The strategy to find novel candidate anti-AD drugs by constructing the interaction networks between drug targets and natural compounds in medical plants (#21844)

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The strategy to find novel candidate anti-AD drugs by constructing the interaction networks between drug targets and natural compounds in medical plants

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Background: Alzheimer' disease (AD) is an ultimately fatal degenerative brain disorder with an increasingly large burden on health and social care systems. There are only five drugs for AD on the market and haven't been any novel effective medicines for quite a few years. Chinese medicinal plants were used for treating diseases for thousands of years and screening herbal remedies is a way to develop new drugs.

Methods: We use molecular docking to screen all compounds from traditional Chinese medicine (TCM) into the comprehensive AD targets. Compounds with excellent binding affinity are drug candidates. The structural similarity with existing drugs and druggability properties of these drug candidates are studied. And we searched CNKI database to obtain anti-AD Chinese plants from 2007 to 2017 and only the articles of the clinical study were remained.

Results: 1654 compounds have excellent binding affinity with 33 AD targets. Most of them are rich in the plants used for treating AD in China. The main plants are from two genera Panax and Morus. We classify the compounds by single target and multiple targets. Structural similarity reveals that 20 candidate anti-AD compounds are structurally identical with 14 existing drugs which were reported as anti-AD compounds in previous study. After ADMET filter, we get 13 anti-AD compounds with favorable druggability properties. And 9 compounds are ingredients of anti-AD Chinese plants.

Discussion: The natural compounds from TCM provide a broad prospect for the screening of anti-AD drugs. We establish networks to systematically study the connection among natural compounds, approved drugs, TCM plants and AD targets and find promising candidate drugs. We hope our study can be helpful for in-depth research for Chinese medicine treatment of AD.

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ABSTRACT

Background

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Results

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Discussion

The natural compounds from TCM provide a broad prospect for the screening of anti-AD drugs. We establish networks to systematically study the connection among natural compounds, approved drugs, TCM plants and AD targets and find promising candidate drugs. We hope our study can be useful for in-depth research for Chinese medicine treatment of AD.

Keywords: Alzheimer's disease, molecular docking, candidate drugs

INTRODUCTION

Alzheimer's disease (AD) is a progressive and ultimately fatal degenerative brain disorder of the central nervous system, which is thought of being one of the main causes for dementia in senior citizens[1,2].(Fan & Chiu 2014; Song et al. 2015) Some psychiatric symptoms are observed in AD patients, such as irritability, changes in mood or personality, paranoid delusions and hallucinations.(Coyle et al. 1983) Pathological diagnoses for AD are the senile plaques and the neurofibrillary degeneration (Dickson 1997). The degeneration is caused by neurofibrillary tangles in the intracellular fibrous aggregation of protein tau, and which exists mainly in areas of the brain involved in learning, memory, and emotional behaviors, for example, the hippocampus, the basal forebrain, the entorhinal cortex and the amygdala (Mattson 2004). Some hypotheses about AD pathogenesis involved in many pathways and targets have been suggested, such as, the amyloid (Goedert & Spillantini 2006), the cholinergic (Craig et al. 2011), the oxidative stress (Pratico 2008), the glutamatergic (Bezprozvanny & Mattson 2008), the inflammatory (Trepanier & Milgram 2010) and the metal hypotheses (Bonda et al. 2011). However, the cause for AD are not very clearly yet, because it is a complex and multifactor disease (Armstrong 2013). Up to now, five drugs of symptom relief can be used to Alzheimer's patients on clinical, including four cholinesterase inhibitors and one N-methyl-D-aspartate(NMDA) -receptor antagonist, but no one can cure the patients or inverse AD (Cummings et al. 2014; Peng et al. 2016). Thus, the new drug discovery for AD is still a challenge.

Traditional Chinese medicines (TCMs) have been used in therapy in various diseases for several thousand years in Chinese history, and some natural ingredients in them have been also developed into the drug successfully, such as artemisinin. Screening natural ingredients or compounds from the herbal remedies and TCMs may be an effective way to develop new drugs.(Normile 2003; Sanderson 2011; Sucher 2013) For example, the interactions between some ingredients from anti-AD herbs and their corresponding target proteins(Sun et al. 2013) and between 12 ginger components and 13 anti-AD targets can be found(Azam et al. 2014). There are many validated AD targets, such as AchE(Yiannopoulou & Papageorgiou 2013), BchE(Darvesh 2016; Mushtaq et al. 2014), RAGE(Cai et al. 2016; Deane 2012), TNF-alpha(Leszek et al. 2016; Wyss-Coray & Rogers 2012), PLA2(Gentile et al. 2012; Lee et al. 2011) and so on. They are involved in various AD associated pathways. Because we want to study comprehensive AD targets, we select 33 targets which have protein crystal structures from all validated AD therapeutic targets as our research objects. In order to explore the interactions between the 33 validated AD therapeutic targets involved in various hypotheses and compounds in TCM plants, the interaction networks among the targets, compounds, approved drugs and TCMs have been established in this study. Finally, 13 candidate anti-AD compounds with favorable druggability properties are structurally novelty, and 9 compounds of them are ingredients of anti-AD Chinese plants. Thus, these 13 compounds may be valuable in anti-AD drug development in the future; of course, they will also be needed to prove in the further drug experiments. The results implicates that the strategy of drug discovery based on the interaction networks may be very helpful for drug development.

MATERIALS AND METHODS

Data collection and preprocessing

More than 60000 natural compounds from 8529 different plants are from TCM Database@Taiwan (http://tcm.cmu.edu.tw/). This database is the web-based database and is also the most comprehensive non-commercial database of traditional Chinese medicine (TCM)(Chen 2011). The 3D structures of molecules are available as mol2 format in the database. The mol2 file format is converted to the pdbqt format and the SMILES string by Open Babel toolbox v2.3.1(O'Boyle et al. 2011).

All 33 validated therapeutic targets of AD are obtained from the Thomson Reuters Integrity database (https://integrity.thomson-pharma.com/integrity/). Protein structures of these targets are from Protein Data Bank (PDB) database (http://www.rcsb.org/pdb/home/). The 3D structures of the proteins are available as pdb format. This format is converted to the pdbqt format by AutoDock tools v1.5.6 (Morris et al. 2009), and the 3D view is shown by Discovery Studio v3.1 (http://accelrys.com/products/collaborative-science/biovia-discovery-studio/).

Molecular docking between natural compounds and AD targets

Docking is tantamount to position the ligand in different orientations and conformations within the binding site to calculate optimal binding geometries and energies. The interaction between natural compounds and AD targets are predicted by AutoDock Vina 1.1.2 (Trott & Olson 2010). The docking binding site center for each target is the structural binding center of ligand embedded. To allow free rotation of the compounds, the search space is set to 25 × 25 × 25 Å in each axis. The default settings are used for all other docking parameters. Each docking is performed by a command that contains space size and three-dimensional coordinate of docking center. Binding pose with the lowest energy for each docking test is considered as the best binding mode of each compound. The lower energy score means stronger binding affinity between the ligand and the receptor. The compounds with top 0.5% docking score are chosen as the candidate ligands for each target.

The interactions among targets, compounds and plants

The networks of target-compound and of target-plant are constructed by Cytoscape v3.4.0(Shannon et al. 2003). The target and the compound will be connected, if the compound is docked to the target successfully. The target and the plant will also be connected, if the plant with the compound can interact with the target. The link strength is represented as the line's thickness, which indicates the number of the compounds between the target and the plant.

Collection of anti-AD plants from Chinese medicine prescription

The word senile dementia is searched in the subject column of CNKI database (http://www.cnki.net/) to retrieve Chinese medicine prescription for anti-AD from the related Chinese articles. The articles from 2007 to 2017 have been collected, and just those articles from the clinical study are remained. Chinese medicine prescriptions and its usage frequency are from these articles too. The common anti-AD plants in traditional Chinese clinical medicines can be found from the prescriptions. The Chinese version of raw data prescription with corresponding English includes, the Latin name of anti-AD plants in each prescription, the patient number (male and female if available), the article title of study and published data (years).

The similarity between candidate compounds and existing drugs

Both Tanimoto coefficient (Tc) and Pybel(O'Boyle et al. 2008) the package of Python are used to measure the structural similarity between two compounds. The fingerprint FP2 implemented in the Pybel is generated for each structure and used to calculate Tc. Tc is defined as Tc = C(i, j)/U(i, j), where C(i, j) is the number of common features in the fingerprints of molecules i and j, and where U(i, j) is the number of all features in the union of the fingerprints of molecules i and j. If the fingerprints of two compounds are Tc = 1, they will be considered structurally identical.

The Cytoscape v3.4.0 is used to construct the network including candidate compounds, their targets and structurally identical drugs. The existing drug in drugbank database(Wishart et al. 2006) and natural compound will be connected, if their Tc score equals to 1. The natural compound and their targets are also connected in this network.

Clusters of potential candidate compounds for AD

1654 of all compounds in docking with 33 targets are located at top 0.5%, they have been regarded as the potential candidate compounds for AD. The cluster ligands protocol in BOVIA Pipeline Pilot V8.5 (http://accelrys.com/products/collaborative-science/biovia-pipeline-pilot/) is used to cluster the 1654 compounds. A set of compounds is assigned to different clusters during clustering, and every cluster compounds have similar properties. The clustering is based on maximal dissimilarity partitioning of a relocation method. Only the fingerprint FP2 is used in this study. Cluster selection can be performed by size or number, and the cluster number is assigned to 10 in this study. If the sum of one member distancing to other members reaches the minimum value, this member is selected as the cluster center.

ADMET properties for candidate compounds for AD

ADMET properties of candidate compounds for AD are estimated by Discovery Studio. These properties, including aqueous solubility, blood brain barrier penetration (BBB), human intestinal absorption (HIA), plasma protein binding (PPB) and hepatotoxicity, are used to filter the compounds. The values of these properties have been set as the controlled parameters, they are 3~4 (3: good; 4: optimal) for aqueous solubility, 1~2 (1: high; 2: medium) for BBB, 0 (0: good) for HIA, FALSE for both PPB and hepatotoxicity.

RESULTS

Molecular docking of natural compounds and embedded ligands to the 33 AD targets

30438 of 60000 compounds in TCM Database contain plant information, and they have been docked with the 33 AD targets' embedded ligands (Table 1). The docking scores of embedded ligand in the protein crystal structure are from −3.31 to −12.65 (kcal/mol). The lowest docking energy scores for the 33 targets are from −8.44 to −14.5 (kcal/mol). Some targets, such as Caspase-3, QC, IDO and GLP-1R, can bind with more than 20000 natural compounds, and the docking scores of compounds are better than those of their embedded ligands. However, the docking scores of the target RAR with natural compounds are worse than those of the RAR with its embedded ligand.

Because lots of TCM compounds can bind to AD targets, just top 0.5% compounds in scores, for each target, are taken as the candidate compounds for AD; all these top 5% compounds include 1654 compounds. The docking results of 1654 compounds indicate that almost all docking energies of the top 0.5% compounds with targets are higher than those of embedded ligands (Fig. 1). Thus, the docking results should be reliable and the 1654 compounds can be taken as candidate compounds for AD.

The analysis of single target and multi-target compounds

There are 976 compounds with single target and 678 compounds with multiple targets in 1654 candidate compounds for AD (see Supplementary Fig. 1 and 2). The single-target compounds corresponding to each target are very different in numbers. For example, target SIRT1 corresponds to 76 compounds, but target lyn just corresponds to 4 compounds. The multi-target compounds are classified into 21 networks based on their corresponding target numbers. For examples, the two-target network contains 274 compounds, and the three-target network includes 131 compounds. Finally, the compound, number 24508, binding to 25 AD targets have been observed.

The candidate compounds for AD and their enrichment plants

1654 candidate compounds for AD have been mapped to the 363 plants corresponding to 33 AD targets. The plant numbers for each target are from 42 to 71, whereas the compounds numbers for each target are from 62 to 123 (Fig. 2 and Supplementary Fig. 3).

101 clinical related articles have been obtained from more than 10000 senile dementia related articles, and 141 anti-AD traditional Chinese plants have been also observed from 101 clinical prescriptions. The 141 traditional Chinese anti-AD plants are classified based on the functional property in the TCM database. Most of the 141 anti-AD plants are in the category 'Tonifying, Replenishing', and the plants in this category reach 28.45% in all anti-AD plants (Supplementary Fig. 4).

The best associated plant for each target containing most compounds can dock with this target (Table 2 and Fig. 3). Thus 33 targets correspond to 18 best associated plants. The top 6 plants corresponding to 17 targets in these 18 plants are anti-AD traditional Chinese plants, they include *Panax* and *Morus* corresponding to 6 targets, respectively, others are *Salvia, Rheum, Paeonia and Glycyrrhiza*.

The similarities between candidate compounds and existing drugs

The structural similarities between existing drugs and top 0.5% natural compounds show that some compounds are identical to existing drugs in similairty (Tc=1). The connection network among candidate compounds, existing drugs and AD targets has been established (Fig. 4). There are 20 candidate compounds, 14 existing drugs and 27 AD associated targets in the network. The 14 drugs include Lutein (DB00137), Vitamin A (DB00162), Vitamin E (DB00163), Azelaic Acid (DB00548), Ergotamine (DB00696), Estradiol (DB00783), Menthol (DB00825), Drostanolone (DB00858), Glyburide (DB01016), Tubocurarine (DB01199), Metocurine (DB01336), Yohimbine (DB01392), Lactose (DB04465), Artemether (DB06697).

10 in these 20 candidate compounds can only bind with one target, but others can interact with more than one target, which is similar to those 14 drugs. For example, compound 18491 can only interact with the target Ftase, and this is same to Menthol, both compound 19476 and 19477

are also same to Tubocurarine and Metocurine, respectively; but compound 18582 and 18583 are similar to Ergotamine, they can combine with 16 and 14 targets, respectively.

The structure cluster of candidate compounds for AD

In order to compare the structural features among candidate compounds for AD, the 1654 candidate compounds for AD have been assigned into 10 clusters (Table 3). All the compounds in cluster center contain the carbocyclic structure, which is similar to the five approved drugs for AD. The size of different clusters is not same, the largest cluster contains 477 compounds, but the smallest cluster is made of just 6 compounds. Every cluster has its primary target that can better combine with the compounds in this cluster.

13 candidate compounds for AD with favorable ADMET properties

13 of 1654 candidate compounds are retained after ADMET analysis (Table 4). 8 of 13 compounds are the single-target compounds, others are the multi-target compounds. For example, compound 5868, 8792, 9593, 10639, 28814, 31515 just can combine with one target, they are MGLUR, GABA(B), XO, MAOB, PDE4, RAR, SIRT1, respectively; compound 5862 and 16167 share one common target, AchE; compound 5863 can combine with three targets, AchE, GABA(B) and MGLUR; compound 5869 and 30713 can interact with two targets, but compound 26629 and 28468 can be interacted with five targets. These 13 compound structures and their corresponding plants have been shown in Table 5. The corresponding plants of 9 compounds have been regarded as the anti-AD plants in TCM, including *Curcuma kwangsiensis, Poria cocos, Lindera aggregate, Ophiopogon japonicus (L. f.) Ker-Gawl.* and *Glycyrrhiza glabra*.

DISCUSSION

The candidate compounds from traditional Chinese plants provide a broad prospect for the screening of anti-AD drugs. The network between all compounds in traditional Chinese plants and comprehensive anti-AD targets involved in various hypotheses has been established. The network among compounds, TCM plants and targets may be very helpful for the anti-AD drug design.

The identical structure between existing drugs used to treat other diseases and the 1654 candidate compounds can provide enlightenment for drug discovery. Except for existing AD drugs, the positive effects on AD in other existing drugs have also been reported. Some studies have shown that Lutein is closely related to preventing cognitive decline and risk of AD, thus Lutein may contribute to the treatment of AD(Kiko et al. 2012; Min & Min 2014; Xu & Lin 2015). Similarly, Vitamin A, Vitamin E, Estradiol, Menthol, Glyburide and Yohimbine are also considered to be helpful for the prevention and therapy of AD.(Bhadania et al. 2012; Dysken et al. 2014; Lamkanfi et al. 2009; Lan et al. 2016; Mohamd et al. 2011; Ono & Yamada 2012; Peskind et al. 1995; Takasaki et al. 2011) All above suggested that compounds with similar structures to existing drugs may also have anti-AD function through interacting with similar targets. For example, Tubocurarine can interact with the target AchE which has been described in Drugbank database. Because candidate compounds have identical structures with these existing drugs, their anti-AD activities can be expected and these compounds should be worth being studied further.

ADMET is one important index in drug development. After five ADMET properties filtering, 13 candidate anti-AD compounds with novel structure are remained. In the 13 compounds, 8 are single-target compounds, 2 are double-target compounds and other 3 compounds combine with more than two targets. The structures and targets of these compounds have known, so they can be study easily in drug development in future. And because these compounds have favorable druggability properties, they may become the promising candidate drugs for AD. Of course, the further experiments are necessary before their becoming real candidate drugs.

Many compounds combining with AD associated targets have been observed in some plants never used in the traditional Chinese clinical prescription. So some non-anti-AD plants may become the anti-AD plants, which will offer more natural compound resource for the new drug discovery for AD and be also helpful for the development of TCMs.

In this study, three verification methods have used to test the result credibility of has been tested. Firstly, the ligand embedded in the protein crystal structure is used as a validation criterion; the results show that docking energy scores of most candidate anti-AD compounds are better than those of the protein-embedded ligands. Secondly, some of candidate compounds with same structures to existing drugs used in other diseases can be identified, and these drugs have been reported to be a positive effect for AD treatment. Finally, many of medical plants used to treat AD in TCM clinical prescriptions can be also observed in this study.

CONCLUSION

In summary, this study offers one strategy to find novel candidate anti-AD drugs from traditional Chinese plants by constructing the interaction networks between AD targets and natural compounds in TCM plants, which may be helpful for understanding the molecular mechanism of anti-AD. In addition, 13 novel anti-AD candidate compounds have also been found.

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Table 1(on next page)

Details of docking results of 33 anti-AD targets with the number of successfully docked TCM compounds

a. the number of compounds with better docking score than that of ligand embedded in the crystal structure.

b. 'Ligand Energy' means the docking energy of ligand embedded in the crystal structure.

Table 1. Details of docking results of 33 anti-AD targets with the number of successfully docked TCM compounds

PCSB ID	Protein Name	Compound Number[a]	Ligand Energy[b]	Lowest docking Energy
1DB4	PLA2(Phospholipase A2, membrane associated)	5290	-7.31	-11.55
1DQA	HMG-COA(3-hydroxy-3-methylglutaryl-coenzyme A reductase)	437	-7.42	-9.78
1NME	Caspase-3	21028	-4.57	-10.24
1OJA	MAOB(Amine oxidase [flavin-containing] B)	11173	-6.58	-12.2
1TB7	PDE4(cAMP-specific 3',5'-cyclic phosphodiesterase 4D)	17375	-6.47	-14.5
1TN6	Ftase(Protein farnesyltransferase subunit beta)	14437	-6.59	-11.9
2AFW	QC(Glutaminyl-peptide cyclotransferase)	23635	-4.48	-11.11
2AZ5	TNF(Tumor necrosis factor)	9261	-5.66	-9.53
2D0T	IDO(Indoleamine 2,3-dioxygenase 1)	20739	-5.71	-12.4
2DQ7	Fyn(Tyrosine-protein kinase Fyn)	63	-10.28	-12.41
2E1Q	XO(Xanthine dehydrogenase/oxidase)	15609	-4.65	-11.05
2VQM	HDAC(Histone deacetylase 4)	5356	-7.11	-11.33
2Z5Y	MAOA(Amine oxidase [flavin-containing] A)	5299	-7.96	-12.8
3A4O	lyn(Tyrosine-protein kinase Lyn)	431	-9.4	-12.53
3G9N	JNK(Mitogen-activated protein kinase 10)	1606	-7.19	-10.36
3IKA	EGFR(Epidermal growth factor receptor)	6324	-7.64	-11.45
3KMR	RAR(Retinoic acid receptor alpha)	0	-12.65	-11.4
3O3U	RAGE(Advanced glycosylation end product-specific receptor)	13309	-7.76	-14.08
4DJU	BACE-1(Beta-secretase 1)	14161	-7.12	-12.2
4EY5	AchE(Acetylcholinesterase)	329	-8.5	-10.6
4KXQ	SIRT1(NAD-dependent protein deacetylase sirtuin-1)	45	-10.3	-12.4
4MS4	GABA(B)(Gamma-aminobutyric acid type B receptor subunit 1)	13107	-5.73	-10.6
4OC7	RXR(Retinoic acid receptor RXR-alpha)	708	-8.48	-11.3
4OTH	PKC(Serine/threonine-protein kinase N1)	2591	-9.4	-13.26
4XAR	MGLUR(Metabotropic glutamate receptor 3)	9244	-4.98	-8.5
4YLK	DYRK1A(Dual specificity tyrosine-phosphorylation-regulated kinase 1A)	7167	-8.13	-12.54
4ZGM	GLP-1R(Glucagon-like peptide 1 receptor)	24782	-3.31	-9.06
5A46	FGFR1(Fibroblast growth factor receptor 1)	699	-8.54	-12.8
5AFH	α7NACHR(Neuronal acetylcholine receptor subunit alpha-7)	6934	-6.02	-9.64
5H8S	AMPA(Glutamate receptor 2)	8926	-5.3	-8.44
5HK1	SIG-1R(Sigma non-opioid intracellular receptor 1)	1281	-9.29	-12.8

5IH5	CKI-δ(Casein kinase I isoform delta)	5998	-7.62	-12.5
5JAU	LP-PLA2(Platelet-activating factor acetylhydrolase)	1402	-8.08	-11.85

a. the number of compounds with better docking score than that of ligand embedded in the crystal structure.

b. 'Ligand Energy' means the docking energy of ligand embedded in the crystal structure.

Table 2(on next page)

Targets and their best associated plant which has the most compounds docking with the target

1 **Table 2.** Targets and their best associated plant which has the most compounds docking with the
2 target

Target	Top1 Plant	Target	Top1 Plant	Target	Top1 Plant
PLA2	Bletilla(5)	HMG-COA	Morus(9)	Caspase-3	Paeonia(4)
MAOB	Corydalis(16)	PDE4	Isatis(4)	Ftase	Panax(8)
QC	Panax(4)	TNF	Panax(10)	IDO	Morus(7)
Fyn	Papaver(11)	XO	Corydalis(17)	HDAC	Bletilla(5)
MAOA	Corydalis(11)	lyn	Claviceps(5)	JNK	Morus(8)
EGFR	Artemisia(7)	RAR	Rauwolfia(8)	RAGE	Fritillaria(7)
BACE-1	Lonicera(6)	AchE	Piper(6)	SIRT1	Glycyrrhiza(7)
GABA(B)	Morus(11)	RXR	Salvia(10)	PKC	Solanum(6)
MGLUR	Morus(4)	DYRK1A	Strychnos(6)	GLP-1R	Panax(9)
FGFR1	Rheum(6)	α7NACHR	Panax(8)	AMPA	Panax(7)
SIG-1R	Corydalis(7)	CKI-δ	Salvia(11)	LP-PLA2	Morus(10)

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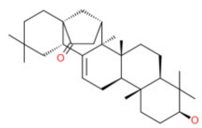
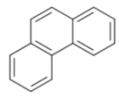
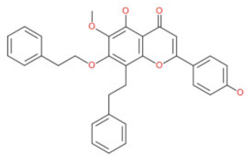
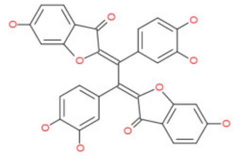
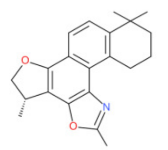
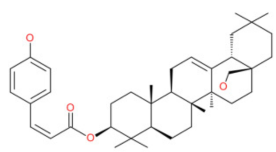
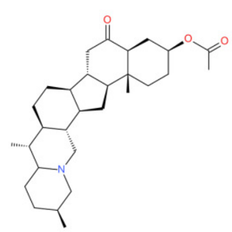
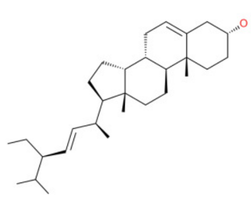
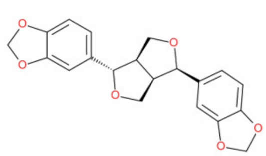
Table 3(on next page)

The 10 clusters of anti-AD TCM compounds and their primary targets

Table 3. The 10 clusters of anti-AD TCM compounds and their primary targets

Cluster	Cluster Center	Structure	Cluster Size	Primary Targets
1	24407		238	SIG-1R(33)
2	5625		6	JNK(4), DYRK1A(4), CKI-δ(4)
3	25654		264	LP-PLA2(40)
4	33348		71	DYRK1A(16)
5	31600		60	RXR(13)
6	35138		477	HMG-COA(64), PDE4(64)
7	5802		39	RAR(8)
8	23679		84	QC(15), PKC(15)
9	23424		81	MAOB(18), SIRT1(18)

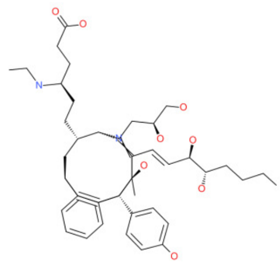
10	1314		334	BACE-1(39)

Table 4(on next page)

ADMET properties of 13 candidate drugs

Table 4. ADMET properties of 13 candidate drugs

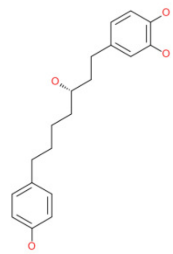
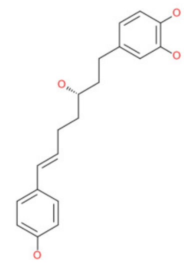
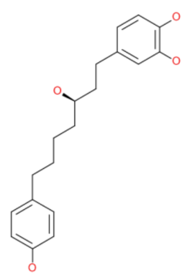
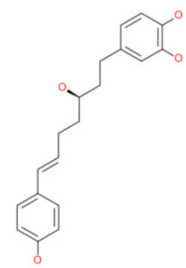
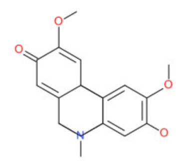
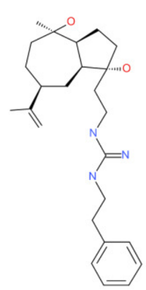
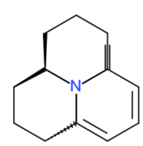
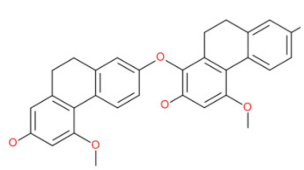
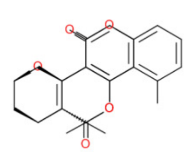
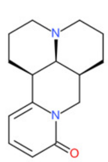
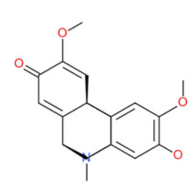
Name(ID)	**Solubility Level**	**BBB Level**	**Hepatotoxic Prediction**	**Absorption Level**	**PPB Prediction**	**Targets**
(3S)-1-(3,4-Dihydroxyphenyl)-7-(4-hydroxyphenyl)heptan-3-ol(5862)	3	2	FALSE	0	FALSE	AchE
(3S)-1-(3,4-Dihydroxyphenyl)-7-(4-hydroxyphenyl)-(6E)-6-hepten-3-ol(5863)	3	2	FALSE	0	FALSE	AchE,GABA(B),MGLUR
(3R)-1-(3,4-Dihydroxyphenyl)-7-(4-hydroxyphenyl)heptan-3-ol(5868)	3	2	FALSE	0	FALSE	GABA(B)
(3R)-1-(3,4-Dihydroxyphenyl)-7-(4-hydroxyphenyl)-(6E)-6-hepten-3-ol(5869)	3	2	FALSE	0	FALSE	XO,AchE
coniferyl,ferulate(8792)	3	2	FALSE	0	FALSE	XO
pallidine(9593)	3	2	FALSE	0	FALSE	MAOB
4,5-di-o-caffeoyl,quinic,acid(10639)	3	2	FALSE	0	FALSE	PDE4
Anagyrine(16167)	3	1	FALSE	0	FALSE	AchE
Blestrin D(26629)	3	2	FALSE	0	FALSE	PLA2,QC,HDAC,JNK,GABA(B)
Dibothrioclinin II(28468)	4	2	FALSE	0	FALSE	Ftase,QC,HDAC,GLP-1R,AMPA
5,7-Dihydroxy-6,8-dimethyl-3-(4'-hydroxy-3'-methoxybenzyl)chroman-4-one(28814)	3	2	FALSE	0	FALSE	RAR
Glabroisoflavanone A(30713)	3	2	FALSE	0	FALSE	TNF,SIRT1

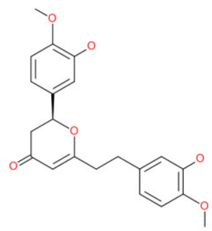
Hupehenidine(31515)	3	2	FALSE	0	FALSE	SIRT1

Table 5(on next page)

2D structure and corresponding plants of 13 compounds with favorable ADMET properties

Table 5. 2D structure and corresponding plants of 13 compounds with favorable ADMET properties

Compound ID	Structure	Plant	Compound ID	Structure	Plant
5862		Curcuma kwangsiensis	5863		Curcuma kwangsiensis
5868		Curcuma kwangsiensis	5869		Curcuma kwangsiensis
8792		Poria cocos	9593		Lindera aggregate
10639		Taraxacum mongolicum	16167		Thermopsis lanceolata R. Br., Laburnum anagyroides, Sophora flavescens Alt., Sophora tonkinensis
26629		Bletilla striata	28468		Gerbera piloselloides Cass.
28814		Ophiopogon japonicus (L. f.) Ker-Gawl.	30713		Glycyrrhiza glabra

31515		Fritillaria hupehensis

3

Figure 1

The docking ennergy scores of the top 0.5% natural compounds and embedded ligands for 33 targets.

Red boxes represent top 0.5% compounds for each target. Blue points represent the targets' embedded ligands.

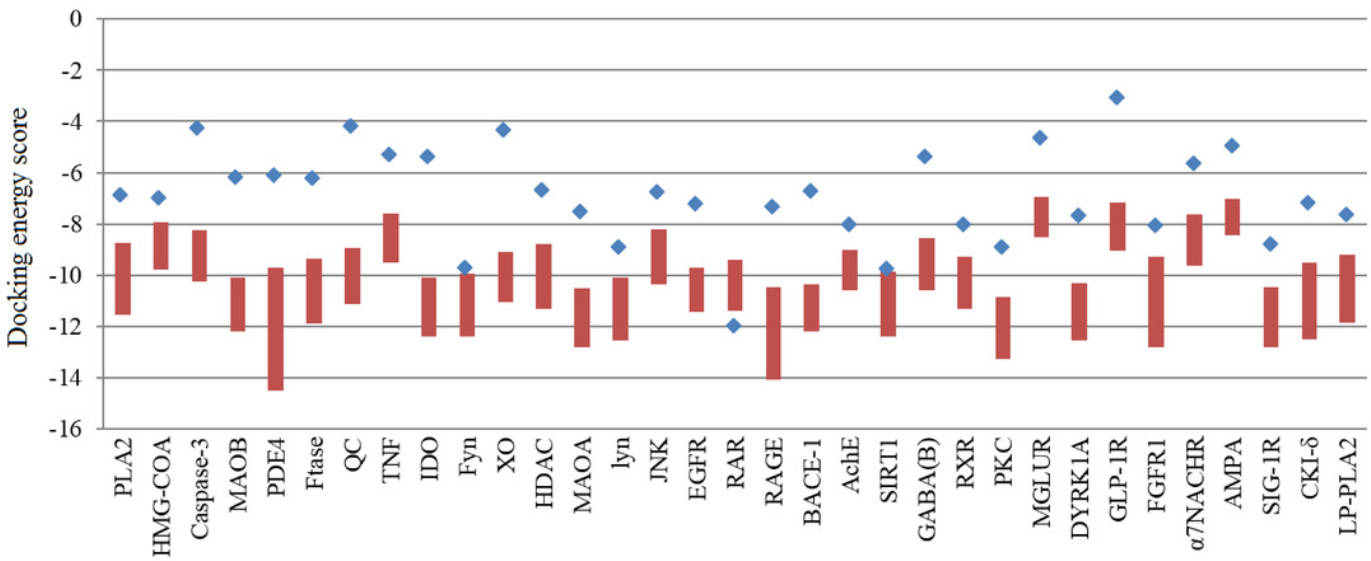


Figure 2

The exact number of candidate anti-AD compounds and their plants for each anti-AD target

The number is tagged above each column, and every target is displayed on the horizontal axis.

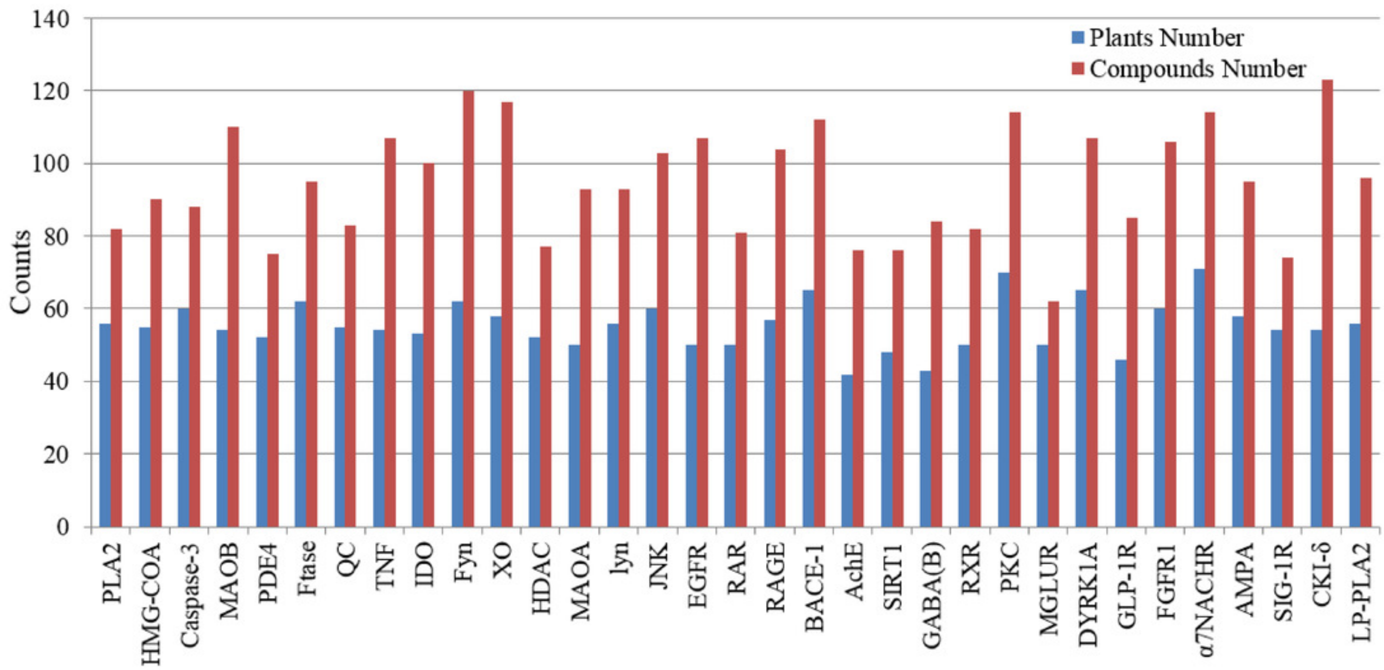


Figure 3

The network contained targets and their best associated plant.

Pink boxes represent targets. Green boxes represent compounds.

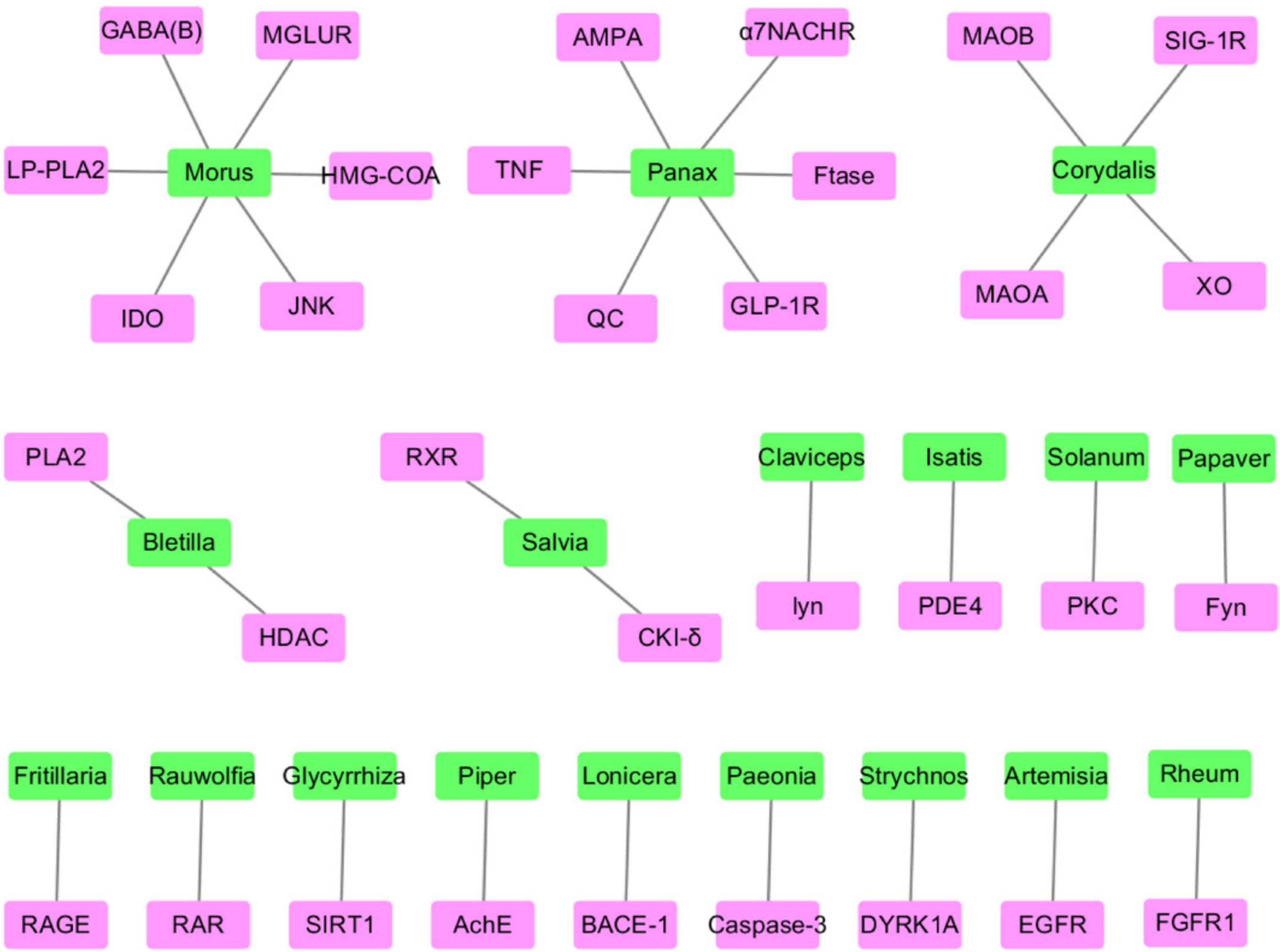


Figure 4

The network contained anti-AD targets, TCM compounds and structurally identical drugs.

Pink boxes represent targets. Yellow boxes represent compounds. Blue boxes represent drugs.