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Elucidation of Mechanism of Anti-Alzheimer activity of Andrographolide and design of new Anti-Alzheimer compounds using Insilco approach

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Abstract

Alzheimer's disease is a degenerative neurological disease that was discovered and named over a century ago. There are currently more than 20 million people with Alzheimer's disease worldwide, but unfortunately, due to the complexity of the causative mechanisms, there is still no accurate research conclusion on the causes of Alzheimer's disease. Andrographolide, the main active ingredient of the natural plant Andrographis paniculata, has shown good potential as a traditional anti-inflammatory drug for the treatment of Alzheimer's disease and in the field of neuroprotection. Therefore, it is necessary to explore the potential targets for the anti-Alzheimer's activity of andrographolide, including through molecular docking, and in turn to explore the potential of andrographolide and its derivatives as therapeutic agents for Alzheimer's disease.

Keywords: Andrographolide, Analogues, Alzheimer's disease, Molecular docking

Introduction

As research progresses, a more comprehensive stage of the causative factors of Alzheimer's disease has been reached. Theories on the causative mechanisms of Alzheimer's disease can be divided into the following directions (1, 2): 1. research directions based on the accelerated aging theory. 2. degeneration of anatomical pathways. 3. the influence of external environmental factors. 4. genetic factors. 5. other factors, including vascular factors, abnormalities in immune system function, mitochondrial dysfunction, infection factors and other theories. A representative of the diterpene lactones, andrographolide is one of the most important active ingredients of *Andrographis paniculata*, and studies have shown that andrographolide has a central neuroprotective effect, as well as potential for the treatment of dementia and potential anti-neuroinflammatory activity (3-5). In addition, andrographolide is consistent with the Lipinski principle and exhibits a multitarget and multi-pathway profile, making it an ideal target drug (4). To further explore the targets of action of andrographolide, in this article, the most important analogs of andrographolide are collected that have been concluded to have anti-Alzheimer's activity, as well as the potentially effective targets, to explore more precise targets of andrographolide in Alzheimer's disease through molecular docking.

Material and Methods

Compound selection

Based on published articles, a set of andrographolide analogs with anti-Alzheimer's potential, including natural products and synthetic compounds, was validated by in vitro activity or animal models (4-6).

Target protein selection

Target protein was selected by searching through published literature for target proteins, with potential involvement in Alzheimer's (4, 7). Protein and its unique ligand files were obtained from the RCSB PDB database(8).

Inverse docking analysis

AutoDock Vina (version:1-1-2) was used for molecular docking (9). Based on unique compound ligands, the coordinates of the docking sites of the ligands were analyzed and recorded. The receptor protein is considered rigid, and the ligand small molecule is flexible.

Functional group analysis and design of new compounds

The docking results of different andrographolide analogs with anti-Alzheimer's activity of target proteins were analyzed, and the main functional group structures of andrographolide and the functional group of the analogs that can better dock with the target proteins were determined. New andrographolide derivatives were designed based on the results of the analysis, and molecular docking and ADMET analyses were performed to verify the results.

Results and Discussion

Molecular docking was performed using AutoDock vina and the binding energies of the best conformations of the docking results were analyzed. The binding energy of the molecular docking results showed in (Table 1). For the potential targets of andrographolide against Alzheimer's disease, the best docking results were for PTGS2 and ACHE. These two targets were therefore chosen as the primary targets for andrographolide activity and analyzed. For the target PTGS2, Compounds 5b, 5d, 5e, 9 and 31 gave significantly better results than andrographolide in the molecular docking results for the andrographolide derivatives. Among them, 5b, 5d, and 5e belong to the same class of analogs, which, according to the structures, can be seen to form a six-membered ring structure containing an oxygen atom between carbon atoms 3 and 18, with the addition of a benzene ring derivative. For the target ACHE, Compounds 12-dideoxyhydro-andrographolide, 14-deoxy-11-oxa-andrographolide, 14-deoxy-15-isopropylidene-11,12- didehydro-andrographolide and and andrographolide B_qt showed better docking results. According to the structure analysis, the five-membered lactone structure of andrographolide is an important functional group, and structural modification at the positions of carbon atom 3 and carbon atom 18 to form an oxygen-containing ring structure can improve the docking results very well. In addition, increasing the length of the carbon chain by adding benzene ring substituents can also have a more pronounced effect.

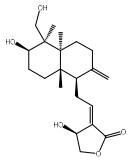
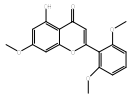
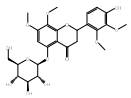
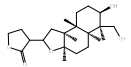
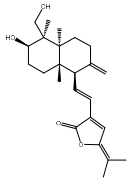
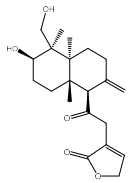
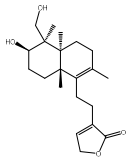
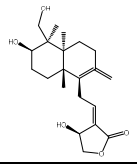
New compound design

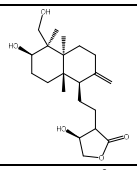
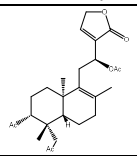
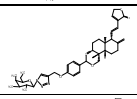
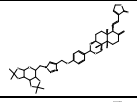
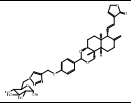
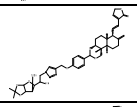
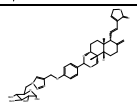
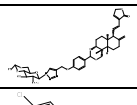
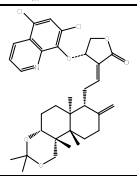
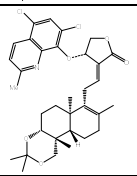
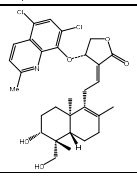
Based on the structure-activity relationship analysis, a new derivative was designed. The five-membered lactone structure of andrographolide was retained, and a new heteroatomic six-membered ring structure was formed at the carbon atom positions 3 and 18 with the addition of hydroxyl-substituted benzene ring substituents. The structure of the new compound is shown in (Figure 1).

Molecular docking and admet analysis of new compounds

Molecular docking of the newly designed compounds with PTGS2 and ACHE target roteins and ADMET analysis by SwissADME gave the following results. The docking energies for the optimal docking conformation of the new compound with PTGS2 and ACHE target protein molecules are -9.7 kcal/mol and -11.2 kcal/mol, respectively. The results were better than the docking results of andrographolide (Figure 2-5). The new compound showed strong intestinal absorption but was unable to cross the blood–brain barrier. As a P-gp substrate, the newly designed compound may have problems with drug excretion. In addition, the compound is not an inhibitor of CYP2C19 and CYP2D6

Table 1: Molecular docking of small molecule compounds with anti-Alzheimer activity to potential targets

Compounds	Structure	Binding energy (Kcal/mol) by AutoDock Vina					
		PED4	PTGS2	ACHE	BACE	DRD2	APH1B
Andrographolide		-7.0	-8.3	-8.9	-7.3	-7.3	-7.9
Andrographidine B_qt		-8.0	-8.6	-10.1	-6.9	-8.5	-7.1
Andrographidine F_qt		-8.4	-8.6	-4.3	-7.2	-6.3	-7.5
Isoandrographolide		-6.6	-7.1	-8.5	-8.3	-6.9	-8.0
14-deoxy-15-isopropylidene-11,12-didehydro-andrographolide		-8.5	-8.3	-10.9	-8.2	-8.5	-8.7
14-deoxy-11-oxa-andrographolide		-7.0	-7.4	-9.9	-7.6	-7.3	-7.8
Deoxyandrographiside		-7.4	-7.3	-9.3	-7.7	-7.5	-7.9
3-Dehydrodeoxyandrographolide		-7.9	-8.3	-9.4	-7.9	-7.8	-8.3

12-dideoxyhydro-andrographolide		-6.9	-7.4	-10.0	-7.5	-7.1	-7.8
12		-7.9	-7.0	-7.2	-6.4	-8.1	-7.9
5a		-7.0	-7.0	-3.9	-9.2	-2.3	-9.4
5b		-10.2	-9.1	-8.3	-10.0	0.2	-12.1
5c		-7.7	-8.6	-4.2	-10.3	1.8	-8.0
5d		-8.7	-9.6	-9.3	-10.9	-4.2	-10.6
5e		-9.3	-9.9	13.2	-7.2	10.6	-2.5
5f		-8.0	-8.1	3.8	-11.2	1.2	-8.1
9		-9.1	-9.5	1.2	-8.2	6.1	-7.4
31		-11.9	-11.7	-2.8	-8.8	-11.1	-12.5
37		-7.9	-8.1	-5.0	-8.1	-5.2	-8.2

Anti-Alzheimer activity

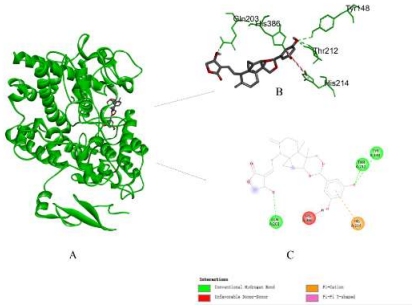


Figure 2: Docking pocket for the new compound with PTGS2 (A), 3D presentation (B) and 2D presentation (C) of docking results.

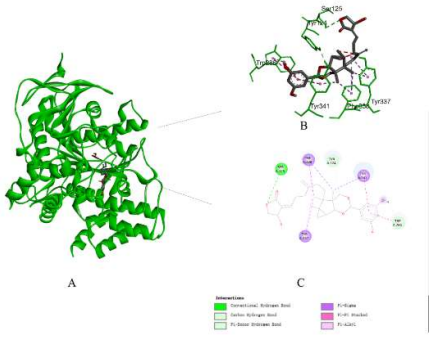


Figure 3: Docking pocket for the new compound with ACHE (A), 3D presentation (B) and 2D presentation (C) of docking.

isozymes, indicating that there is no risk of drug accumulation or toxicity due to interactions. The newly designed compound followed the Lipinski, Verber, and Egan rules while achieving a bioavailability of 0.55, indicating high similarity

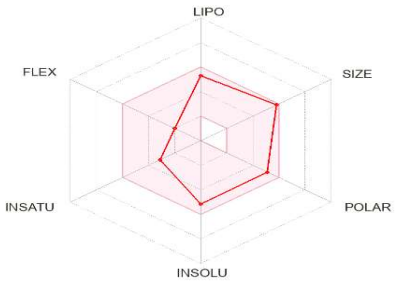


Figure 1 : New compound.

Figure 4: Swiss ADME predicted bioavailability.

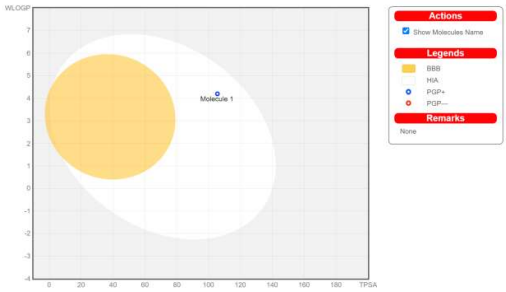


Figure 5: BOILED-Egg prediction graph for the new compound

parameters. The synthesis score was 5.74, with possible synthesis difficulties at some rare compound sites. The ability of andrographolide to act on multiple pathways and targets has great potential for the development of andrographolide-based therapeutics for Alzheimer's disease. Among these, attention should be focused on the cholinergic neurotransmitter-related activity and anti-inflammatory effects of andrographolide, i.e., PTGS2 and ACHE targets.

Conclusion

Through reverse molecular docking, ptgs2 and ache were identified as potential targets for the main anti-Alzheimer's activity of andrographolide. Based on the analysis of the functional groups, new andrographolide derivatives were designed, and the molecular docking results were superior to those of andrographolide.

Conflict of Interest

The authors declare no conflict of interest.

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