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Identification of phytochemicals from North African plants for treating Alzheimer's diseases and of their molecular targets by in silico network pharmacology approach

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A B S T R A C T

Background: The global social expenses of Alzheimer's disease (AD) have been increased to US$1 trillion due to high cost, side-effects, and low efficiency of the current AD-therapies. Another reason is the lack of preventive drugs and the low-income situation of Asian and African countries. Accordingly, patients rather prefer traditional herbal remedies. Network-pharmacology has been a well-established method for the visualization and the construction of disorder target protein-drug framework. This could aid in the identification of drugs molecular-mechanisms.

Aim: The aim of this study is to investigate the phytochemical constituents that could target Alzheimer's disease from the North African plants. This could be done by exploring their possible mechanisms of action through molecular network pharmacology-based approach.

Experimental procedure: The Phytochemical-compounds of North-African plants (NAP) have been accessed from open-databank. ADME-screening has been conducted for filtering of the NAP phytochemical-constituents utilizing Qikprop-software. The open STITCH databank has been utilized for the prediction of the phytochemical-constituents target-proteins; UniProt and TDD-DB databanks have been utilized for distinguishing AD-related proteins. Phytochemical constituent-target protein (C-T) and plant-phytochemical constituent-target protein (P-C-T) frameworks have been assembled utilizing Cytoscape to interpret the anti-Alzheimer's disease mechanism of action of the targeted phytochemical constituents.

Results: The NAP 6842 phytochemical-constituents (from more than 1000 plants) have been exposed to ADME and CNS modulating filtration, generating 94 phytochemical-constituents which have been subjected to target-prediction investigation. The 94 phytochemical-constituents and the 4 AD-identified targets have been associated through 155 edges which formed the main pathways related to AD. Cuparene, alpha-selinene, beta-sesquiphellandrene, calamenene, 2-4-dimethylheptane, undecane, *n*-tetradecane, hexadecane, nonadecane, *n*-eicosane, and heneicosane have had C-T network highest combined-score, whilst the proteins MAO-B, HMG-CoA, BACE1, and GCR have been the most enriched ones by comprising the uppermost combined-scores of C-T. *Hypericum perforatum, Piper nigrum, Juniperus communis, Levisticum officinale, Origanum vulgare* acquired the uppermost number of P-C-Target interactions.

Conclusion: The phytochemical-targets prediction of NAP utilizing molecular-network pharmacology-based investigation has paved the way for networking multi-target, multi-constituent, and multi-pathway mechanisms. This may introduce potential future targets for the regulation and the management of Alzheimer's disease.

Abbreviations: Abeta, amyloid-β peptide; AD, Alzheimer's disease; AChEIs, Acetylcholine esterase inhibitors; ADME, Absorption Distribution Metabolism Excretion; BACE1, Beta-Secretase 1; C-T, phytochemical constituent-target network; GCR, Glucocorticoid receptor; HMG-CoA, Beta-Hydroxy Beta-methylglutaryl-CoA; MAO-B, Monoamine oxidase B; NAPDB, North-African plants-database; OB, oral-bioavailability; P-C-T, plant-constituent-target network.

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Taxonomy (classification by EVISE): Alzheimer's disease, Network pharmacology, In-silico computer based approach

1. Introduction

Epidemiologically, the prevalence of Alzheimer's disease (AD) is about 50 million people world-wide. This number is expected to augment by 3 folds in the coming 30 years.[1] The global social expenses have been increased to US$1 trillion in 2018.[2] AD is a chronic age-dependent neurodegenerative disorder that is marked by the occurrence of neuro-fibrillary tangles, amyloid-deposition, neuronal synaptic-dysfunction, and neuronal cell-death.[3–5] One of the most common AD etiological factors is the cumulating of β-amyloid (Abeta) which has a numerous lethal effects on the synaptic activity leading to neuro-degeneration.[5–7] MAO-B (Monoamine oxidase B) has an important role in the pathogenicity of Alzheimer's disease (AD), including the establishment of amyloid plaques from amyloid-β peptide (Abeta) formation and aggregation, production of neuro-fibrillary tangles, and impaired cognition through the destroying of the cholinergic-neurons. Therefore, MAO inhibitors might be considered as AD possible therapeutic agents.[8] Moreover, HMG-CoA (Beta-Hydroxy Beta-methylglutaryl-CoA) has a crucial contribution in AD pathogenesis. The beta-amyloid peptide (Abeta) has been known to be the major constituent of senile-plaques combined with neuro-fibrillary tangles and atrophy, are the core neuro-pathological characters in AD. HMG-CoA reductase inhibitors result in diminished Abeta production, and, therefore decrease the risk of developing AD.[9] Furthermore, BACE1 (Beta-Secretase 1) has been a significant target for therapeutic intervention by considering its role in the Abeta generation. Thus, BACE1 inhibition might significantly impact AD patients' cognitive functions.[5] GCR (Glucocorticoid receptor) has also a central role in AD etiology. Therapeutic agents targeting GCR were found to modulate hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and thus have a potential role in decreasing the risk of developing AD[10]

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Moreover, HMG-CoA (Beta-Hydroxy Beta-methylglutaryl-CoA) has a crucial contribution to AD pathogenesis. The Abeta has been known to be the major constituent of senile-plaques, which combined with neuro-fibrillary tangles and atrophy. They are the core neuro-pathological characters in AD. HMG-CoA reductase inhibitors resulting in diminished Abeta production, and, therefore decreasing the risk of developing AD.[9]

Furthermore, BACE1 (Beta-Secretase 1) has been a significant target for therapeutic intervention by considering its role in the Abeta generation. Thus, BACE1 inhibition might significantly impact AD patients' cognitive functions.[5] GCR (Glucocorticoid receptor) has also a central role in AD etiology. Therapeutic agents targeting GCR were found to modulate hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and thus have a potential role in decreasing the risk of developing AD[10]

Ought to socio-economical challenges, WHO estimates that ca. 80% of the Asian and African population depends on medicinal-plants as the main source of medical treatment.[11–13] Accordingly, the incorporation of the traditional medical-measures in health-plans of these countries has been one of the WHO recommendations.[12–14]

As a consequence of the high cost, side-effects, low efficiency of the current AD-therapies, lack of preventive drugs, and the low-income status of these countries, patients rather prefer natural herbal remedies.[12,15,16] A systematic review has shown that numerous natural plants/products (like *Curcuma longa*, *Chamilia sinensis*, *Vitis vinifera*, *Lycopodium clavatum*, *Piper nigrum*, and flavonoid-rich medicinal plants) have demonstrated clinical and preclinical AD therapeutic potentials.[16]

Recently, network-pharmacology has been a well-established method for the visualization and construction of disorder-protein-target drug-network which could aid in the assessment of drug molecular-mechanisms from a multivariate approach.[12,15,17,18] The network-pharmacology method has been identified also as one of the appropriate approaches for investigating the mechanism of action of herbal products own to their multivariate character.This emphasizes the concept of "framework target, multi-component therapeutic agents" in a comprehensive approach the same as the complex matrices of herbal products.[19–23] Molecular framework-pharmacology could be implemented in the prediction of the protein-targets of the phytochemical-active constituents and also the targeted disorders' mechanisms.[12] The approach of multivariate target-recognition via network-pharmacological investigation has been developing for prediction of the principle phytochemical-active constituents and possible target-proteins of herbal products.[19–23]

Despite that there are few accounts on the utilization of herbal products for the AD management,[24–29] literature-search demonstrated the absence of any comprehensive molecular network-pharmacology researches targeting North-African plants identification for their most active phytochemical ingredients and their possible mechanisms of action.

Thus, this study aims at investigating the phytochemical constituents that could target Alzheimer's disease from the North African plants. This could be done by exploring their possible mechanisms of action through molecular network pharmacology-based approach.

2. Methods

2.1. Study-design

Phytochemicals of NAP have been retrieved from the NANPDB databank.[30–33] These phytochemicals were short-listed through the CNS modulation, absorption, distribution, metabolism, and excretion (ADME) relevance. Accessible open databanks have been employed for recognizing target Alzheimer's disease proteins. Only proteins linked to Alzheimer's disease have been chosen and retrieved to employ human disease databanks. Alzheimer's disease investigations have been also implemented through accessible open-databanks. The work-flow has been shown in Fig. 1 as detailed hereunder.

2.2. Chemical-databases

NAP (ca. one thousand plant-resources) and their phytochemical-

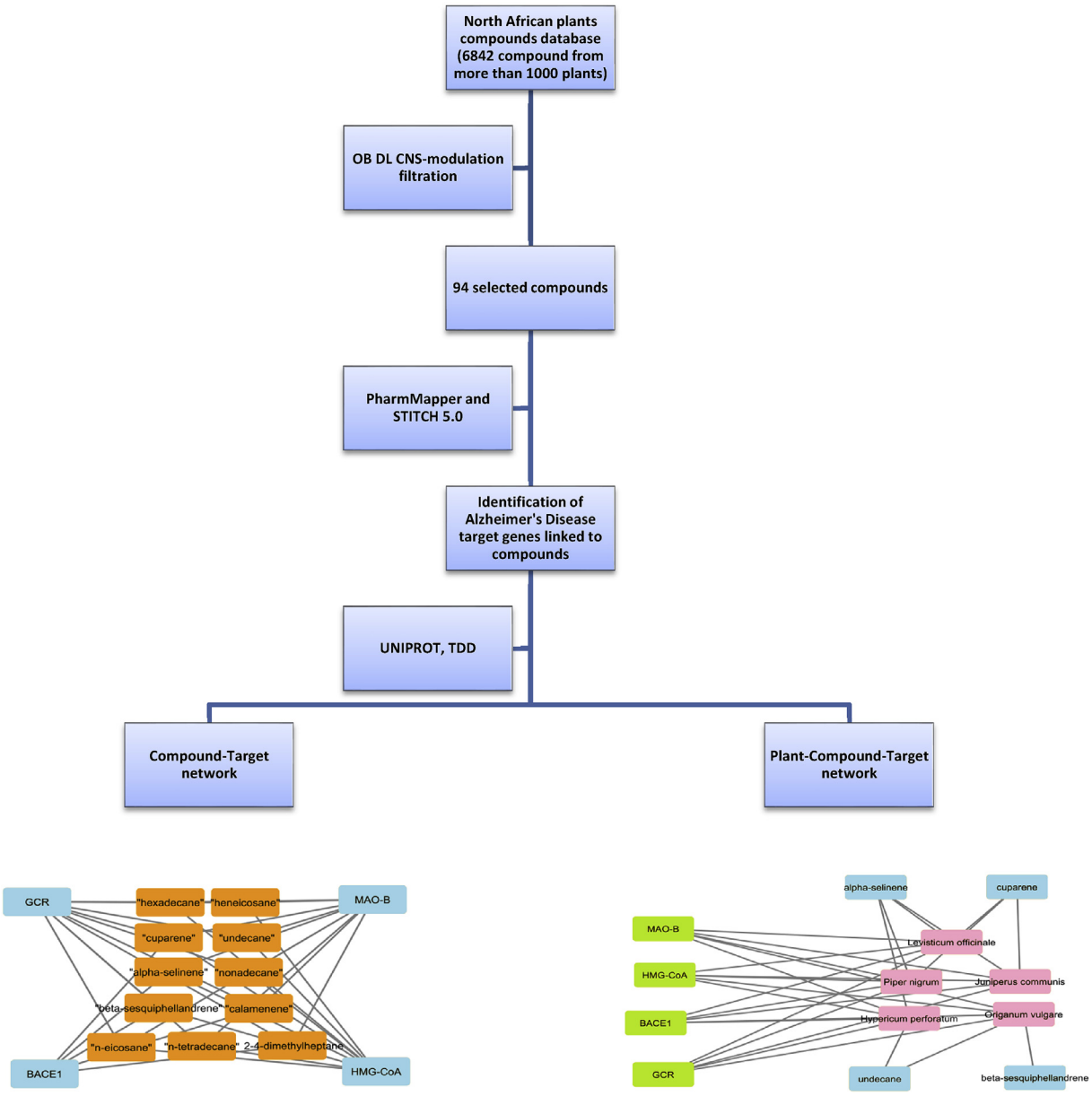

Fig. 1. Workflow of the network pharmacology analysis of North African plants constituents against Alzheimer's disease targets.

constituents (6842) have been acquired from the NAP database "http://african-compounds.org/nanpdb”. Identification of the phytochemical-structures, molecular-weights, 2D-structures has been reached through PubChem "http://pubchem.ncbi.nlm.nih.gov/” and ChEMBL "http://www.ebi.ac.uk/chembl/”. Then, the phytochemical-structures have been analyzed utilizing Schrodinger-software (2017A).

2.3. CNS modulation filtration

CNS modulation has been utilized for filtration of the phytochemical-constituents in the open databanks established estimation performed by Qikprop-software (Schrodinger suite 2017A). Phytochemical-constituents possessing positive CNS modulation have been retained.

2.4. Drug-likeness and ADME filtration

Furthermore, the ADME system has been utilized for filtration of compounds in the databank following estimations established by Qikprop-software. Phytochemical-compounds with estimated oral-bioavailability (OB) $\geq$30 have been kept.[34]

2.5. Alzheimer's disease proteins linked to the identified phytochemical-compounds

STITCH-database "http://stitch.embl.de/, ver. 5.0" utilizing the "*Homo-sapiens*" species entry has been utilized for the identification of the Alzheimer's disease proteins linked to the selected phytochemical-constituents. UniProt-database (http://www. uniprot.org/) has been used for protein information retrieval, comprising organism, protein name, and ID. Therapeutic Target

Database (TTD) "http://bidd.nus.edu.sg/BIDD-Databases/TTD/TTD.asp” have been researched for information on Alzheimer's disease target proteins.[35]

2.6. Networks and pathway investigations

To exploit the NAP phytochemical-constituents mechanisms of action in Alzheimer's disease phytotherapy, 2 types of networks have been assembled by Cytoscape 3.5.1 "http://www.cytoscape.org/": Plant-Compound and Constituent-target protein. In the graphical-framework, every phytotherapeutic-constituent has been resembled by node, and the interactions have been described by edges. The molecular network-parameters have been estimated utilizing the Cytoscape network-analyzer plug-in. The Cytoscape interaction composite-scores have been utilized for predicting the significance of nodes in each network. Important pathways with *P*-values < 0.05 have been chosen. Target-pathway and constituent-Pathway frameworks have been assembled to reveal an overview of the interactions between targets and Alzheimer's disease-related mechanisms.[12,36,37]

3. Results and discussion

Six thousand eight-hundred and forty-two (6842) phytochemical structures have been retrieved from the NAP databank comprising more than one thousand plant resources. The NAP databank has been filtered from duplicate-results which have been omitted resulting in an outcome composed of 6431 compounds.

3.1. Selection of phytochemical compounds using CNS modulation and ADME-investigation

CNS modulation has been utilized for filtration of the phytochemical-compounds in the open NAP databank established estimation carried out, and the phytochemical-constituents with predicted positive CNS modulation have been retained. Moreover, in agreement with Lipinski's rule "rule of five", a compound is expected to have good permeation and/or absorption if it has ˂5 hydrogen-bond donors, ˂10 hydrogen-bond acceptors, an estimated log P (ClogP) ˂5, 10 or lesser rotatable bonds, and has a Mwt ˂500 Da. Phytochemical compounds with Mwt ˂500 Da has been retained. In the meantime, OB of the listed phytochemical-constituents has been estimated, which gives significance to the percentage of a *per-os* dose of unchanged-drug getting to the circulation. This signifies the conjunction of the ADME investigation.[38] Phytochemical compounds having positive CNS modulation, cross-matching as a minimum of 3 criteria in the rule of five. OB $\geq$ 30% have been kept and the remainder has been disregarded, generating a databank of 94 phytochemical-constituents (Fig. 1).[39]

3.2. Target proteins identification of NAP compounds utilizing network-pharmacology

Owing to the elevated expense of wet-laboratory filtering of an enormous number of plants together with their multi-factorial phytochemical compounds, an *in-silico* investigation has been utilized in the current work to provide an efficient, rapid, and elevated productive method to identify potential targets of NAP phytochemical compounds linked to Alzheimer's disease comple mentary-management. To explore the mechanism of action of NAP phytochemical compounds and Alzheimer's disease targets, a compound-target (C-T) framework anchored to 94 phytochemical compounds and possible targets have been assembled utilizing filtering results acquired from STITCH 5.0 and PharmMapper open-databanks.

PharmMapper is a web-server for possible drug-target recognition by reversed-pharmacophore matching compared to the database internal-pharmacophore model.[12] Moreover, the STITCH database clusters high-experimental data, manual-database, and the outcomes of numerous prediction-methods leading to one universal-framework of protein–chemical interactions and more.[12]

The resources of established protein–chemical interactions have been accompanied with automatic text-mining and a chemical structure-based forecasting-approach. The text-mining database comprises concurrent text-mining and natural-language reprocessing of accessible PubMed text-articles, all MEDLINE-abstracts, and NIH grant-abstracts Reporter.[40]

The role of every target and its association with Alzheimer's disease was retrieved from TTD and UniProt databases. The TTD database comprises more than sixty-million sequences containing an up-to-date data. This data comprises target-drug regulatory proteins in drug-resistance mutations, differential expression-reports of targets in the AD-relevant compound-targeted patients' tissues, and expression-reports of targets in the healthy individuals' non-targeted tissues.[12,41,42]

The UniProt databank is a huge resource of protein-sequences and their linked detailed annotation. UniProt KB/Swiss-Prot comprises over 550 000 sequences that have been formed by experts where experimental data was extracted from the trust-worthy publications, organized and summarised.[12,42–45]

Four Alzheimer's disease targets have been recognized and have been used for the development of the compound-target network (Fig. 2). Each target with interaction-scores ˂0.8 has not been included. Additionally, phytochemical compounds presenting interaction scores ˂0.5 have not been also included. These standards permitted for maintaining only the compounds and proteins exhibiting strong interactions. The Constituent- Target (C-T) network comprised 98 nodes (94 constituents and 4 targets) and 155 edges (Fig. 2), with 38.75 average numbers of targets for each item, demonstrating multi-target characteristics of the NAP phytochemical compounds under investigation. The C-T framework revealed that the same-constituent could interact with several targets. Exploration of the distribution of C-T interactions on the 94 constituents utilizing network-topological investigation revealed that cuparene (cyclopentyl benzene) possessed the largest percentage of C-T interactions by interacting with the 4 targets, followed by alpha-selinene (octahydronaphthalenes), beta-sesquiphellandrene (terpene volatile oil), calamenene (tetrahydronaphthalene), 2-4-dimethylheptane (heptane hydrocarbon), undecane (alkane hydrocarbon), *n*-tetradecane (alkane hydrocarbon), hexadecane (alkane hydrocarbon), nonadecane (alkane hydrocarbon), *n*-eicosane (alkane hydrocarbon), and heneicosane (saturated hydrocarbon) by interacting with 3 targets (Fig. 4, Table 2). The hit-list comprised the 94 phytochemical constituents have been shown in Table 1. By the careful investigation of the targeted-proteins revealed that the proteins MAO-B, HMG-CoA, BACE1, and GCR have been the most enriched by having the uppermost Cytoscape composite scores with the compounds in this network demonstrating that they might be the key nodes in this framework (Figs. 2 and 3). Investigating the C-T sub-network of the 11 top-scoring compounds revealed the target-proteins MAO-B, HMG-CoA, BACE1, and GCR to be the uppermost enriched ones (Fig. 4).

MAO-B (Monoamine oxidase B) has an important role in the pathogenicity of Alzheimer's disease (AD), including the establishment of amyloid plaques from amyloid-β peptide (Aβ) formation and aggregation, production of neuro-fibrillary tangles, and impaired cognition through the destroying of the cholinergic-neurons. Therefore, MAO inhibitors might be considered as AD possible therapeutic agents.[8]

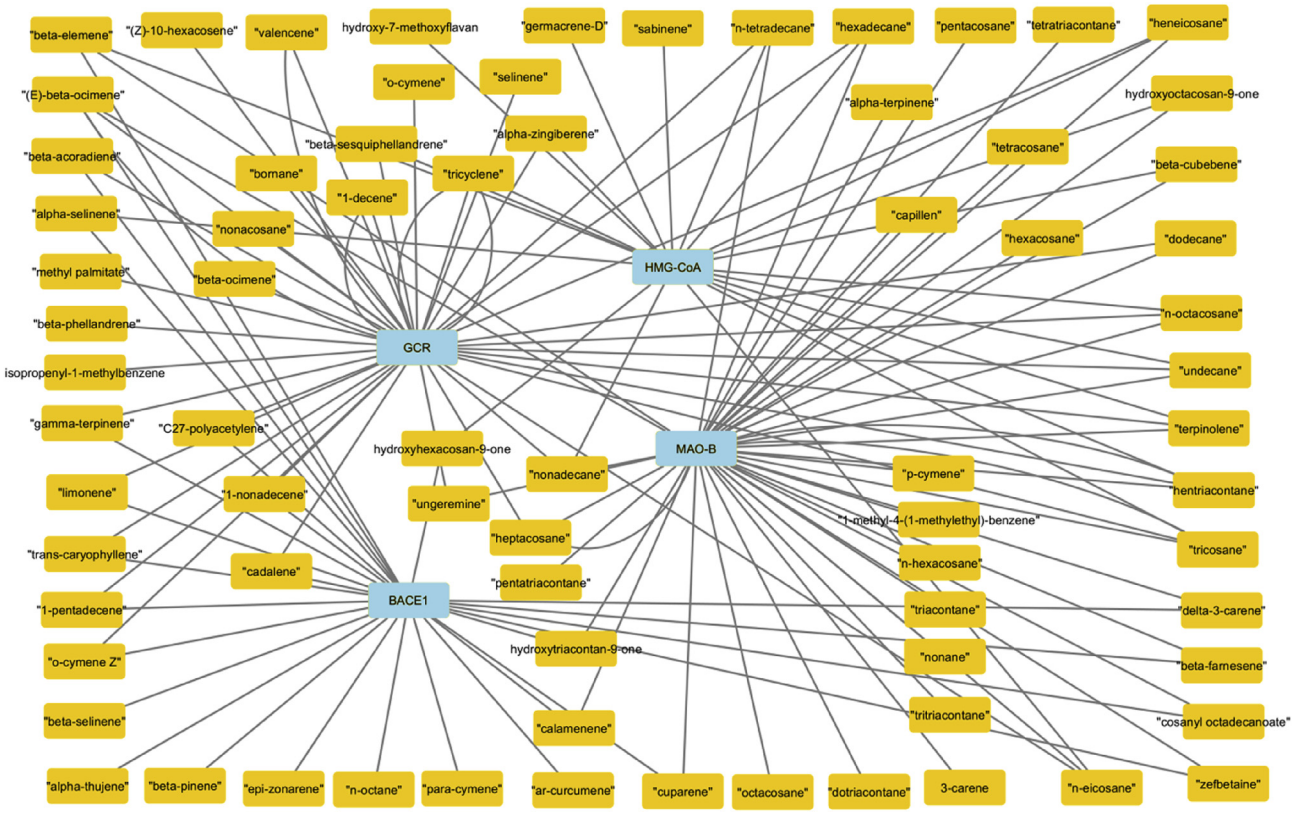

Fig. 2. Network of compound-target gene interactions (Cytoscape 3.5.1) for North African plants constituents by linking 94 compounds and 4 target proteins.

Moreover, HMG-CoA (Beta-Hydroxy Beta-methylglutaryl-CoA) has a crucial contribution in AD pathogenesis. The beta-amyloid peptide (Abeta) has been known to be the major constituent of senile-plaques. It is combined with neuro-fibrillary tangles and atrophy that are the core neuro-pathological characters in AD. HMG-CoA reductase inhibitors result in diminished Abeta production, and, therefore decreasing the risk of developing AD.[9]

Furthermore, BACE1 (Beta-Secretase 1) has been a significant target for therapeutic intervention by considering its role in the Abeta generation. Thus, BACE1 inhibition might significantly impact AD patients' cognitive functions.[5]

GCR (Glucocorticoid receptor) has also a central role in AD etiology. Therapeutic agents targeting GCR was found to modulate hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and thus have a potential role in decreasing the risk of developing AD[10]

To investigate the signaling-mechanisms and roles of the identified target proteins, functional enrichment investigation has been carried out using the TDD pathway approach (Table 1).

3.3. Alzheimer's disease target proteins of NAP utilizing composite-network pharmacology

The distribution of the 155 C-T interactions on the NAP has been explored and a linked plant-compound-target framework has been constructed. Natural medicines have been distributed in accordance with their Cytoscape composite-score of C-T reactions. Fig. 5 illustrates that *Hypericum perforatum* L., *Piper nigrum* L., *Juniperus communis* L., *Levisticum officinale* L., *Origanum vulgare* L. acquired the uppermost number of P-C-T reactions which may justify that these medicinal remedies comprise more active-compounds that could be used in Alzheimer's disease management.

To validate the suggestions' obtained, PubMed researches linked to the top 5 plants with the uppermost reaction scores have been kept (Fig. 5). As detected, *Hypericum perforatum* has several reports indicated their role in the management of Alzheimer's disease.[46,47] These accounts have shown that terpenoid derivatives are responsible for this activity facilitated by ATP-binding cassette transporter (ABCC1) and microglial activation.[47]

Moreover, *Piper nigrum* has shown significant antidepressant and anxiolytic effects.[48] Its neuroprotective effect might be owed to the alleviation of oxidative stress in the amygdale region, and might offer a useful complementary therapy in the prevention or the management of AD symptoms.[48–50]

There are few accounts on the *folk* medicinal use of *Juniperus communis* fruit in the management of AD[51] Its fruit's anti-cholinesterase activity together with its high antioxidant activity against neuro-degeneration associated with the AD. This might be the reason for its utilization of *Juniperus communis* fruit extracts as complementary management of AD[51] Furthermore, *Levisticum officinale* and some species of *Origanum* have shown some anti-cholinesterase activity which might be possible for future candidates to screen for their activity against AD[52,53]

Although Acetylcholine esterase inhibitors (AChEIs) has a crucial role in targeting AD, neither of the selected substances analyzed has shown direct interaction with AChEIs, as shown before in literature.[54,55]

Additionally, a combined framework has been assembled by linking the Plant-compound-target framework of the top 5 scoring natural remedies and compound–target mechanism, to get more knowledge about the molecular-targets of each medicinal remedy (Fig. 6). The proteins MAO-B, HMG-CoA, BACE1, and GCR were the most important nodes in the target protein network on one hand, while the phytochemical-compounds, cuparene, beta-sesqui phellandrene, alpha-selinene, undecane, and the plants,

Table 1
Potential protein targets of the different compounds in North African plants.

Short name of protein	Full name of protein	Interacting compound (s)
MAO-B	Monoamine oxidase B	*n*-hexacosane, cosanyl octadecanoate ungeremine, zefbetaine hydroxyoctacosan-9-one hydroxytriacontan-9-one, methyl palmitate p-cymene, alpha-terpinene beta-elemene, (penta-1,3-diyn-1-yl)benzene capillen, heptacosane (2-chlorovinyl)-2,4,5-trichloro-1, beta-cubebene p-mentha-1,3,8-triene, 3-carene alpha-selinene, 1-methyl-4-(1-methylethyl) benzene tricosane, tetracosane pentacosane, hexacosane heptacosane, octacosane triacontane, hentriacontane dotriacontane, tritriacontane tetratriacontane, pentatriacontane terpinolene, cuparene calamenene, delta-3-carene beta-farnesene, nonane (E)-beta-ocimene, ar-curcumene Dodecane, *n*-octane, 2,4-dimethylheptane Undecane, *n*-tetradecane Hexadecane, 6,10,14-trimethyl-2-pentadecene Nonadecane, *n*-eicosane Heneicosane, tricosane *n*-octacosane, hentriacontane
HMG-CoA	β-Hydroxy β-methylglutaryl-CoA	hydroxy-7-methoxyflavan, hydroxyhexacosan-9-one hydroxyoctacosan-9-one, beta-elemene germacrene-D, sabinene 4,6-dimethylhept-5-en-2-yl)benzene, alpha-selinene Cuparene, terpinolene beta-cubebene, alpha-zingiberene beta-sesquiphellandrene, undecane *n*-tetradecane, hexadecane nonadecane, *n*-eicosane heneicosane, tricosane *n*-octacosane, hentriacontane
BACE1	Beta-Secretase 1	cosanyl octadecanoate, zefbetaine hydroxyhexacosan-9-one, beta-pinene limonene, C27-polyacetylene Tricyclene, 1,2,4-trimethylbenzene 1,2,3-trimethylbenzene, gamma-terpinene Valencene, (3E)-2,5,5-trimethylhepta-1,3,6-tri ethenyl-2,5-dimethylhexa-1,4-dien 1-pentadecene, (E)-beta-ocimene ar-curcumene, beta-sesquiphellandrene *n*-octane, 2,4-dimethylheptane 6,10,14-trimethyl-2-pentadecene
GCR	Glucocorticoid receptor	Ungeremine, methyl palmitate Limonene, C27-polyacetylene Tricyclene, 1-decene gamma-terpinene, heptacosane (2-chlorovinyl)-2,4,5-trichloro-1 (2-chlorovinyl)-2-bromo-4,5-dichl *o*-cymene, (Z)-10-hexacosene isopropenyl-1-methylbenzene, beta-phellandrene p-mentha-1,3,8-triene, selinene 1-pentadecene, 1-nonadecene Bornane, nonacosane beta-ocimene, cuparene beta-acoradiene, calamenene (E)-beta-ocimene, Terpinolene *trans*-caryophyllene, cadalene isopimara-9-(11),15-diene, *o*-cymene Z alpha-zingiberene, beta-sesquiphellandrene dodecane, *n*-octane 2,4-dimethylheptane, undecane *n*-tetradecane, hexadecane nonadecane, *n*-eicosane heneicosane, tricosane *n*-octacosane, hentriacontane

Hypericum perforatum, Piper nigrum, Juniperus communis, Levisticum officinale, Origanum vulgare, on the other, were the most enriched AD-related plant-compound-target interactions (Fig. 6).

In conclusion, for the aim of recognizing complementary targets from medicinal plants and creating multi-target drugs, framework pharmacology has turned out to be a helpful tool.

Instead of modifying the single molecular part from a folkloric point of view, the framework pharmacology concentrates on the biological systems' complex-interactions. Network pharmacology investigation of the NAP phytochemical-constituents together with AD targets brought about 94 phytochemical constituents and 4 targets identified with the primary pathways related to AD disease. The principal constituents were cuparene, beta-sesquiphellandrene, alpha-selinene, and undecane. The possible AD regulation mechanism of action of these compounds might comprise the modulation of MAO-B, HMG-CoA, BACE1, and GCR as fundamental hit-targets.

Plant-compound-target framework showed that *Hypericum perforatum, Piper nigrum, Juniperus communis, Levisticum officinale, Origanum* vulgare acquired the largest number of C-T interactions which might imply that these plants contain more active constituents that can be utilized in AD management.

These outcomes permitted to a better understanding of the possible mechanisms of activity of NAP natural remedies that may have possible use in the management of Alzheimer's disease.

Table 2
Summary of literature survey on the top scoring NAP phytochemical constituents in Alzheimer's disease therapy.

Compound	Plant Source*	Nature/Warnings
alpha-selinene	*Apium graveolens* L.	octahydronaphthalenes
	Eucalyptus globulus L.	
	Psidium guajava L.	
	Piper nigrum L.	
	Pimenta dioica L.	
	Metrosideros sclerocarpa L.	
	Juniperus communis L.	
	Chrysanthemum x morifolium L.	
	Eucalyptus forrestiana L.	
	Levisticum officinale L.	
	Eucalyptus incrassata L.	
	Eucalyptus nova-anglica L.	
	Eucalyptus stoatei L.	
	Eucalyptus leucoxylon L.	
	Eucalyptus tetraptera L.	
	Eucalyptus cuprea L.	
	Umbellularia californica L.	
	Eucalyptus sparsa L.	
	Eucalyptus behriana L.	
	Eucalyptus largisparsa L.	
	Eucalyptus dolichorhyncha L.	
	Eucalyptus erythrandra L.	
	Eucalyptus desquamata L.	
	Murraya koenigii L.	
	Hypericum perforatum L.	
	Eucalyptus odorata L.	
	Eucalyptus intertexta L.	
	Eucalyptus angulosa L.	
	Eucalyptus porosa L.	
	Sassafras albidum L.	
	Eucalyptus lansdowneana L.	
	Eucalyptus ceratocorys L.	
	Callicarpa americana L.	
	Eucalyptus viridis L.	
	Citrus reticulata L.	
	Eucalyptus populnea L.	
	Eucalyptus fasiculosa L.	
	Myrtus communis L.	
	Eucalyptus melanophloia L.	
	Salvia dorisiana L.	
cuparene	*Coleus barbatus* L.	Cyclopentyl benzene
	Piper nigrum L.	
	Juniperus virginiana L.	
	Juniperus communis L.	
	Angelica archangelica L.	
	Levisticum officinale L.	
	Thymus funkii L.	
calamenene	*Hyssopus officinalis* L.	Tetrahydronaphthalene
	Salvia gilliesii L.	
beta-sesquiphellandrene	*Zingiber officinale* L.	Terpene volatile oil
	Thymus longicaulis L.	
	Citrus reticulata L.	
	Scutellaria parvula L.	
	Lindera benzoin L.	
	Aralia cordata L.	
	Angelica archangelica L.	
	Origanum vulgare L.	
2-4-dimethylheptane	*Eucalyptus grandis* L.	Heptan hydrocarbon
	Alpinia oxyphylla L.	
	Tragia involucrata L.	
undecane	*Hypericum perforatum* L.	alkane hydrocarbon
	Nepeta racemosa L.	
	Citrus aurantiifolia L.	
	Ephedra sinica L.	
	Origanum vulgare L.	
	Rheum palmatum L.	
	Micromeria myrtifolia L.	
***n*-tetradecane**	*Echinops ilicifolius* L.	alkane hydrocarbon
	Foeniculum vulgare L.	
hexadecane	*Plectranthus coleoides* L.	alkane hydrocarbon
	Angelica archangelica L.	
	Glycyrrhiza glabra L.	
	Rheum palmatum L.	
nonadecane		alkane hydrocarbon

Table 2 (*continued*)

Compound	Plant Source*	Nature/Warnings
	Aloe vera L.	
	Carica papaya L.	
	Citrullus lanatus L.	
	Cocos nucifera L.	
	Helianthus annuus L.	
	Magnolia denudata L.	
	Malus domestica L.	
	Melissa officinalis L.	
	Oenanthe javanica L.	
	Pastinaca sativa L.	
	Petasites hybridus L.	
	Piper nigrum L.	
	Plantago ovata L.	
	Sambucus nigra L.	
	Scutellaria baicalensis L.	
	Vanilla planifolia L.	
***n*-eicosane**	*Vanilla planifolia* L.	alkane hydrocarbon/Possible skin, eye and respiratory Irritations
	Glycyrrhiza glabra L.	
	Angelica archangelica L.	
	Rheum palmatum L.	
Heneicosane	*Carthamus tinctorius* L.	saturated hydrocarbon
	Periploca laevigata L.	
	Rosa damascene L.	
	Sambucus nigra L.	

*(Medicines, 2015).
*Medicines, N., 2015. Natural Medicines Database. www.naturalmedicinefacts.info/chemical/5964.html (accessed December 11, 2019.2019).

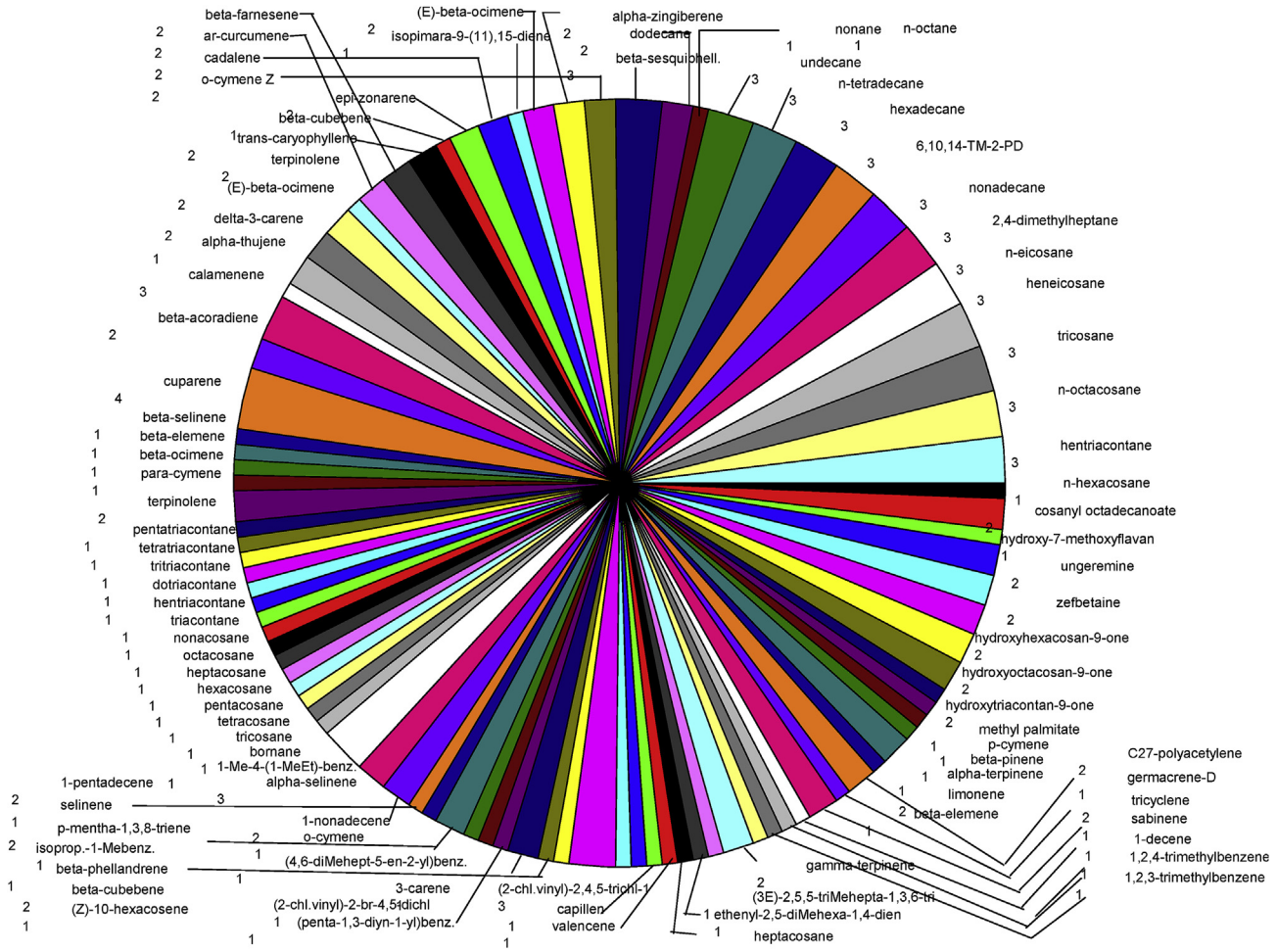

Fig. 3. The distributions (OriginPro 2016) of the number (1–4) of C-T interactions on the plant constituents.

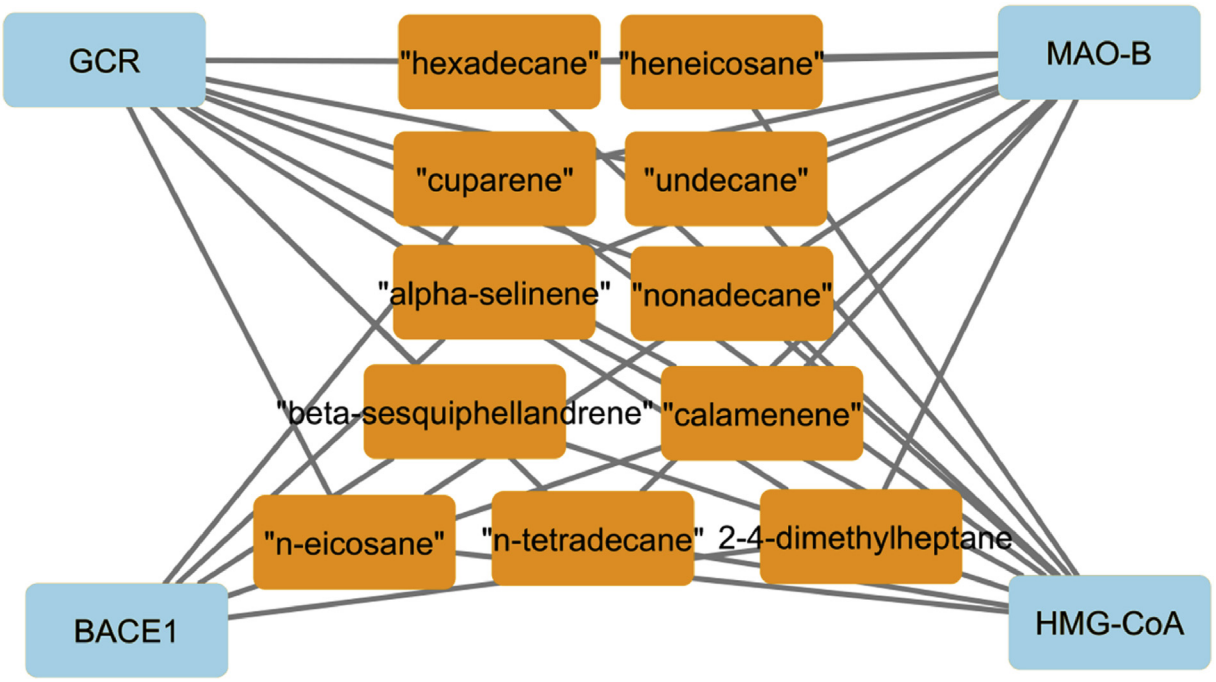

Fig. 4. Top scoring compounds-target (Cytoscape 3.5.1) network.

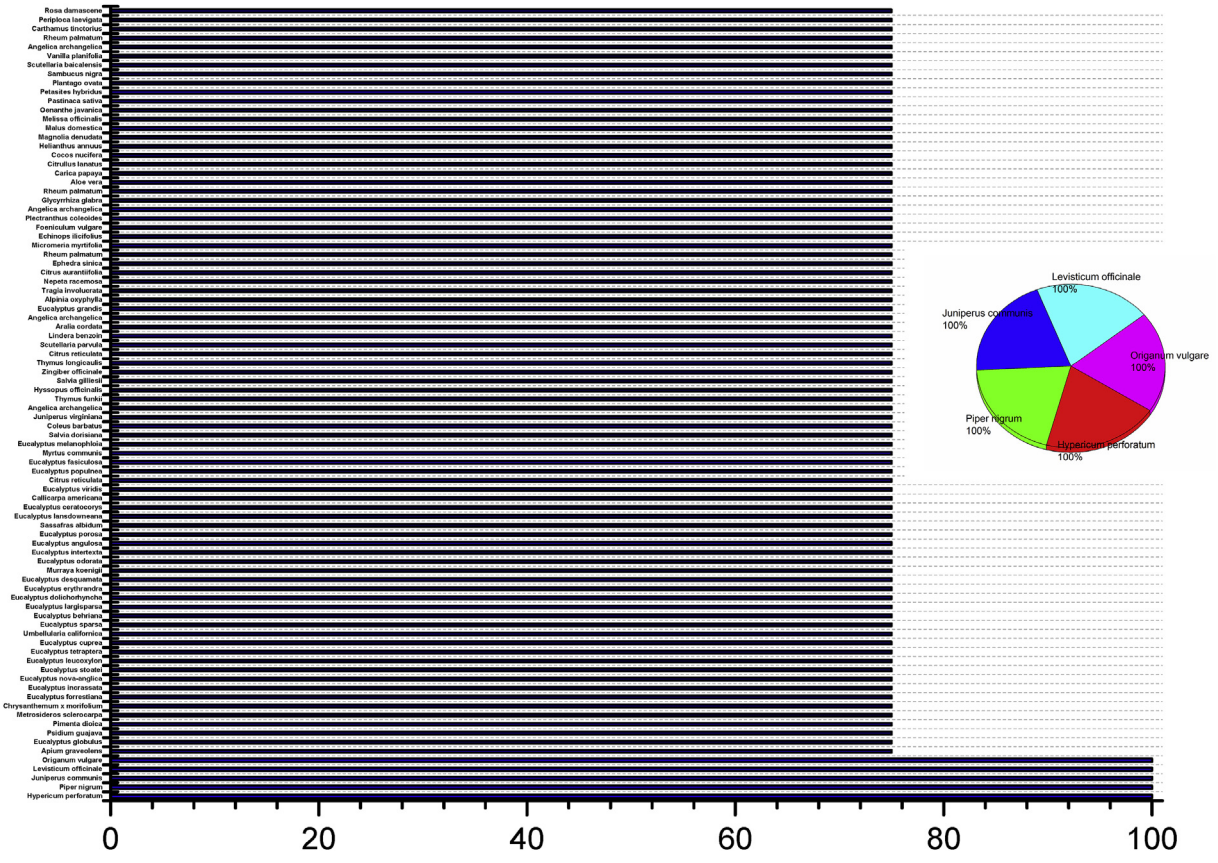

Fig. 5. The distributions % of C-T interactions (OriginPro 2016) on the top North African plants in the database.

Therefore, endeavors should be made to comprehend what the active herbal compounds are and how they interrelate with Alzheimer's disease in support of framework-pharmacology.

Further investigations are recommended to feature molecular-docking, pre-clinical and clinical studies.

These results suggested that the identified constituents and

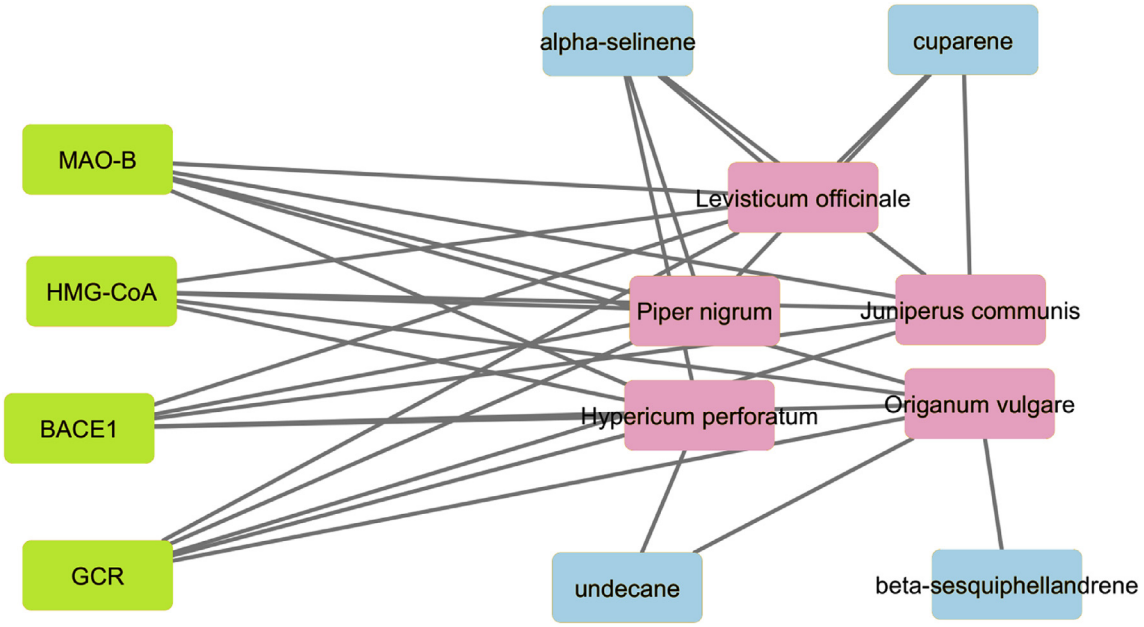

Fig. 6. Merged networks (Cytoscape 3.5.1) showing plant-compound-target interactions of the five plants having the highest combined scores.

medicinal plants might contribute to the regulation of Alzheimer's disease-related target-proteins, for further investigation.

Declaration of competing interest

The author declares no conflicts of interest.

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