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Mechanistic insight of the potential of geraniol against Alzheimer's disease

Ying Liu^{1*†}, Shujing Zhou^{2†}, Xufeng Huang^{3†} and Hafiz Muzzammel Rehman^{4,5†}

Abstract

Background: Alzheimer's disease (AD) as a neurodegenerative disease occupies 3/5–4/5 cases among patients with dementia, yet its pathogenetic mechanism remains unclear. Geraniol, on the other hand, is a well-known extract from essential oils of aromatic plants and has been proven that it has outstanding neuroprotective effects as well as ameliorating influence in memory impairment. Therefore, the present study aims to elucidate the potential of geraniol against AD by network pharmacology-based approach combined with molecular modeling study.

Materials and methods: Firstly, we evaluated the druggability of geraniol by ADME method. Then, we obtained the geraniol targets and AD-related targets from multiple open data sources. Afterward, we calculated the intersection through a Venn diagram to find common targets, and via Panther classification system to categorize them. In order to gain a macroscopic understanding of these common targets, we carried out GO terms and KEGG pathways enrichment analyses, according to which we constructed a compound–target–pathway–disease network. In addition, we built a preliminary PPI network which was further analyzed both functionally and topologically. Consequently, five hub targets were sorted out. Finally, we conducted molecular docking and molecular dynamic simulation to validate our findings.

Results: In the present study, the pharmacological properties of geraniol were assessed according to ADME and Lipinski's rule, which demonstrate promising druggability. Then, from 10,972 AD-related targets and 33 geraniol targets, 29 common targets were identified, among which 38.1% of them are metabolite interconversion enzymes, 23.8% are protein modifying enzymes, 33.3% are transmembrane receptors, and the rest are transporters. Enrichment analyses hint that geraniol is involved in cholinergic synapse, serotonergic synapse, and neuroactive ligand–receptor interaction. We also built a preliminary PPI network to investigate the interplay between these targets and their extensive interactions. Then, by functionally clustering the preliminary PPI network, we gained a cluster of proteins which formed a subnetwork with score of 8.476, and 22 nodes. Its results of GO terms and KEGG pathways enrichment analyses once again suggests that geraniol actively participates in cholinergic synapse, serotonergic synapse, and neuroactive ligand–receptor interaction, which are believed to be strongly associated with AD pathogenesis. Besides, topological analyses of the preliminary PPI network helped find 5 hub targets (i.e., CHRM3, PRKCA, PRKCD, JAK1, JAK2). To verify their interaction with geraniol molecule, we conducted molecular docking, and found that CHRM3 possesses the highest affinity in binding, indicating that geraniol molecules are closely bound to each hub target, and CHRM3

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may serve as a key target of geraniol against AD. It was then further confirmed by molecular dynamic simulation, the result of which supports our hypothesis.

Conclusion: The present study shares a mechanistic insight of the potential of geraniol against AD, giving a reference to future experimental studies.

Keywords: Network modeling, Drug discovery, Data integration, Geraniol, Alzheimer’s disease

Introduction

Alzheimer’s disease (AD) has been a common neurodegenerative disease that occupies 3/5–4/5 cases among patients with dementia, yet its pathogenetic mechanism of AD is very complicated and thus remains unclear [1, 2]. The current hypotheses include Aβ amyloid cascade theory, the theory of microtubule-associated protein abnormalities, the theory of central cholinergic damage, the theory of infection, the abnormal growth of gut microbes, etc. [3–7]. Due to the blood–brain barrier, most of the drugs such as steroid hormones have limited therapeutic effects on AD, which urges researchers to develop new drugs for its prevention and treatment [8]. On the other hand, thanks to the rapid development of modern bioinformatics, publicly accessible databases provide an unprecedented wealth of information to help drug discovery. By combining data available in these databases with the proper bioinformatical tools, we can elucidate the molecular targets of natural compounds [9]. One such molecule is geraniol, a well-known component

of essential oils of aromatic plants and has been proven possessing outstanding neuroprotective effects as well as ameliorating influence in memory impairment [10–13]. Therefore, the present study aims to elucidate the potential of geraniol against AD by network pharmacology-based approach combined with molecular modeling study.

Figure 1 demonstrates the workflow of the present study in a graphical manner.

Materials and methods

Druggability assessment

The sdf file of geraniol’s structure was downloaded from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) and was input into SwissADME (www.swissadme.ch) [14] that provides literature and structure-based pharmacological information of geraniol, including molecular weight, number of H-bond acceptors and donors, topological polar surface area, GI absorption, blood–brain barrier, Lipinski’s rule, etc. From this server, we obtained the

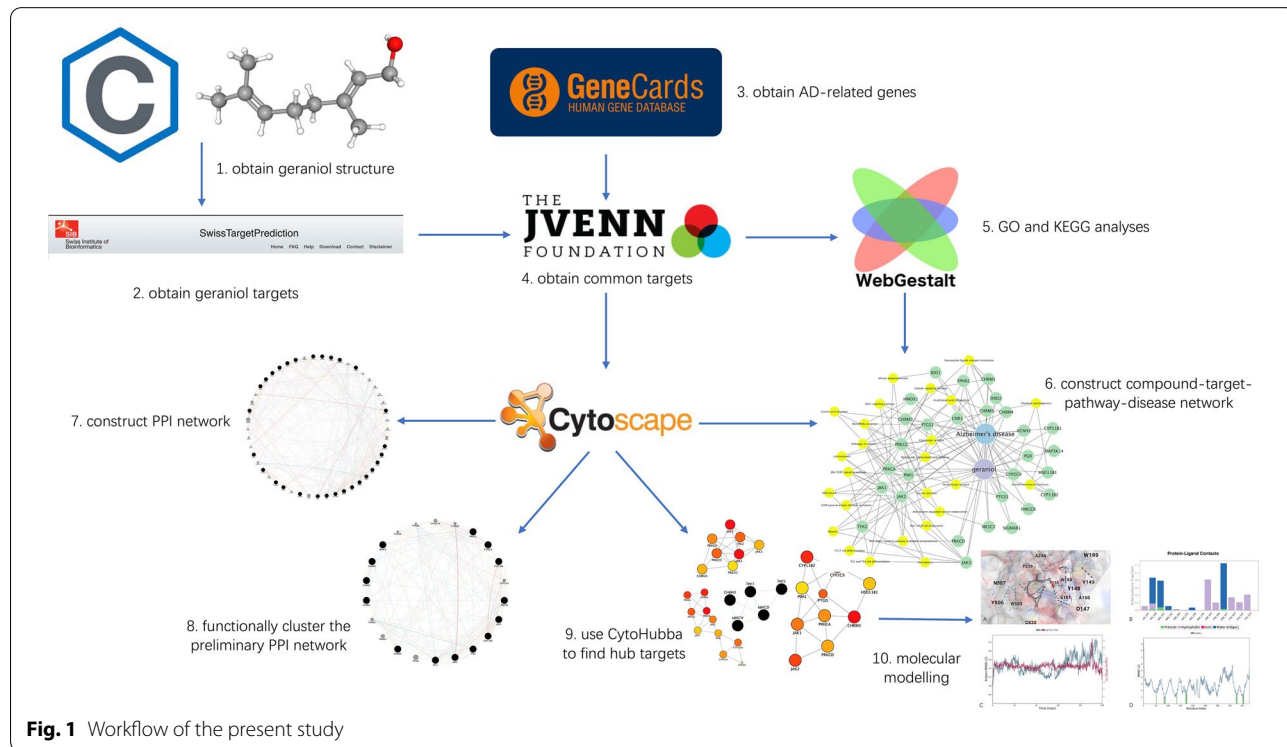


Fig. 1 Workflow of the present study

Table 1 Basic pharmacological data of geraniol

Name	MW (Da)	Hdom	Hacc	RBN	TPSA (Å ²)	GI	BBB	LogKp (cm/s)	Lipinski
Geraniol	154.25	1	1	4	20.23	High	Yes	-4.71	No violation

MW molecular weight, *Hdon* hydrogen donor, *Hacc* hydrogen acceptor, *RBN* number of bonds that can perform free rotation, *TPSA* surface sum over all polar atoms, primarily oxygen and nitrogen, also including their attached hydrogens, *GI* *absorp* gastrointestinal absorption, *BBB* blood–brain barrier, *LogKp* an improved measurement of skin permeation coefficient, *Lipinski* Lipinski’s rule of five, an empirical rule to evaluate whether a molecule is suitable to be developed into orally administrated drug

corresponding pharmacological properties for ADME and Lipinski’s rule evaluation.

Target identification

We used the sdf file again, but with Swiss Target Predictor (www.swisstargetprediction.ch) this time to find the putative targets of geraniol [15]. Then, we searched from GeneCard (<https://www.genecards.org>) to obtain the AD-related targets [16]. Afterward, we used the JVenn program (<http://jvenn.toulouse.inra.fr/app/example.html>) to calculate the intersection of them which are their common targets [17]. These targets were then classified by the Panther classification system (<http://www.pantherdb.org/>) [18].

Enrichment analyses of the common targets

WebGestalt (www.webgestalt.org), as a robust online bio-informatic toolkit, was used for GO and KEGG pathway enrichment analyses of the common targets [19].

Network construction

Based on the results, we constructed the geraniol–target–pathway–AD network by Cytoscape (v3.9.0) for better visualization [20]. In addition, we exerted the list of common targets into GeneMANIA, a Cytoscape plug-in, to build a preliminary protein–protein interaction (PPI) network [21].

Functional clustering and in-depth enrichment analyses of the preliminary PPI network

We used a Cytoscape plug-in, “MCODE” to functionally cluster the preliminary PPI network, which created a subnetwork [22]. With the newly created subnetwork, we conducted GO and KEGG analyses again to gain a more comprehensive understanding of the role that geraniol may play in the mechanism against AD.

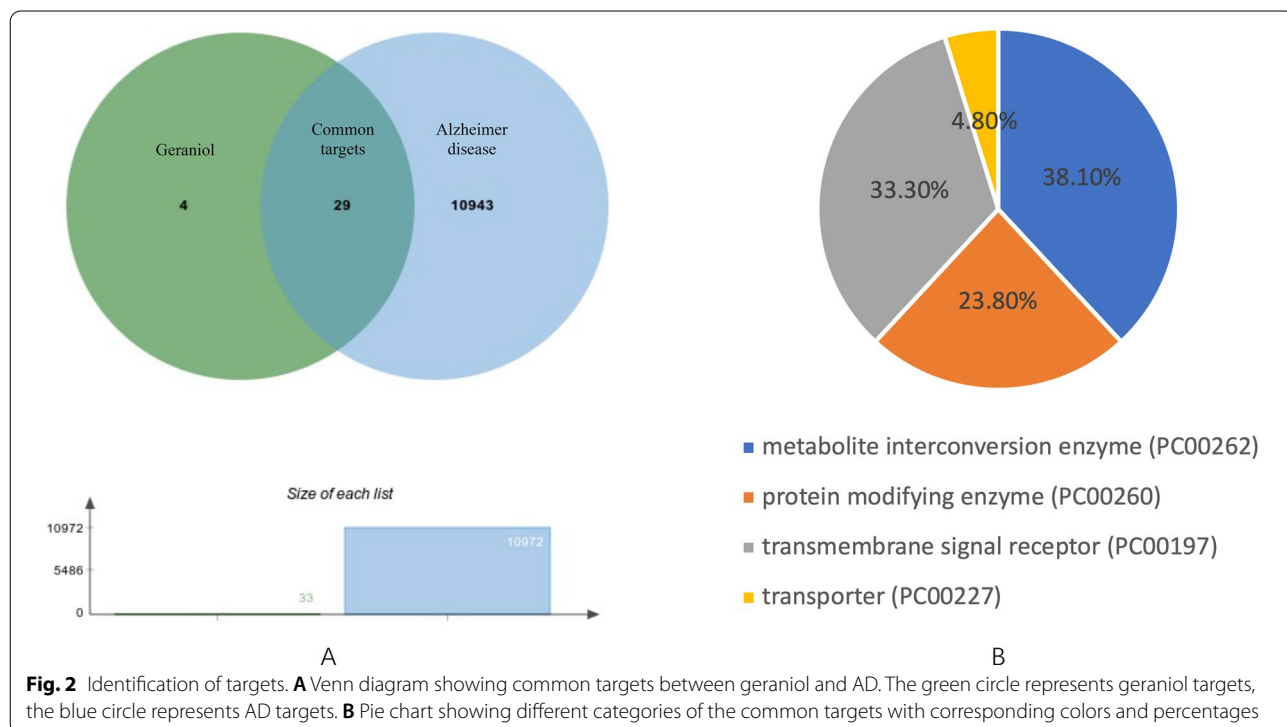
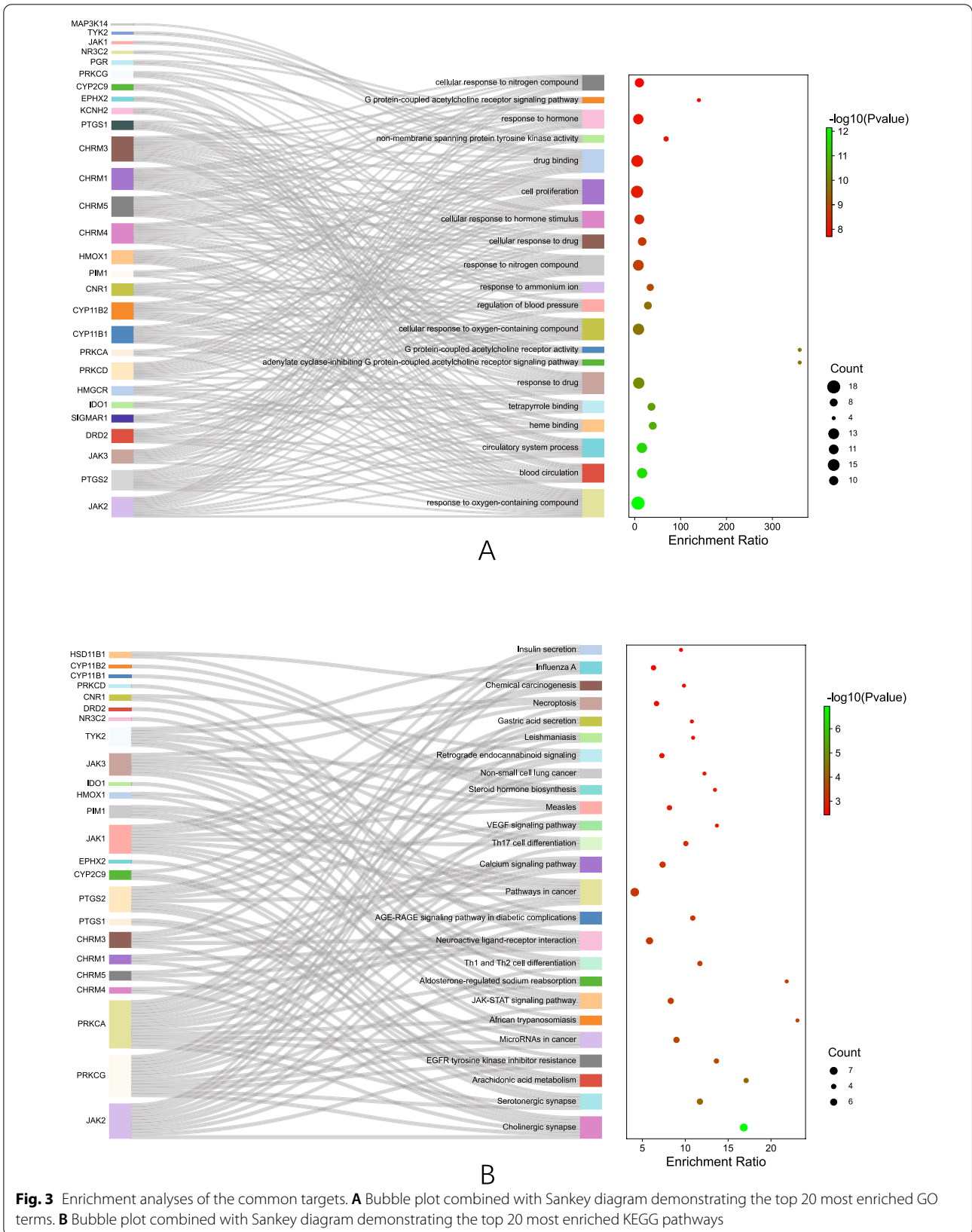
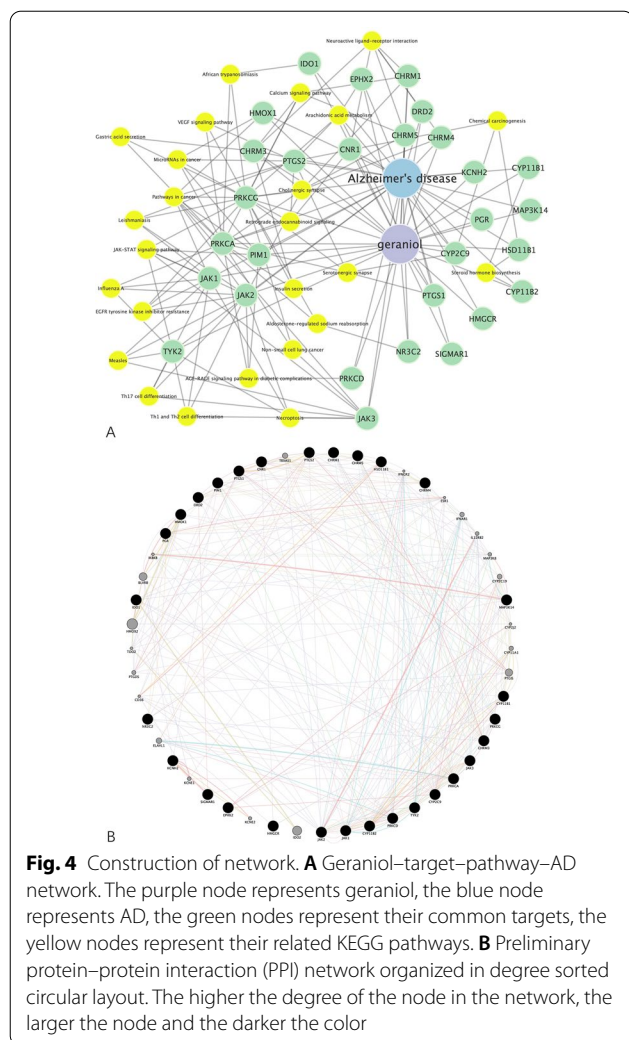


Fig. 2 Identification of targets. **A** Venn diagram showing common targets between geraniol and AD. The green circle represents geraniol targets, the blue circle represents AD targets. **B** Pie chart showing different categories of the common targets with corresponding colors and percentages





Hub target screening via topological analysis of the preliminary PPI network

We used another Cytoscape plug-in, “CytoHubba”, to extract a core PPI network that frames the preliminary PPI network via intersectional merge of the subnetworks created from degree, closeness, and betweenness methods [23].

Molecular docking verification

To predict the interaction between the targets and the compounds, we downloaded the crystal structures of the 5 hub targets from PDB library (i.e., 3egy, daj, 2b7a, 3iw4, 1yrk) and then docked them with geraniol molecule on CB-dock platform (<http://clab.labshare.cn/cb-dock/php/blinddock.php>) based on AutoDock Vina [24, 25]. Afterward, we obtained the corresponding affinity energy values and the binding sites, the center, and the customized docking box size. To further validate the binding mode, we performed molecular dynamic simulation.

The simulation was performed by Desmond at 100 ns to investigate the binding conformational stability of the protein–ligand complex [26]. The stability of the protein–ligand complex was observed to be maintained during the whole 100 ns simulation for compounds based on RMSD, RMSF, and hydrogen bond interactions.

Results

Druggability assessment

As usually a molecule fulfilling the parameters of $RBN < 10$, $OB \geq 20\%$, $DL \geq 0.1$, $TPSA < 60 \text{ \AA}^2$, and Lipinski’s rule of five (i.e., $MW < 500 \text{ Da}$, $AlogP < 5$, $Hdon < 5$, $Hacc < 10$) is considered as potential druggable substance, geraniol possessing $MW = 154.25 \text{ Da}$, $Hdom = 1$, $Hacc = 1$, $RBN = 4$, $TPSA = 20.23 \text{ \AA}^2$, $LogKp = -4.71 \text{ cm/s}$, therefore is deemed to be one of such molecules that can be further optimized into orally administered drug.

Details are shown in Table 1.

Target identification

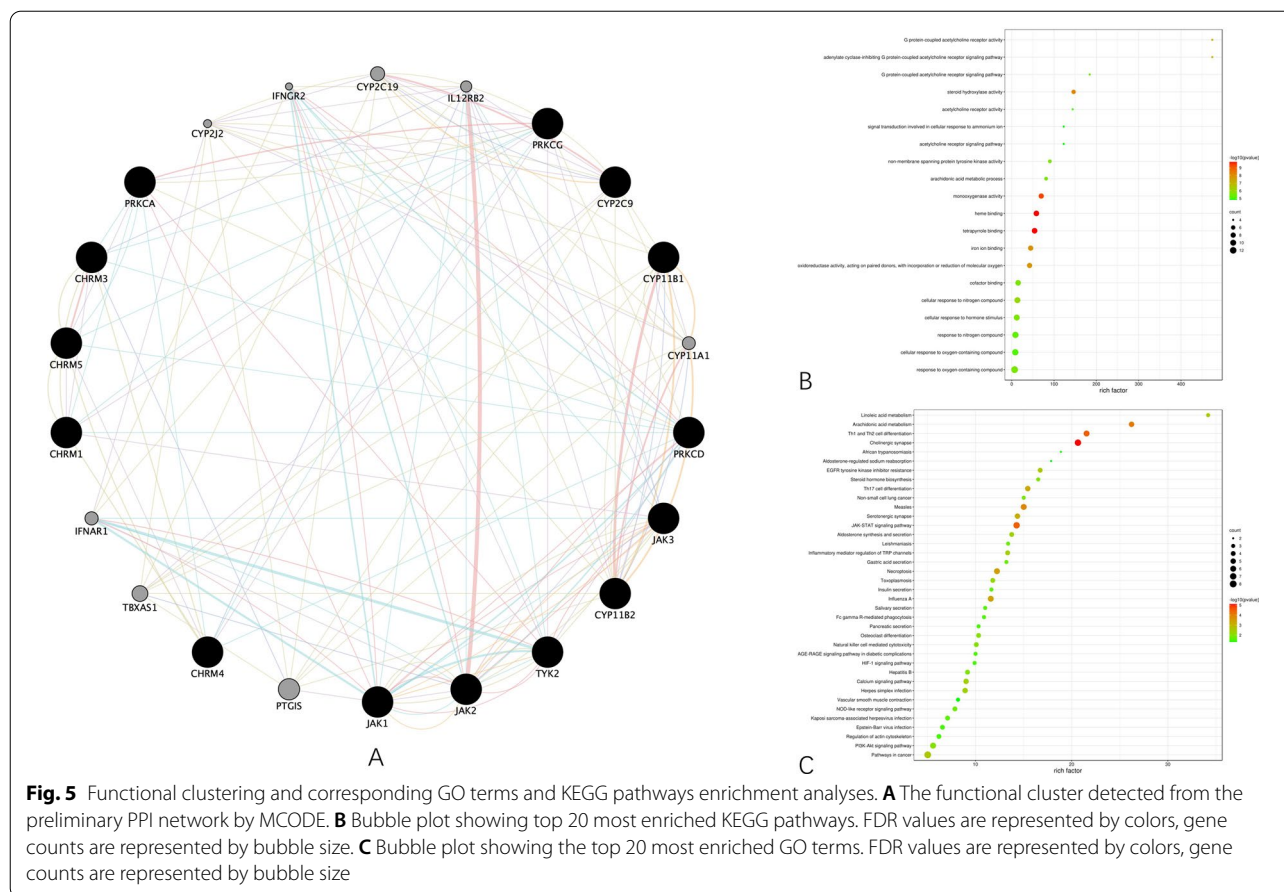
Through searching, 10,972 AD-related targets and 33 geraniol targets were found from which 29 of them are common targets. They are demonstrated as an intersection in the Venn diagram in Fig. 2A. After being categorized by the Panther classification system, it appears that 38.1% of them are metabolite interconversion enzymes, 23.8% are protein modifying enzymes, 33.3% are transmembrane receptors, and the rest are transporters. The percentage of each category is indicated in the pie chart in Fig. 2B.

Enrichment analyses of the common targets

With the common targets, we conducted GO terms and KEGG pathways enrichment analyses to gain a macroscopic understanding of their functions, from which we found that GO:1901700 (response to oxygen-containing compound) is the most enriched GO term, followed by GO:0008015 (blood circulation), GO:0003013 (circulatory system process), and hsa04725 (cholinergic synapse), hsa04726 (serotonergic synapse), hsa00590 (arachidonic acid metabolism) are the most enriched KEGG pathways, as shown in Fig. 3A, B. The rare data of the enrichment analyses can be visited in the Additional file 1 S2_Rare data for GO terms and KEGG pathways analyses.

Network construction

Based on the enrichment results, we constructed the geraniol–target–pathway–AD network, as shown in Fig. 4A, with 56 nodes and 165 edges. For the data used during the construction of the network, please visit the



Additional file 1 S1_Rare data for target identification. The characteristic path length is 2.421, network density is 0.107, the heterogeneity is 0.938, the network centralization is 0.436. In addition, in Fig. 4B, we built a PPI network for deeper analyses to see the logic behind. The preliminary PPI network contains 49 nodes and 317 edges, with 2.087 characteristic path length, 0.190 network density, 0.367 network heterogeneity, and 0.106 network centralization.

Functional clustering and in-depth enrichment analyses of the preliminary PPI network

By setting *K* core value to 3 and keeping the rest parameters in default values, we functionally clustered the proteins involved in the preliminary PPI network as what Fig. 5A shows. The modulation score of the cluster is 8.476 which consists of 22 nodes representing 22 genes.

Based on these genes, we conducted the GO terms and KEGG pathways analyses to have a deeper insight of their functions. The results in Fig. 5B, C further suggest that geraniol may be against AD by participating in cholinergic synapse, serotonergic synapse, and neuroactive ligand–receptor interaction, as these pathways have more

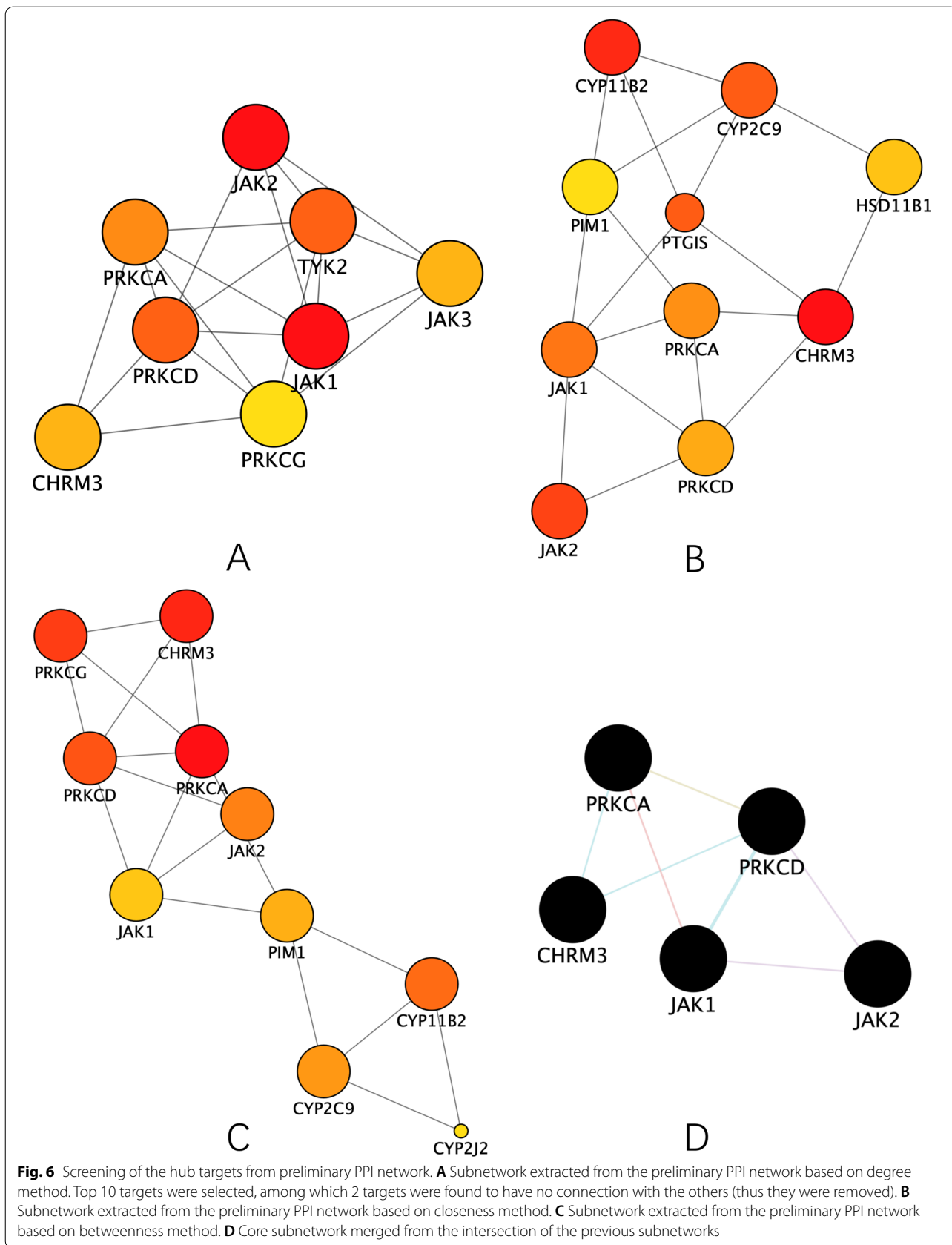
genes involved. The rare data of the enrichment analyses can be visited in the Additional file 1 S3_Rare data for GO terms and KEGG pathway analyses of functional clustering.

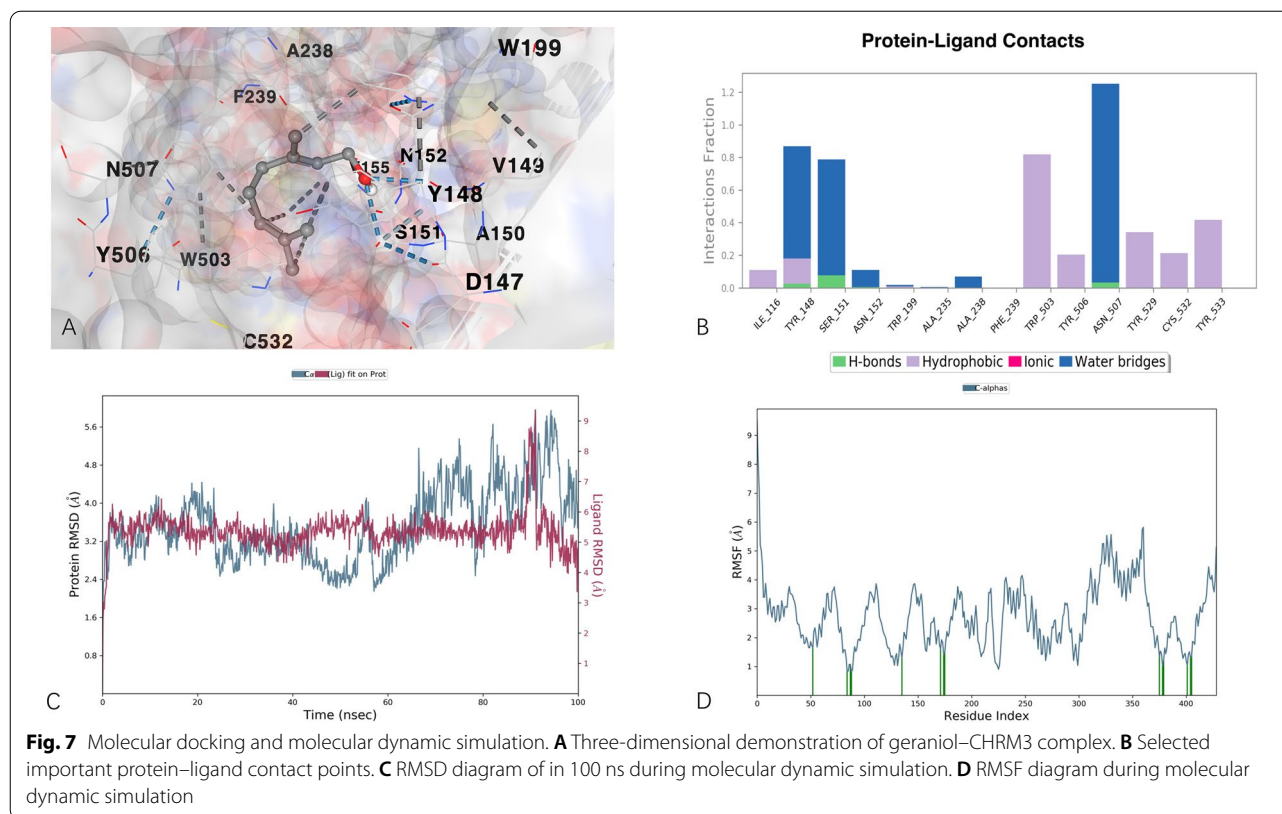
Hub target screening via topological analysis of the preliminary PPI network

By using the CytoHubba plug-in, we can make a further in-depth analysis of the topology of the network. We screen 3 subnetworks with top 10 ranking nodes in Fig. 6A–C based on degree, closeness, betweenness methods, respectively. Then, these subnetworks underwent intersectional merge, creating a core PPI subnetwork in Fig. 6D composed of 5 hub targets: JAK1, JAK2, PRKCD, PRKCA, CHRM3.

Molecular docking and molecular dynamic simulation

Molecular docking between geraniol and the hub targets was carried out to ascertain the binding mode between them. It was found that the best run came with CHRM3 with the lowest affinity energy of -5.9 kcal/mol, followed by JAK1, JAK2 and PRKCA (all of them are -5.8 kcal/mol), and PRKCD (-4.8 kcal/mol), which suggests that





CHRM3 may serve as the most important player of the underlying mechanism against AD. Detailed of the binding modes are available in the Additional file 1 S4_Rare data for molecular docking. We further verified the binding mode between CHRM3 and geraniol through molecular dynamic simulation which was performed on the top hit containing high binding energies. Over the simulation period, the projected conformational changes from the initial structure were presented in terms of root mean square deviation (RMSD). Moreover, structural stability, atomic mobility, and residue flexibility at times of interaction of protein-hit were expressed with root mean square fluctuation (RMSF) values. The RMSD values for protein-ligand complex were calculated and given in Fig. 7B. RMSD of the complex showed deviation of about 2 Å at 90 ns and then there was no significant fluctuation and the simulation converges, suggesting a good stability of the protein-ligand complex. For RMSF, there was not much fluctuation observed and the structure was stabilized comparatively and there was no fluctuation where ligand made contacts with protein, as shown in Fig. 7C. Overall, the ligand showed significant different types of intermolecular interactions during the entire simulation including hydrogen bonds, ionic, water bridges, and hydrophobic. The residues participating in these

interactions include ILE 116, TYR 148, SER 151, ASN 152, TRP 199, ALA 235, PHE 239, TRP 503, TYR 506, ASN 507, TYR 529, ASN 507, TYR 529, CYS 532 and TYR 533, as shown in Fig. 7D.

Discussion

Although there has been numerous research on geraniol and AD separately, to the best of our knowledge, the present study is the very first one to integrate network pharmacology and molecular modeling to give a mechanistic insight of the potential mechanisms of geraniol in AD treatment.

The network pharmacological analysis identified 10,972 AD-related targets, 33 geraniol targets, among which 29 of them are common targets. Among the 29 common targets, 38.1% of them are metabolite interconversion enzymes, 23.8% are protein modifying enzymes, 33.3% are transmembrane receptors, and the rest are transporters. They mainly participate in cholinergic synapse, serotonergic synapse, and neuroactive ligand-receptor interaction. Earlier progress in neuroscience revealed that high density of cholinergic synapse in the human central nervous system is critically important in terms of memory, learning, as well as attention and thus significantly associated with age-dependent neurological

declines, such as AD [6]. Dysregulation of serotonergic synapse was argued to be a major cause of the AD in recent years (i.e., the serotonergic hypothesis) [27]. Therefore, it is thought that geraniol may exert its effects against AD through such neurology-related pathways.

In addition, we constructed a preliminary PPI network aiming to sort out the hub targets. After topological optimization of the network, 5 hub targets (i.e., CHRM3, PRKCA, PRKCD, JAK, JAK2) were screened out. CHRM3 has been found to heterodimerize with CHRM2 which contributes to memory and cognition [11–13, 28]. PRKCA is said to be related to amyloid protein formation in AD [29–31]. Besides, previous scientific research has reported the dual role of PRKCD in proapoptotic kinase activation and apoptotic caspase cascade activation, which is important in the pathogenesis of neurodegenerative disorders including AD [32]. Clinical studies have also shown that dysregulation of the expression of JAK1 and JAK2 associates with brain inflammatory processes and neuronal or glial survival, which are consequently involved in most brain disorders including the pathogenesis of AD [33]. In short, the 5 hub targets are in strong correlation with AD pathogenesis and deterioration.

Furthermore, we conducted molecular modeling to study the robustness of the interaction between each hub target and geraniol molecule. Subsequently, it is found that CHRM3 possesses the highest affinity with geraniol molecule and thus may serve as the key target of geraniol molecule in AD treatment.

In conclusion, the present study shares a mechanistic insight of the potential of geraniol against AD, giving a reference to future experimental studies.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s40001-022-00699-8>.

Additional file 1. S1_Rare data for target identification, S2_Rare data for GO terms and KEGG pathways analyses, S3_Rare data for GO terms and KEGG pathway analyses of functional clustering, S4_Rare data for molecular docking.

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Author contributions

SZ and XH wrote the main body of the manuscript. YL edited and proofread the manuscript text. YL, SZ, and XH designed the study and are responsible for the conceptualization. YL curated the data. SZ and XH analyzed the data. YL prepared Fig. 1. XH prepared Figs. 2, 3. YL and SZ prepared Figs. 4, 5 and 6. YL and HMR prepared Fig. 7.

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Availability of data and materials

All data, models, and code generated or used during the study appear in the submitted article. No copyright is owned by individuals/organizations other than the authors.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors agreed to publish the present manuscript.

Competing interests

The authors declare no competing interests.

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