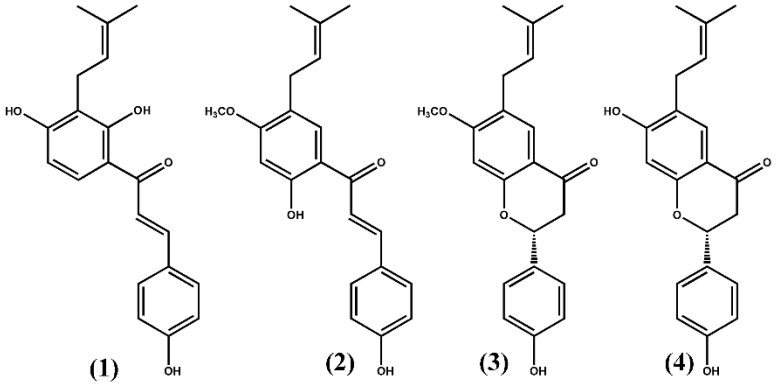
-pore formation in the membrane

-interaction of Aβ with the membrane receptors

-oxidative stress.

Aim of work

Four prenylflavonoid compounds (**1-4**) of Psoralea Fruits PF were suggested to generate valuable effects in AD prophylaxis and treatment. The inhibitory rates percent of 100 μM PF compounds **1-4** on Aβ42 aggregation were reported as 98, 90, 68 and 19 % respectively.



Aim of work

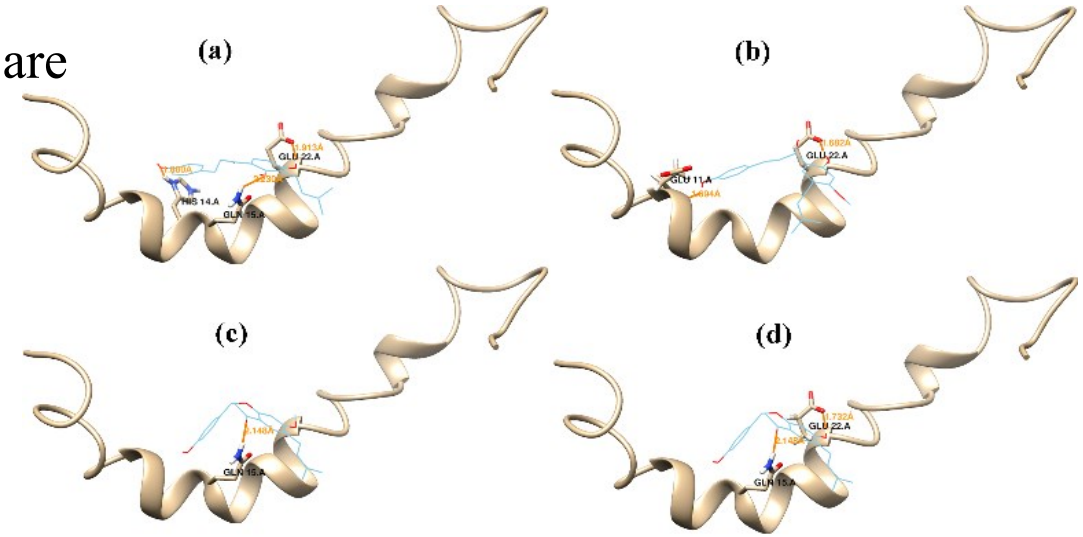
Purpose: The *in silico* modeling was performed to explore the mode of binding of the Aβ42 protein by Aβ42-aggregation inhibitors **1-4** and to identify the crucial active site residues.

Methods: Molecular docking, molecular dynamics (MD) simulations, and Molecular Mechanics/Poisson−Boltzmann Surface Area (MM/PBSA) calculations.

Outcomes: Provide structural insights to design more active compounds as novel Aβ1-42 aggregation inhibitors.

Results and discussion

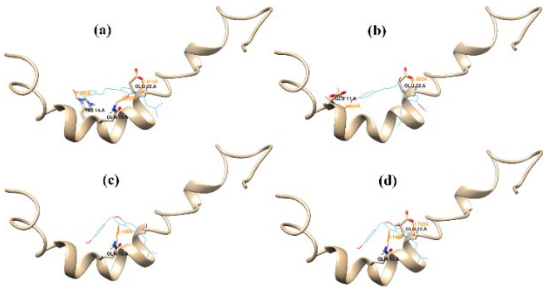
Docking results. Binding conformations of compounds 1 (a); 2 (b); 3 (c) and 4 (d) at the binding site of Aβ1-42 (PDB ID 1Z0Q) . Hydrogen bonds are represented as yellow lines and their distances are labeled in Angstrom



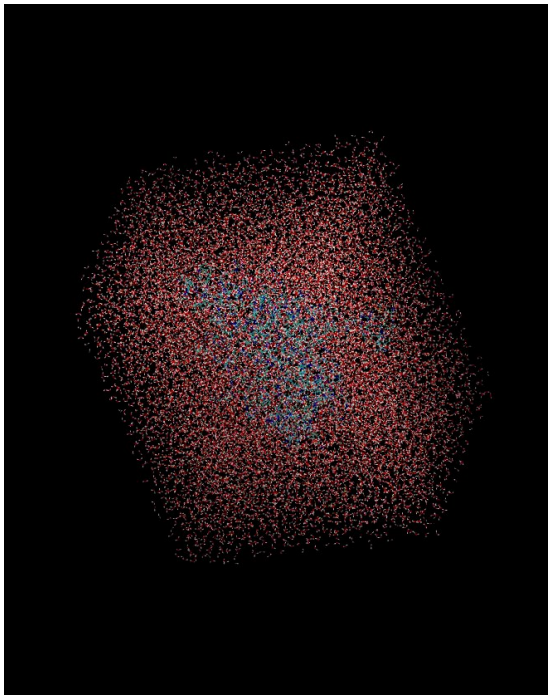
Results and discussion

Molecular dynamics simulations

Considering both protein structure flexibility and protein–ligand electrostatic interactions, MD simulations deemed necessary to justify the understanding of ligands binding modes obtained from molecular docking.



Using Amber 18 program, the docking study-obtained ligand-protein complex models were optimized in an aqueous solvent box to simulate the real physiological environs.



Results and discussion

Molecular dynamics simulations

During 100 ns MD simulation time frame, the stability of the structure was calculated by its deviance from the starting conformation in RMSD terms.

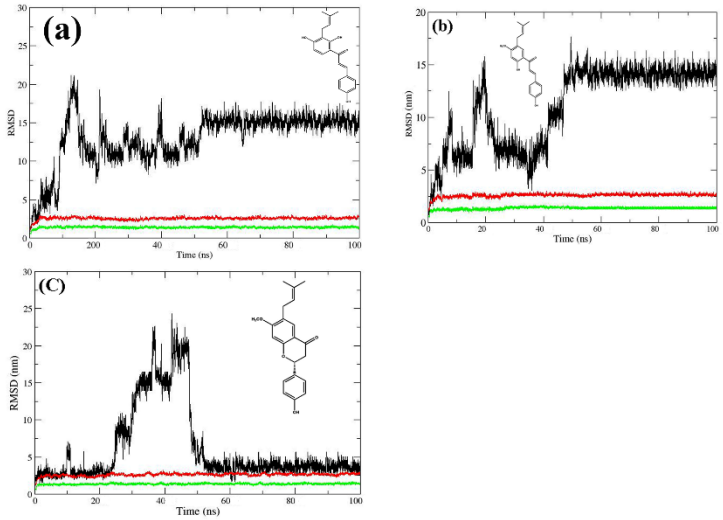
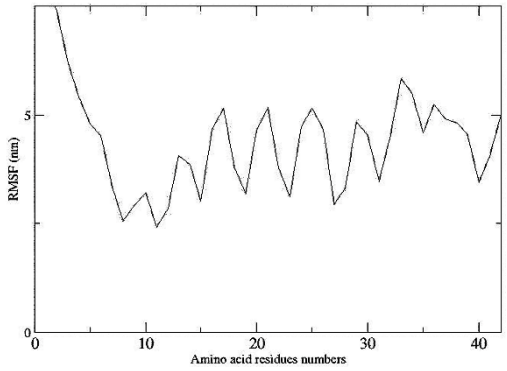
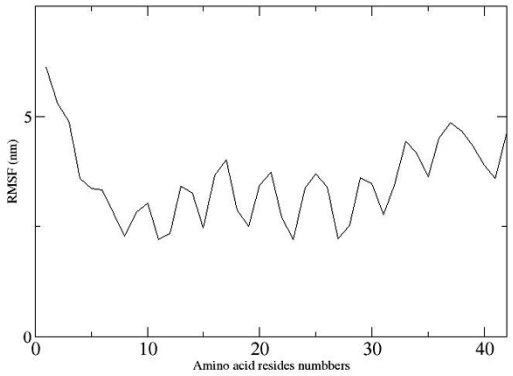


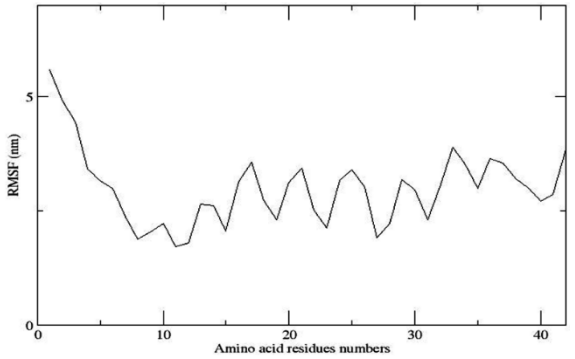
Fig 5. Root-Mean-Square Deviation (RMSD) in MD simulations of compounds protein backbones (green lines), protein all atoms (red lines) and ligands (black lines).

Results and discussion

Molecular dynamics simulations







The RMSF was plotted during the last 20 ns. Presence of peaks indicates the areas fluctuates the most during the simulation. For compounds 1-4, the most fluctuating amino acids residues are, Phe20, Ala21, Val24, Gly25, Ser26, Ala30, Leu34 and Val36. These amino acids has hydrophobic side chain that suggest dominant contributions of the hydrophobic interactions in the total binding energy of the complex system.

Results and discussion

Molecular dynamics simulations

The binding free energies of the ligands **1-4** to AB42 were calculated using MM/GBSA methods according to the MD simulation trajectories through the last 6 ns using 1000 snapshots.

To develop an insight into the interactions between the binding site and each of the compounds 1-4, the MM/PBSA-pairwise per-residue decomposition analysis was performed . The results showed that the amino acid residues Hie14, Gln15 and Glu22 play a crucial role in effective binding interactions with compounds 1-4 and showed absolute decomposed energy kcal mol^{-1}

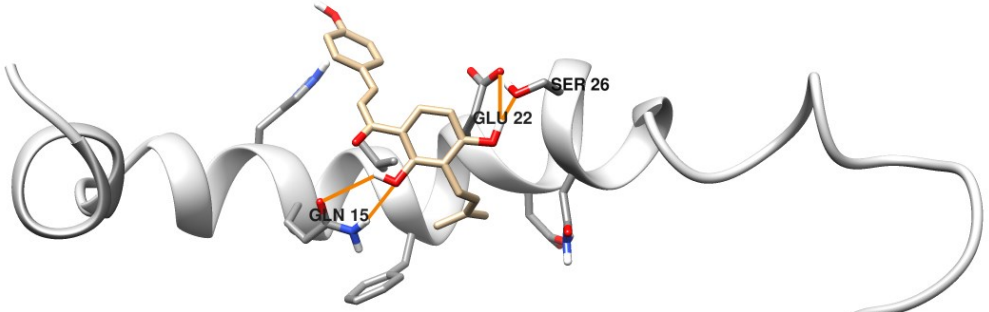
Results and discussion

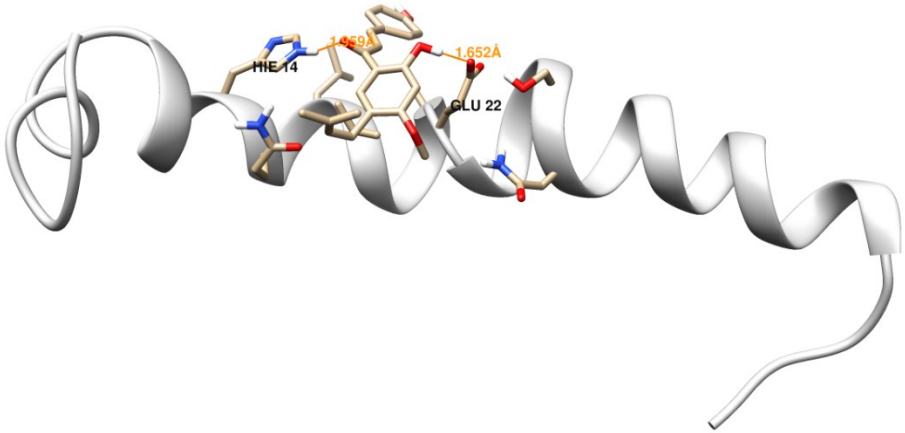
Molecular dynamics simulations

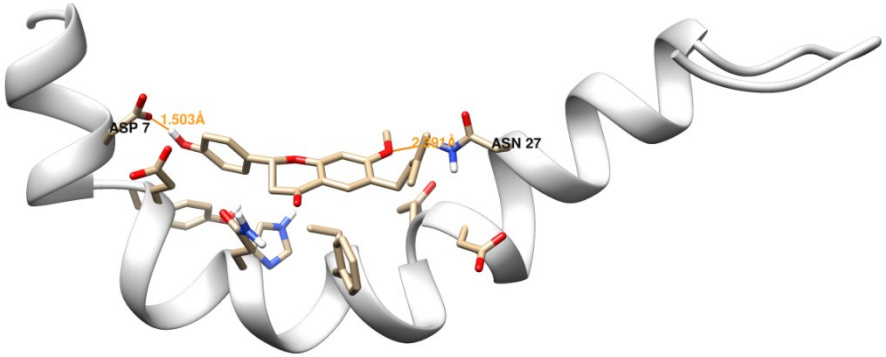
To develop an insight into the interactions between the binding site and each of the compounds 1-4, the MM/PBSA-pairwise per-residue decomposition analysis was performed . The results showed that the amino acid residues Hie14, Gln15 and Glu22 play a crucial role in effective binding interactions with compounds 1-4 and showed absolute decomposed energy kcal mol^{-1} (Table 3).

Results and discussion

Molecular dynamics simulations







Conclusions

Knowledge of the prenylated flavonoid compounds' binding free energies is crucial to evaluate its Aβ42-aggregation inhibitory activities and to study the ligand-protein binding mechanism. Three amino acids represent hot-spots in the binding of AB42 with the ligands at the binding site and possibly played an essential role in the Aβ42 aggregations process. The results of our work on binding interactions between the ligands and Aβ42 would be beneficial for more studies for development of potential effective anti-AD agents.

Acknowledgments

This Project was funded by the National Plan for Science, Technology and Innovation (MAARIFAH), King Abdulaziz City for Science and Technology, Kingdom of Saudi Arabia, Award Number (14-MED-622-02).