Heliyon 10 (2024) e35943

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Plant extracts as emerging modulators of neuroinflammation and immune receptors in Alzheimer's pathogenesis

Intisar E. Mohamed [a], Elbadri E. Osman [b], Ahmed Saeed [c], Long Chiau Ming [d], Khang Wen Goh [e], Pakhrur Razi [f,*], Amar Daud Iskandar Abdullah [g], Mahmoud Dahab [b,**]

[a] Department of Biochemistry, Faculty of Medicine, University of Bahri, P.O. Box 2469, Khartoum, 12223, Sudan
[b] Department of Microbiology, Faculty of Pure and Applied Sciences, International University of Africa, P.O. Box 2469, Khartoum, 12223, Sudan
[c] Medicinal and Aromatic Plants and Traditional Medicine Research Institute, National Centre for Research, P.O. Box 2404, Khartoum, 12223, Sudan
[d] Department of Medical Sciences, School of Medical and Life Sciences, Sunway University, Sunway City, 47500, Malaysia
[e] Faculty of Data Science and Information Technology, INTI International University, Nilai, Malaysia
[f] Center of Disaster Monitoring and Earth Observation, Universitas Negeri Padang, Padang, Indonesia
[g] Department of Biological Sciences, School of Medical and Life Sciences, Sunway University, Sunway City, 47500, Malaysia

ARTICLE INFO

Keywords:
Medicinal plants
AChE inhibition
Protein docking
Neuroinflammation
Neuroprotective
Immunomodulation
Mental disorder
Human and diseases

ABSTRACT

Memory loss is becoming an increasingly significant health problem, largely due to Alzheimer's disease (AD), which disrupts the brain in several ways, including causing inflammation and weakening the body's defenses. This study explores the potential of medicinal plants as a source of novel therapeutic agents for AD.

First, we tested various plant extracts against acetylcholinesterase (AChE) *in vitro*, following molecular docking simulations with key AD-related protein targets such as MAO-B, P-gp, GSK-3β, and CD14. Rosemary extract was found to be the most inhibitory towards AChE. The compounds found in rosemary (oleanolic acid), sage (pinocembrin), and cinnamon (italicene) showed promise in potentially binding to MAO-B. These chemicals may interact with a key protein in the brain and alter the production and removal of amyloid-β. Luteolin (from rosemary), myricetin (from sage), chamigrene, and italicene (from cinnamon) exhibited potential for inhibiting tau aggregation. Additionally, ursolic acid found in rosemary, sage, and chamigrene from cinnamon could modulate CD14 activity.

For the first time, our findings shed light on the intricate interplay between neuroinflammation, neuroprotective mechanisms, and the immune system's role in AD. Further research is needed to validate the *in vivo* efficacy and safety of these plant-derived compounds, as well as their interactions with key protein targets, which could lead to the development of novel AD therapeutics.

* Corresponding author.
** Corresponding author.
E-mail addresses: fhrrazi@fmipa.unp.ac.id (P. Razi), mahmouddahab4@gmail.com (M. Dahab).

https://doi.org/10.1016/j.heliyon.2024.e35943
Received 26 March 2024; Received in revised form 5 August 2024; Accepted 6 August 2024
Available online 10 August 2024

1. Introduction

Alzheimer's disease (AD), a progressive neurodegenerative disorder characterized by memory loss and cognitive decline, represents a growing global healthcare challenge [1,2]. The pathological hallmarks of AD include the accumulation of amyloid-β (Aβ) plaques and tau protein tangles in the brain [3]. These proteins damage brain cells and cause inflammation, ultimately leading to neural cell death. Existing therapeutic strategies primarily focus on managing symptoms and lack disease-modifying capabilities, failing to address the underlying pathological mechanisms [4,5]. Targeting key inflammatory pathways and their effector molecules holds promise for disease modification.

Early central nervous system inflammation is now known to contribute to AD, prompting studies and clinical trials evaluating anti-inflammatory medicines. McGeer et al. observed a lower prevalence of Alzheimer's disease in rheumatoid arthritis patients, which led to an investigation into anti-inflammatory mechanisms for AD [6]. The inflammatory cascade contributes to neuronal damage, synaptic impairment, and severe cognitive decline [7–10]. Additionally, the cholinergic system is severely compromised in AD due to the degeneration of cholinergic neurons and dysregulation of acetylcholinesterase (AChE). Acetylcholinesterase is the enzyme responsible for acetylcholine (ACh) breakdown [11], leading to a decline in ACh levels and exacerbating cognitive decline [12].

Oxidative stress plays a crucial role in AD pathogenesis. Increasing oxidative stress contributes to neuronal damage, mitochondrial dysfunction, and ultimately, cognitive decline [13]. The dysregulation of monoamine neurotransmitters, such as dopamine, is another key pathological feature of AD [14,15]. Monoamine oxidase-B (MAO-B) is an enzyme responsible for the breakdown of these neurotransmitters. Increased MAO-B activity in AD leads to decreased neurotransmitter levels, further impairing cognitive function and other symptoms. Moreover, MAO-B is liable for the production of reactive oxygen species (ROS) that directly damage neuronal cells, making it another potential target in the fight against AD [16]. Amyloid-β peptides clump together to form plaques in the brain, disrupting neuronal communication and contributing to neurodegeneration [3]. Inhibiting Aβ aggregation or promoting its clearance remains a key strategy for AD treatment. P-glycoprotein (P-gp), a transporter protein at the blood-brain barrier (BBB), acts as a gatekeeper, effluxing harmful substances from the brain [17,18]. Inhibiting P-gp activity could enhance the delivery of therapeutic agents to the brain, improving treatment efficacy.

The tau protein, a microtubule-associated protein, plays a major role in maintaining microtubules in nerve cells. In AD, hyperphosphorylation of tau proteins results in neurofibrillary tangle accumulations in neurons [19]. Both amyloid-β (Aβ) and tau proteins

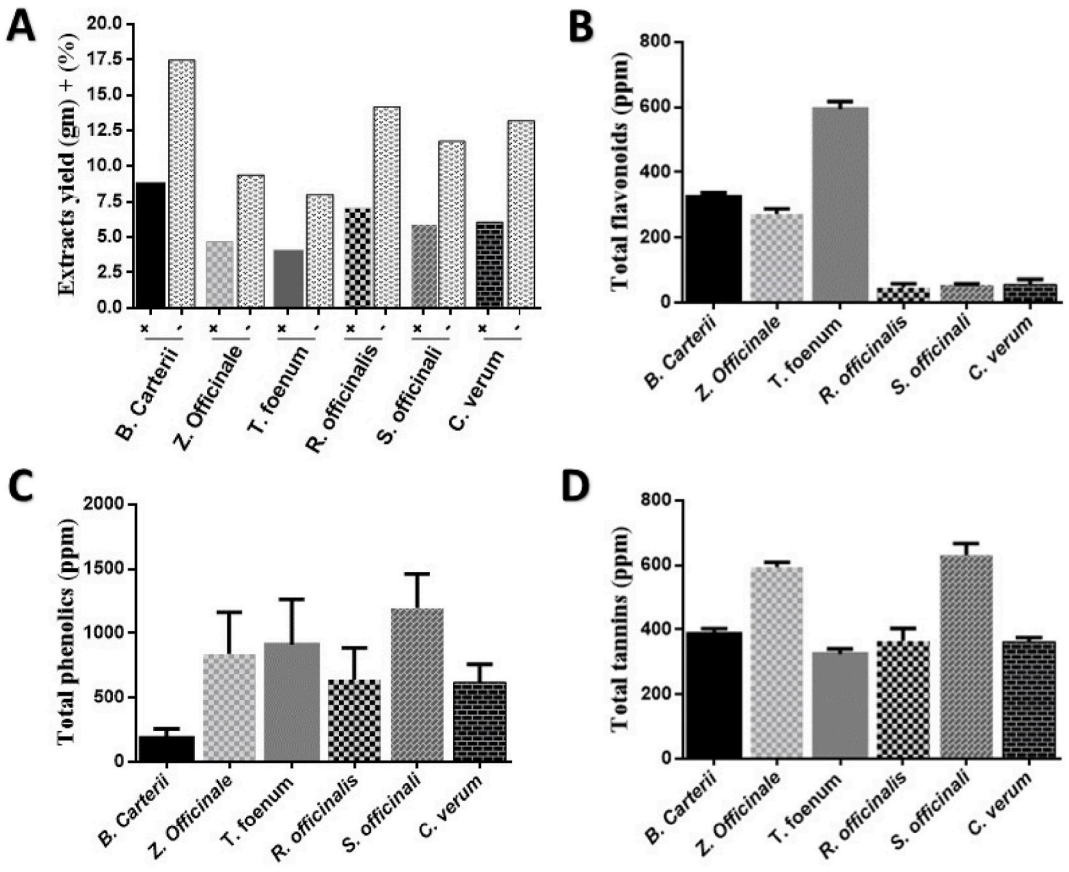

Fig. 1. Variations in ethanolic extraction yields and phytochemical contents. (**A**), Crude yield extract, (**B**) Total flavonoid content per part per million (ppm), (**C**) Total phenolic content, (**D**) Total tannin content.

contribute to neurotoxicity through pathways tightly regulated by a network of kinases and phosphatases [20]. A promising therapeutic approach for AD is the inhibition of glycogen synthase kinase-3β (GSK-3β) [21]. GSK-3β is a key enzyme responsible for tau protein hyperphosphorylation, a critical step in the formation of neurofibrillary tangles within neurons [22]. By modulating GSK-3β activity, we may be able to prevent tau aggregation, promote tau clearance, and ultimately slow down AD progression.

Cluster differentiation 14 (CD14) is a pattern recognition receptor expressed on the plasma membrane of most myeloid cells [23]. CD14 plays a pivotal role in initiating and amplifying neuroinflammation [24]. Modulating CD14 expression or function could be a promising therapeutic strategy in AD.

The complex, multifaceted nature of AD is not addressed by current single-target medications, which focus on separate pathways despite their limitations [25]. Unlike conventional single-target drugs, dual-target therapeutics simultaneously modulate multiple disease processes implicated in the complex etiology of AD. Medicinal plants, with their vast collection of natural chemicals like phenolics and flavonoids, show promise for treating AD. A diverse array of plant materials, including *Ginkgo biloba* leaves [26], *Galanthus caucasicus* leaves [27], *Cinnamomum verum* bark [28], and *Salvia officinalis* leaves [29], have been tested in the management

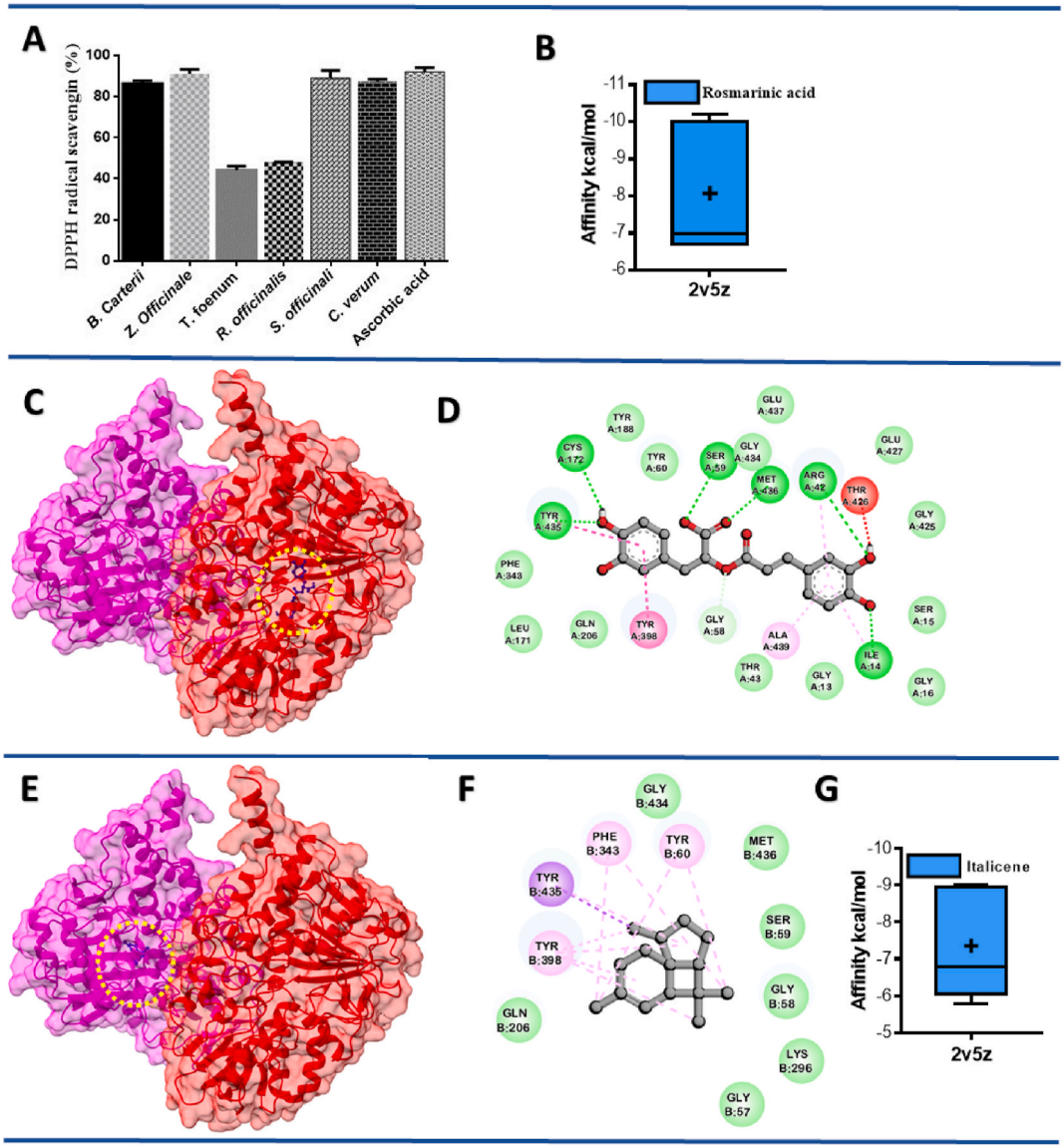

Fig. 2. Antioxidant activity of plants ethanolic extract and molecular docking analysis of the most compounds affinity targeting monoamine oxidase-2 (MAO-2). (A) Antioxidant activity of plant crude extracts, ascorbic acid used as standard (**B**) Box plot depicted binding affinity scores for predictions of rosmarinic acid (rosemary, sage) (blue) with MAO-2, (**C**) Pose view of the interaction of rosmarinic acid to MAO-2, (**D**) 2D interaction of rosmarinic acid with key residues, (**E**) Pose view of the interaction of italicene to MAO-2, (**F**) 2D interaction of rosmarinic acid with key residues, (**G**) Box plot depicted binding affinity scores for predictions of italicene (cinnamon) (blue) with MAO-2. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of mild to moderate AD. Notably, the essential oil of these plants exhibits acetylcholinesterase inhibitory activity, potentially mitigating memory loss by increasing acetylcholine levels [30].

Existing treatments primarily focus on symptom management, failing to address the underlying causes of AD. Therefore, the development of novel therapeutic strategies targeting multiple aspects of AD pathogenesis, such as oxidative stress, cholinergic decline, neuroinflammation, and tau aggregation, is crucial. We aimed to identify the structure-function relationships of phytochemical compounds derived from medicinal plants as natural therapeutic agents for neurodegenerative diseases by targeting diverse aspects of AD pathogenesis. Among six plants exhibiting substantial AChE inhibitory activity, only three demonstrated consistent and potent effects, warranting their selection for subsequent docking studies. By using molecular docking of these compounds with a total of four proteins (i.e., 2v5z, 3g60, 1j1b, and 4glp), which have diverse activities relevant to AD pathogenesis, the outcomes of our computational study serve as a benchmark for exploring the promising potential of medicinal plants in modulating these processes. This study aims to unravel the intricate link between neuroinflammation, neuroprotection, and human CD14 in AD, opening a novel avenue for therapeutic intervention.

2. Results

2.1. Variations in extraction yields and phytochemical content

Extraction of the six plants yielded varying amounts. *Boswellia Carterii* was showed the highest yield (8.74) g, followed by *Rosmarinus officinalis* seeds at 7.09 g (Fig. 1A). Despite potential variations in flavonoid content, *Rosmarinus officinalis*, *Salvia officinalis*, and *Cinnamomum verum* extracts consistently were yielded the lowest values (Fig. 1B). Phytochemical screening was confirmed the presence of a spectrum of secondary metabolites in crude ethanloic extracts, notably flavonoid, phenolic, and tannin (Fig. 1C and D).

2.2. Identification of potent antioxidant extracts through in vitro screening

Evaluation of antioxidant capacity using the DPPH assay (Fig. 2A) identified *Zingiber Officinale* and *S. officinalis* as the most potent free radical scavengers among the six tested ethanolic extracts, exhibiting IC50 values of 91 ± 0.88 % and 89.02 ± 1.23 %, respectively. *Boswellia Carterii* and *Cinnamomum verum* also demonstrated substantial activity, while *Rosmarinus officinalis* and *Trigonella foenum* showed lower scavenging potential.

2.3. Identification of potent anti-acetylcholinesterase and cytotoxic agents through in vitro studies

Among the tested extracts, *R. officinalis* emerged as the most potent AChE inhibitor, exhibiting 76 ± 0.6 % inhibition in vitro (Fig. 3A). *S. officinalis*, *C. verum*, *B. Carterii*, and *Z. Officinale* displayed moderate to weak activity (<50 % inhibition), while *T. foenum* lacked noticeable AChE inhibitory. Meanwhile, cytotoxicity of plants ethanolic extract is showed in Fig. 3B.

2.4. Molecular docking analysis of selected small molecules with protein

The spatial relationships between the selected compounds and their target receptors were elucidated through molecular docking simulations. Binding affinity between receptor and plant-derived molecules was predicted based on calculated binding free energy (ΔG) values, with lower (more negative) scores indicating stronger interaction, and a more stable complex (Table 1).

Rosmarinic acid, isolated from *R. officinalis* and *S. officinalis* demonstrated the strongest predicted binding affinity for MAO-2 among the tested plant-derived compounds, exhibiting a docking score of −10.2 kcal/mol (Fig. 2B). Structural analysis of the

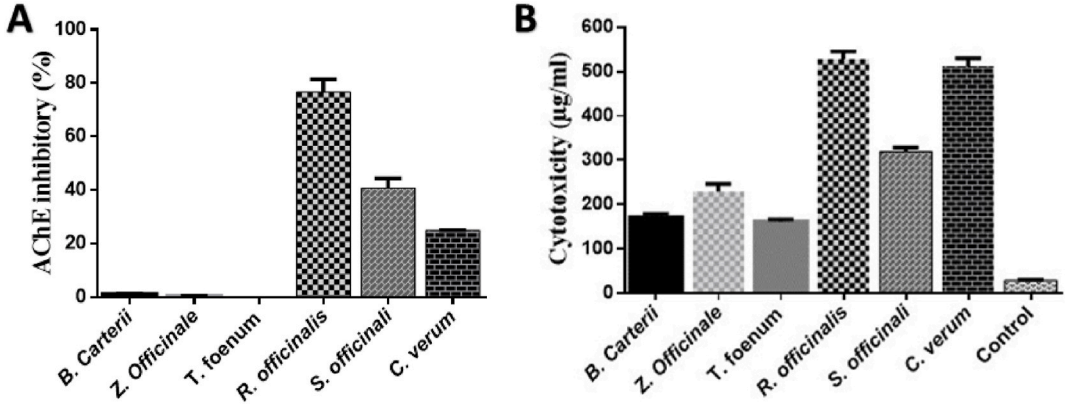

Fig. 3. AChE inhibitory activity of plant extracts and cytotoxicity. (**A**) Anti-acetylcholinesterase activity of plant crude extracts, (**B**) Cytotoxicity of plants ethanolic extract; IC50 > 30 µg/mL considered to be high toxic; Control; Triton-x100 (0.2 µg/mL).

Table 1
Binding energy (kcal/mol) of plant-derived compounds with the monoamine oxidase-B.

NO.	Rosemary	Energy	Sage	Energy	Cinnamon	Energy
1-	Rosmarinic acid	−10.2	Rosmarinic acid	−10.2	Ferulic acid	−7.0
2-	Ursolic acid	−7.3	Ursolic acid	−7.3	Pyrogallol	−5.6
3-	Oleanolic acid	−8.3	Apigenin	−9.4	Vanillin	−5.9
4-	Carnosic acid	−7.3	Carnosic acids	−7.3	p-Coumaric acid	−6.9
5-	Chlorogenic acid	−8.5	Rutin	−8.8	Gallic acid	−6.8
6-	Luteolin	−9.7	Luteolin	−9.7	Ascorbic acid	−6.5
7-	Caffeic acid	−7.1	Caffeic acid	−7.1	Caffeic acid	−7.1
8-	Alpha-pinene	−6.6	Abscisic acid	−8.3	Palmitic acid	−6.5
9-	Camphor	−7.0	Myricetin	−9.1	Heptenal	−4.9
10-	Carnosol	−7.7	Ellagic acid	−9.9	Italicene	−9.0
11-	Eucalyptol	−6.6	Quercetin	−9.5	Butanamine	−3.5
12-	Rosmanol	−7.6	Rosmanol	−7.6	Chamigrene	−8.2
13-	Eugenol	−6.4	Pinocembrin	−9.4	Hexanoic acid	−5.0

docked rosmarinic acid-MAO-2 complex (Fig. 2D) revealed key interactions including conventional hydrogen bonds with Ile14, Arg42, Ser59, Cys172, Tyr435, and Met436, pi-alkyl bonds with Ile14, Arg42, and Ala439, and a pi-pi stack with Tyr398, and Tyr435. However, one unfavorable interaction was also observed. In contrast to rosmarinic acid, italicene isolated from *C. verum* exhibited a predicted binding affinity of −9 kcal/mol for MAO-2, primarily through pi-alkyl interactions with Tyr60, Phe343, and Tyr398 residues of the B chain (Fig. 2E, F and 2G).

Docking simulations singled out oleanolic acid from *R. officinalis* as a promising P-glycoprotein binder (Fig. 4A), exhibiting substantial binding affinity (Table 2). Its predicted binding pose involved key interactions, including a hydrogen bond with Phe339, and alkyl/pi-alkyl bonds with Ala225, Leu335, Ala338, and Phe339. Docking predicts pinocembrin from *S. officinalis* binds P-gp via hydrogen bond, pi-Sigma, and pi-pi stacking. The top-ranked italicene-P-gp binding pose (Fig. 4H) involves diverse interactions with multiple amino acid residues, including alkyl, pi-alkyl, and pi-Sigma bonds. 2D interaction of oleanolic acid with key residues, and Box plot depicted binding affinity scores for predictions of oleanolic acid (blue) with P-gp are showed in Fig. 4B and C. Pose view of the interaction of pinocembrin (sage) with P-gp, 2D interaction of pinocembrin with key residues, and Box plot depicted binding affinity scores for predictions of pinocembrin with P-gp are depicted in Fig. 4D, E and 4F respectively. Pose view of the interaction of italicene (cinnamon) with P-gp, 2D interaction of italicene with key residues, and Box plot depicted binding affinity scores for predictions of italicene (blue) with P-gp are showed in Fig. 4G, H and 4I respectively.

Molecular docking analysis of the most compounds affinity targeting glycogen synthase kinase-3β (GSK-3β). Pose view of the interaction of luteolin (rosemary) with GSK-3β, 2D interaction of luteolin with key residues, and Box plot depicted binding affinity scores for predictions of luteolin (blue) with GSK-3β are showed in Fig. 5A, B and 5C. Pose view of the interaction of myricetin (sage) with GSK-3β, 2D interaction of myricetin with key residues are illustrated in Fig. 5D and E. Among the explored small molecules, luteolin displayed the highest predicted binding affinity for the GSK-3β target site based on docking simulations (Fig. 5C). Notably, rosmarinic acid turned out to be the second best (next to luteolin) having a binding affinity of −9.8 kcal/mol with GSK-3β protein (Table 3). While a fellow *S. officinalis* molecule and other small molecules displayed promising binding affinity, myricetin emerged as a strong contender with comparable or even superior predicted performance (Fig. 5F). Despite their structural differences, italicene and chamigrene from *C. verum* displayed remarkable convergence in their predicted binding to GSK-3β. Docking simulations (Fig. 5H and K) identified overlapping sets of stabilizing interactions for both compounds, featuring highly similar interaction profiles with the target protein, including identical alkyl/pi-alkyl, pi-pi stacked, and pi-sigma contacts with the same amino acid residues of Val263, Lys292, Pro294, Val587, and Phe567 respectively. Box plot depicted binding affinity scores for predictions of italicene (blue) and chamigrene (red) with GSK-3β is presented in Fig. 5I. Pose view of the interaction of chamigrene (cinnamon) with GSK-3β, (K) 2D interaction of chamigrene with key residues is showed in Fig. 5J.

Ursolic acid, isolated from both *R. officinalis* and *S. officinalis*, exhibited potential for CD14 interaction based on docking simulations (Table 4). Pose view of the interaction of ursolic acid (rosemary) with CD14, 2D interaction of ursolic acid with key residues, and Box plot depicted binding affinity scores for predictions of ursolic acid (blue) and oleanolic acid (red) with CD14 are showed in Fig. 5A, B and 5C. Pose view of the interaction of oleanolic acid (sage) with CD14, 2D interaction of oleanolic acid with key residues, Box plot depicted binding affinity scores for predictions of oleanolic acid with CD14 are presented in Fig. 5D, E, and 5F respectively. Pose view of the interaction of chamigrene (cinnamon) with CD14, 2D interaction of chamigrene with key residues, and Box plot depicted binding affinity scores for predictions of chamigrene (blue) with CD14 are showed in Fig. 5G, H and 5I.

Its predicted binding mode (Fig. 6B and E) involves a network of alkyl and pi-alkyl bonds. Interestingly, oleanolic acid and ursolic acid predicted binding affinity stems from interactions involving alkyl/pi-alkyl bonds with the same amino acid residues of Phe69, and Ala109. Stimulatingly, chamigrene, isolated from *C. verum,* may act as CD14 receptor binding antagonist (Fig. 6G).

3. Discussion

Chronic inflammation and immune system dysfunction are increasingly recognized as pivotal players in the development of Alzheimer's disease (AD). This neurodegenerative disease is characterized by multiple factors, including damaged neurons, inappropriate immune responses, and the release of inflammatory mediators [10]. Finding the right balance between protecting brain cells

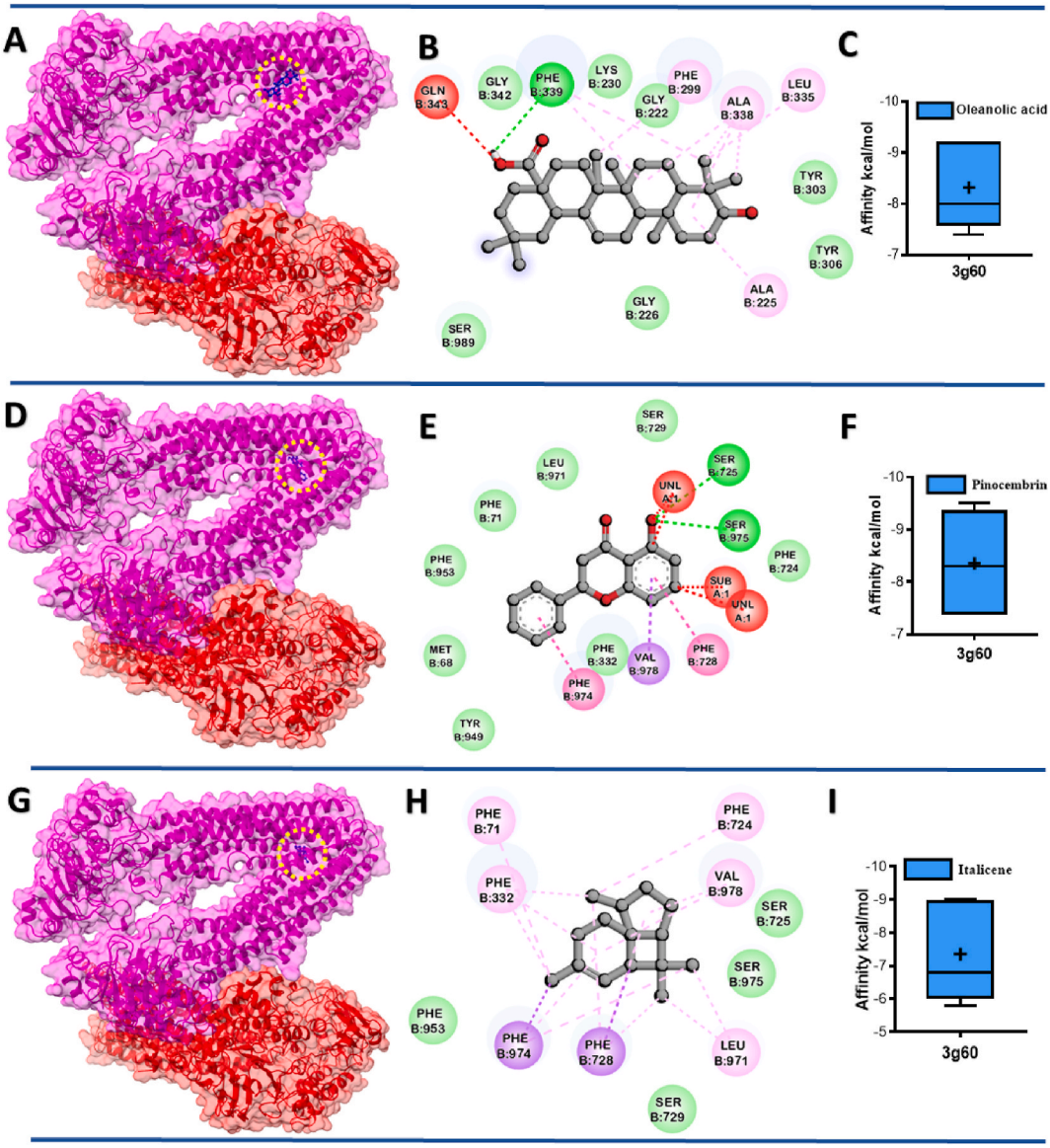

Fig. 4. Molecular docking analysis of the most compounds affinity targeting P-glycoprotein (P-gp). (**A**) Pose view of the interaction of oleanolic acid (rosemary) with P-gp, (**B**) 2D interaction of oleanolic acid with key residues, (**C**) Box plot depicted binding affinity scores for predictions of oleanolic acid (blue) with P-gp, (**D**) Pose view of the interaction of pinocembrin (sage) with P-gp, (**E**) 2D interaction of pinocembrin with key residues, (**F**) Box plot depicted binding affinity scores for predictions of pinocembrin with P-gp, (**G**) Pose view of the interaction of italicene (cinnamon) with P-gp, (**H**) 2D interaction of italicene with key residues, (**I**) Box plot depicted binding affinity scores for predictions of italicene (blue) with P-gp.

and preventing damage is key to developing effective treatments. This study reveals promising links between medicinal plants and this complex process. We used computer simulations to investigate how specific plant chemicals might interact with important proteins in the brain linked to AD. Moreover, docking analysis explored the interactions of these compounds with human CD14, a receptor involved in inflammatory processes relevant to AD progression. This computational approach enabled us to probe the atomic details of these crucial processes and understand how these chemicals might work to treat AD.

There could be promising therapeutic intervention opportunities using medicinal plants. Native to the Mediterranean, rosemary (Rosmarinus officinalis L.), is a global food herb that possesses a rich history of therapeutic applications in various folk medicine systems, particularly for the treatment of inflammatory disorders [31]. An extensive review of the PubMed database reveals numerous studies demonstrating the potential therapeutic applications of various bioactive constituents in R. officinalis. Rosemary features prominently among European herbs with a pan-cultural tradition of use in alleviating cognitive decline [32]. In traditional knowledge systems, rosemary has a long-standing association with improved memory function and alleviating age-related memory decline [33].

Numerous Salvia species, collectively known as sage, have shown promise as sources of bioactive compounds with antioxidant,

Table 2
Binding energy (kcal/mol) of plant-derived compounds with the P-glycoprotein.

NO.	Rosemary	Energy	Sage	Energy	Cinnamon	Energy
1-	Rosmarinic acid	−8.7	Rosmarinic acid	−8.7	Ferulic acid	−6.8
2-	Ursolic acid	−9.0	Ursolic acid	−9.0	Pyrogallol	−5.7
3-	Oleanolic acid	−9.2	Apigenin	−8.9	Vanillin	−6.2
4-	Carnosic acid	−9.0	Carnosic acids	−9.0	p-Coumaric acid	−7.3
5-	Chlorogenic acid	−8.8	Rutin	−9.1	Gallic acid	−6.3
6-	Luteolin	−8.7	Luteolin	−8.7	Ascorbic acid	−6.2
7-	Caffeic acid	−6.9	Caffeic acid	−6.9	Caffeic acid	−6.9
8-	Alpha-pinene	−7.0	Abscisic acid	−8.3	Palmitic acid	−6.9
9-	Camphor	−6.6	Myricetin	−8.9	Heptenal	−5.1
10-	Carnosol	−7.7	Ellagic acid	−9.0	Italicene	−9.0
11-	Eucalyptol	−7.0	Quercetin	−8.8	Butanamine	−3.9
12-	Rosmanol	−8.9	Rosmanol	−8.9	Chamigrene	−8.3
13-	Eugenol	−6.9	Pinocembrin	−9.5	Hexanoic acid	−5.0

anti-inflammatory, and neuroprotective properties [34,35]. Sage (Salvia officinalis) contains a wide range of naturally occurring compounds, including phenolics and terpenoids, which present promising opportunities for the discovery of novel health benefits and therapies. A search of the PubMed database reveals a wealth of evidence supporting the therapeutic potential of diverse compounds in sage [36]. While commonly known for its culinary applications, *S. officinalis* is increasingly being studied for its potential therapeutic effects in cognitive dysfunction, mood disorders, and cerebral ischemia [37]. *S. officinalis* has garnered extensive research interest for its enhanced memory and cognitive function [38,39]. The flavonoid composition of *S. officinalis* extracts reveals a consistent pattern, with rosmarinic acid and ellagic acid prominent in both aqueous and alcoholic preparations. Interestingly, these extracts also contain significant amounts of rutin, chlorogenic acid, and quercetin, suggesting a wide range of possible bioactivities [40]. Chemical analysis and biological assays of extracts from ginseng and Salvia serratifolium have identified quercetin and terpenoids as potentially active compounds against AD [41,42]. Analysis of bioactive compounds from bamboo leaves has revealed apigenin, also one of the sage components, as a potential anti-Aβ agent, holding promise for AD [43]. Building upon the traditional medicinal uses of cinnamon (Cinnamomum verum J), scientific studies have identified strong bioactive compounds in the plant that have therapeutic value in treating oxidative stress, inflammatory responses, abnormal cholesterol levels, and various immune system imbalances [44,45].

The enzyme that breaks down acetylcholine (ACh), acetylcholinesterase (AChE), becomes dysregulated in AD [11]. The AChE inhibitory action of the chosen plants facilitates an overall neuroprotective effect in AD. Among the tested extracts, rosemary stood out as the most effective AChE inhibitor, exhibiting remarkable activity in vitro. The potent AChE inhibitory potential of rosemary, followed by sage and cinnamon, indicates their ability to reduce cholinergic dysfunction. Numerous biological activities are connected to the essential oils of rosemary and polar phenolic extracts. These effects cover a wide range of functions, such as anti-inflammatory [46], antioxidant, and nervous system protection [47]. Additionally, rosemary has been shown to have memory-enhancing qualities [48], providing scientific validation for many of its traditional applications. Adding to its varied therapeutic uses, sage has been shown to possess acetylcholinesterase inhibitory activity, suggesting that it may help manage cognitive decline associated with conditions such as AD. Cholinesterase inhibition by sage has been shown to affect mood, anxiety, and performance on emotional response tests [49,50]. Several compounds found in cinnamon oil, including (−)-alloaromadendrene, β-himachalene, and italicene, exhibit the ability to scavenge free radicals and inhibit cholinesterase activity, suggesting a wide range of medical uses [51,52].

Free radicals produced by metabolism play a role in the etiology of many diseases, including AD. By scavenging free radicals and reactive oxygen species (ROS), antioxidants exhibit potential in mitigating inflammatory pathways, suggesting their possible role in neurodegenerative protection for AD [53,54]. Polar phenolic currant extract may preserve cellular redox homeostasis through its antioxidant free radical-scavenging properties [55]. Previous studies suggest that cinnamon essential oil might help treat conditions related to oxidative stress [56]. In addition to its well-established function in the metabolism of dopamine, MAO-B activity, which produces hydrogen peroxide, has gained attention as a possible therapeutic target for AD because of its connection to oxidative stress and neurodegeneration [15]. Inhibiting MAO-B activity leads to increased levels of monoamine neurotransmitters, improving cognitive function and alleviating AD symptoms. Polyphenols demonstrate well-documented potential to inhibit MAO-B activity. Documented antioxidant inhibitory potential includes curcumin, its metabolite tetrahydrocurcumin, and ellagic acid [57,58]; additionally, **Berry anthocyanins** [59], *Annurca apple* polyphenols [60], and *Uncaria rhynchophylla* have been reported [61,62]. In this study, we examined the relationship between a brain enzyme (MAO-B) and certain active compounds derived from plants using computer simulations. This enzyme is a possible target for Alzheimer's disease treatment, which might help address some of the major AD processes. Another study suggests that luteolin might help prevent AD [63]. Medications that target MAO-B may help AD by preventing the breakdown of important brain chemicals, potentially improving memory and preventing the breakdown of monoamine neurotransmitters.

The amyloid-β cascade hypothesis focuses on the accumulation and aggregation of Aβ peptides as the initiating event in AD pathogenesis [64]. Targeting Aβ aggregation and promoting its clearance remain key strategies for developing effective therapeutic interventions [65]. Therefore, multi-targeted strategies for Aβ, with the ability to cross the blood-brain barrier (BBB), could improve their efficiency [65]. P-glycoprotein might be useful in AD because it can target and remove harmful clumps of beta-amyloid protein [66]. It specifically recognizes and binds to the fibrillary conformation of Aβ with high affinity and selectivity, potentially disrupting Aβ aggregation and preventing plaque formation [67,68]. Certain natural compounds found in rosemary (oleanolic acid), sage

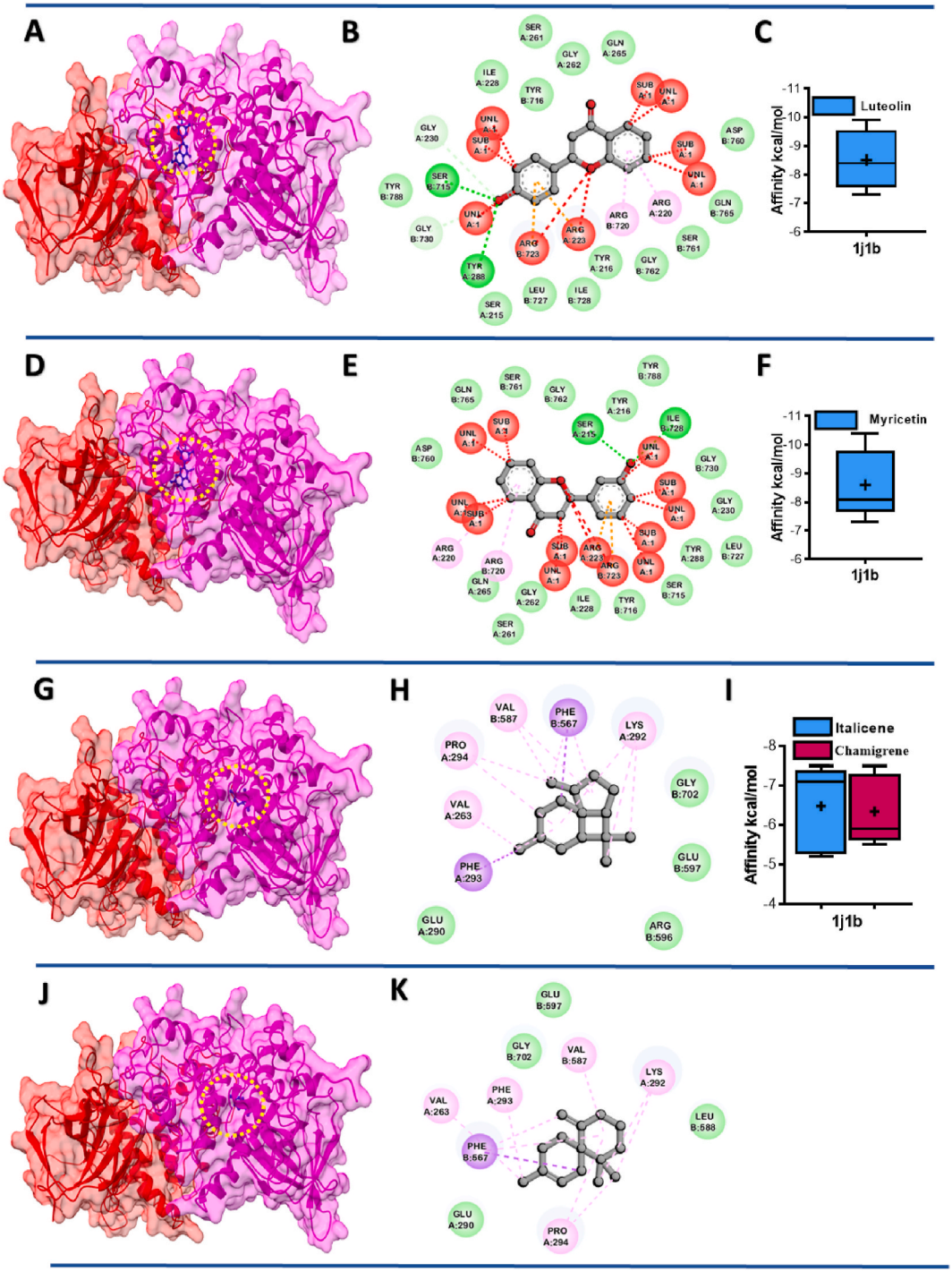

Fig. 5. Molecular docking analysis of the most compounds targeting human cluster of differentiation 14 (CD14). (A) Pose view of the interaction of ursolic acid (rosemary) with CD14, (B) 2D interaction of ursolic acid with key residues, (C) Box plot depicted binding affinity scores for predictions of ursolic acid (blue) and oleanolic acid (red) with CD14, (D) Pose view of the interaction of oleanolic acid (sage) with CD14, (E) 2D interaction of oleanolic acid with key residues, (F) Pose view of the interaction of chamigrene (cinnamon) with CD14, (G) 2D interaction of chamigrene with key residues, (H) Box plot depicted binding affinity scores for predictions of chamigrene (blue) with CD14.

(pinocembrin), and cinnamon (italicene) may help clear harmful proteins from the brain in AD. By increasing P-glycoprotein activity, these compounds could facilitate the removal of this neurotoxic protein, thereby reducing neuroinflammation and protecting neurons.

Tau helps stabilize microtubules, and amyloid-beta accumulation triggers tau hyperphosphorylation, ultimately leading to

Table 3
Binding energy (kcal/mol) of plant-derived compounds with the glycogen synthase kinase-3β.

NO.	Rosemary	Energy	Sage	Energy	Cinnamon	Energy
1-	Rosmarinic acid	−9.8	Rosmarinic acid	−9.8	Ferulic acid	−7.3
2-	Ursolic acid	−7.7	Ursolic acid	−7.7	Pyrogallol	−5.7
3-	Oleanolic acid	−7.9	Apigenin	−9.8	Vanillin	−6.2
4-	Carnosic acid	−7.7	Carnosic acids	−7.7	p-Coumaric acid	−6.6
5-	Chlorogenic acid	−9.0	Rutin	−9.9	Gallic acid	−7.2
6-	Luteolin	−9.9	Luteolin	−9.9	Ascorbic acid	−6.6
7-	Caffeic acid	−7.3	Caffeic acid	−7.3	Caffeic acid	−7.3
8-	Alpha-pinene	−5.7	Abscisic acid	−7.5	Palmitic acid	−6.4
9-	Camphor	−6.2	Myricetin	−10.4	Heptenal	−4.3
10-	Carnosol	−8.7	Ellagic acid	−7.3	Italicene	−7.5
11-	Eucalyptol	−6.2	Quercetin	−7.1	Butanamine	−3.5
12-	Rosmanol	−8.1	Rosmanol	−8.1	Chamigrene	−7.5
13-	Eugenol	−6.0	Pinocembrin	−9.1	Hexanoic acid	−4.6

Table 4
Binding energy (kcal/mol) of plant-derived compounds with the human cluster of differentiation 14.

NO.	Rosemary	Energy	Sage	Energy	Cinnamon	Energy
1-	Rosmarinic acid	−7.8	Rosmarinic acid	−7.8	Ferulic acid	−5.9
2-	Ursolic acid	−9.6	Ursolic acid	−9.6	Pyrogallol	−4.9
3-	Oleanolic acid	−9.6	Apigenin	−7.6	Vanillin	−4.8
4-	Carnosic acid	−9.4	Carnosic acids	−9.4	p-Coumaric acid	−5.7
5-	Chlorogenic acid	−7.2	Rutin	−8.0	Gallic acid	−5.8
6-	Luteolin	−7.6	Luteolin	−7.6	Ascorbic acid	−5.8
7-	Caffeic acid	−5.9	Caffeic acid	−5.9	Caffeic acid	−5.9
8-	Alpha-pinene	−5.3	Abscisic acid	−6.4	Palmitic acid	−5.7
9-	Camphor	−4.8	Myricetin	−7.3	Heptenal	−4.6
10-	Carnosol	−7.8	Ellagic acid	−7.6	Italicene	−6.7
11-	Eucalyptol	−4.9	Quercetin	−8.2	Butanamine	−3.2
12-	Rosmanol	−7.2	Rosmanol	−7.2	Chamigrene	−6.8
13-	Eugenol	−5.4	Pinocembrin	−7.3	Hexanoic acid	−4.4

neuronal death [69]. Hyperphosphorylated tau detaches from microtubules, accumulating within neurons and disrupting their function, morphology, and viability. This aggregation leads to the formation of neurofibrillary tangles and neuronal threads, hallmarks of AD [70]. Roda et al. reviewed how Aβ accumulation, followed by tau protein dysfunction, contributes to neuronal cell death in AD [69]. Luteolin from rosemary, myricetin from sage, and chamigrene and italicene from cinnamon emerged as promising GSK-3β binders, a protein involved in tau protein hyperphosphorylation. Targeting this critical protein involved in neuronal survival with a diverse arsenal of compounds, rather than one, provides a more robust approach to neuroprotection. Alzheimer's disease (AD) is characterized by the recruitment of monocytes to both Aβ deposits and the surrounding inflammatory microenvironment. Monocytes migrating to the injured brain exhibit the capacity to differentiate into macrophages and subsequently clear protein aggregates like Aβ through phagocytosis [71]. Aβ-activated microglia produce the chemokine monocyte chemoattractant protein-1 (MCP-1) [72]. Previous studies demonstrated a reduction in non-classical monocytes (CD14+/CD16++) in AD patients compared to mild cognitive impairment (MCI) subjects or healthy controls, suggesting a potential protective role for this monocyte subset in AD pathogenesis [73]. Furthermore, Erin et al. suggested that CD14 acts as a key regulator of the microglial inflammatory response, modulating Aβ deposition [74]. Docking simulations reveal ursolic acid (from rosemary and sage) as a promising CD14 modulator to mitigate neuroinflammation in AD, highlighting the need for further research into its potential therapeutic applications.

Oleanolic acid can interact with CD14, which can trigger inflammation in the brain. By modulating CD14, oleanolic acid might help clear harmful beta-amyloid proteins. Notably, the presence of both ursolic acid and oleanolic acid in rosemary suggests a potential synergistic effect in mitigating neurodegeneration. Cinnamon's chamigrene could interact with CD14 chain A, triggering downstream signaling pathways and promoting the removal of harmful tau clumps. This mechanism aligns with italicene's observed neuroprotective effects.

Conventional single-molecule approaches may fall short in addressing the multifaceted nature of AD. This study, however, emphasizes the potential of a multi-target, multi-plant approach. By harnessing the synergistic effects of diverse bioactive compounds within various medicinal plants, we can potentially target multiple aspects of AD pathology, including oxidative stress, cholinergic decline, neuroinflammation, and tau aggregation. This holistic approach, exemplified by the identified activities of extracts and their constituent compounds, paves the way for exploring novel, plant-based interventions for AD treatment.

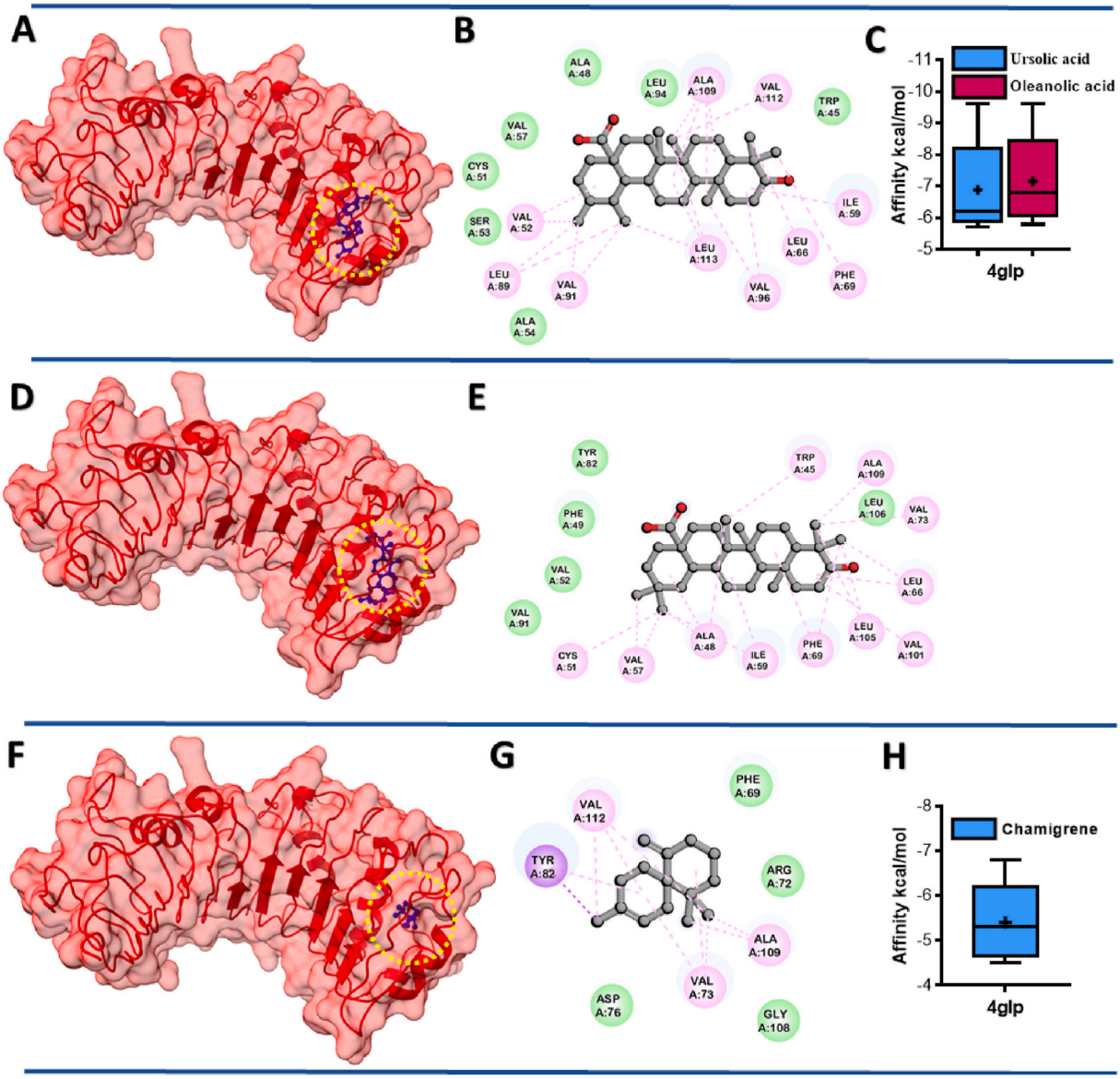

Fig. 6. Molecular docking analysis of the most compounds affinity targeting human cluster of differentiation 14 (CD14). (**A**) Pose view of the interaction of ursolic acid (rosemary) with CD14, (**B**) 2D interaction of ursolic acid with key residues, (**C**) Box plot depicted binding affinity scores for predictions of ursolic acid (blue) and oleanolic acid (red) with CD14, (**D**) Pose view of the interaction of oleanolic acid (sage) with CD14, (**E**) 2D interaction of oleanolic acid with key residues, (**F**) Pose view of the interaction of chamigrene (cinnamon) with CD14, (**G**) 2D interaction of chamigrene with key residues, (**H**) Box plot depicted binding affinity scores for predictions of chamigrene (blue) with CD14.

4. Materials and methods

4.1. Plants collection

Six plant specimens were sourced from central Sudan and their identifications were confirmed by taxonomists at the Medicinal and Aromatic Plants and Traditional Medicine Research Institute (MAPTMRI) in Khartoum. Following air-drying under shade with adequate ventilation, the plants were grounded using a blender. The resulting powder was subsequently sieved through a mesh with a 0.3 mm aperture size.

4.2. Crude extract preparation and yield optimization

Plant part (50 g), (Table 1S), were macerated in 250 mL ethanol for 3 h at room temperature, followed by overnight shaking (24 h).

The supernatant was decanted, filtered, and concentrated by rotary evaporation at 55 °C. Yield (%) was calculated based on the remaining residue. Insoluble materials were further extracted using the same method. Extracts were freeze-dried for 48 h, their yield (%) calculated and stored at 4 °C until use.

4.3. Total phenolic content determination

Total phenolic content (TPC) was estimated using the Folin-Ciocalteau method [75] with slight modifications. Briefly, 0.5 mL of extract (1 mg/mL) was mixed with 0.4 mL diluted Folin-Ciocalteau reagent (1:10 v/v) and 0.91 mL sodium carbonate (75 %). The mixture was incubated for 90 min at room temperature for color development, and absorbance was measured at 765 nm.

4.4. Total flavonoid content determination

Total flavonoid content (TFC) was determined using a modified colorimetric method by Chun et al. [76]. Briefly, 1 mL of extract (1 mg/mL in methanol) was mixed sequentially with 0.3 mL each of 5 % NaNO2, 10 % AlCl3, and 1 M NaOH at 5-min intervals. After a 15-min incubation at room temperature, absorbance was measured at 510 nm against a blank. TFC was quantified using a calibration curve prepared with different concentrations of quercetin.

4.5. Total tannin content determination

Tannin content was assessed. Briefly, 1 mL of extract (1 mg/mL) was mixed with 1 mL each of 1 % $K3Fe(CN)_6$ and 1 % FeCl3 and diluted to 10 mL with water. After 5 min, absorbance was measured at 510 nm against a blank.

4.6. Cytotoxic screening of plant extracts

Cytotoxicity of the plant extracts was assessed using the MTT assay. Briefly, 5 mg of each extract were dissolved in 1 mL of 1 % DMSO solution and vortexed for homogeneity. Vero cells were counted using a hemocytometer and trypan blue exclusion. After plating cells in 96-well plates, 10 μL of extract solutions were added. Following incubation, cell viability was determined by measuring formazan production at 570 nm % growth inhibition was calculated relative to controls using the formula:

% Inhibition = 100 - [(At/Ac) x 100]

Where; At and Ac are the absorbance values of treated and control groups, respectively. IC50 determination was restricted by <50 % inhibition at 500 μg/mL.

4.7. DPPH assay for scavenging activity

Plant extracts (5 mg/mL in DMSO) were evaluated for their radical scavenging activity against DPPH (300 μM in ethanol) in a 96-well plate assay. After 30 min' incubation at 37 °C, absorbance readings at 517 nm were recorded. Percentage radical scavenging activity was calculated relative to a DMSO control, with ascorbic acid used as a reference standard. All experiments were performed in triplicate. The ability to scavenge DPPH radical was calculated by the following equation:

DPPH radical scavenging activity (%) = 100 - [(Abs sample – Abs blank) × 100] / (Abs control)]

where Abs sample is the absorbance of DPPH radical + sample; Abs blank is the absorbance of sample+ 5 % DMSO; and Abs control is the absorbance of DPPH radical + 5 % DMSO.

4.8. Evaluation of acetylcholinesterase inhibitory activity

Acetylcholinesterase activity was determined using Ellman's method in a 96-well plate [77]. Each well contained a 200 μL reaction mixture comprising 20 μL of enzyme solution, 140 μL of phosphate buffer (pH 8) containing 0.5 mM DTNB (5,5′-dithiobis-(2-nitrobenzoic acid)), 20 μL of acetylthiocholine iodide, and 10 μL of plant extract (5 mg/mL in ethanol). Absorbance at 412 nm was monitored, and the percentage inhibition of AChE activity was calculated based on the change in absorbance:

% Inhibition = 100 - (ΔAbs test/ΔAbs control) x 100.

4.9. Receptor targeting refinement

Four protein structures relevant to neuroprotection and neuroinflammation of monoamine oxidase-2 (MAO-2) (PDB: 2v5z), murine P-glycoprotein (P-gp) (PDB: 3g60), Tau protein kinase 1 (GSK-3β) (PDB: 1j1b), and human CD14 (PDB: 4glp) were sourced from the Protein Data Bank (https://www.rcsb.org/, accessed January 11, 2024) for structure-based virtual screening. The protein structures were prepared for docking by removing co-crystallized commpound, selecting relevant water molecules and cofactors, and energy

minimization. Prior to docking, all inhibitors and water molecules were eliminated from the structures, atomic and bond anomalies were corrected using AutoDockTools in ChimeraX software (v. 1.6.1), and missing hydrogen atoms were added. These optimized PDB files were then used for subsequent docking simulations.

4.10. Plant-derived molecules preparation

Guided by literature reports of anti-inflammatory and antioxidant activity in PubMed database (accessed December 25, 2023), we aimed to explore the neuroprotective and neuroinflammatory effects of specific phytochemicals from *R. officinalis*, *S. officinalis*, and *C. verum* in the context of AD. The targeted plant-derived molecules were retrieved from PubChem-NCBI database as a structure data file (SDF) (https://pubchem.ncbi.nlm.nih.gov/, accessed January 10, 2024). Selected compounds (Supplementary Information Table S1, S2, S3, S4) from diverse spices underwent structural optimization prior to docking analyses. Using Avogadro software (v. 1.2.0), 3D structures were optimized with Molecular Force Field (MMFF), a conjugate gradient algorithm, and 1000 steps. Minimization continued until reaching a convergence criterion of 10^{-6}. Optimized structures were then saved in MOL2 format.

4.11. Molecular docking

Molecular docking simulations of selected commpounds with macromolecular receptors were performed using the CB-Dock2 web server (https://cadd.labshare.cn/cb-dock2/, accessed January 13, 2024). This platform combines cavity detection, docking, and template-based refinement to predict compound-receptor binding modes and energies. Default parameters were employed, generating potential binding poses for each compound within identified cavities. The highest-scoring pose for each compound, indicating the most stable conformation for binding, was selected for further analysis. CB-Dock2 provided comprehensive results for these poses, including binding energies, interaction diagrams, and detailed descriptions of compound-protein interactions. The top binding poses were assessed based on their binding affinities and visualized using Discovery Studio Visualizer (v. 21.1.0.20298) and UCSF Chimera X. Both 2D and 3D representations of the plant-derived molecules-receptor interactions were generated.

4.12. Statistical analysis

Statistical analysis was performed using (GraphPad Prism 5) and data presentation (mean ± SEM) followed standard conventions.

5. Conclusions

This study explored the potential of medicinal plants, namely rosemary, sage, and cinnamon, in the treatment of Alzheimer's disease (AD). Using a multi-pronged approach, we investigated the plants' bioactivities through *in vitro* assays and molecular docking simulations. Our findings suggest that these plants possess multifaceted properties that target various hallmarks of AD, including acetylcholinesterase inhibition, neuroprotection, anti-amyloidogenic effects, and modulation of neuroinflammation.

Overall, this study highlights the potential of a multi-target, multi-plant approach for AD intervention. While the docking results indicate that these compounds can potentially bind to the target proteins, they have not been experimentally validated for their binding affinities or biological activity. By harnessing the synergistic effects of various bioactive compounds, these medicinal plants might offer a holistic strategy for combating the devastating effects of AD. Further research is warranted to explore the therapeutic efficacy of these plants *in vivo* and their potential to translate into clinical applications.

Funding statement

Not applicable.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Data availability statement

Data are contained within the article and the supplementary Materials.

Disclaimer/Publisher's note

The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of Heliyon and/or the editor(s). Heliyon and/or the editor(s) disclaim responsibility for any injury to people or property resulting

from any ideas, methods, instructions, or products referred to in the content.

CRediT authorship contribution statement

Intisar E. Mohamed: Writing – original draft, Resources, Methodology, Conceptualization. **Elbadri E. Osman:** Writing – review & editing, Project administration, Formal analysis, Data curation. **Ahmed Saeed:** Writing – review & editing, Resources, Methodology, Investigation. **Long Chiau Ming:** Writing – original draft, Visualization, Validation, Software, Resources. **Khang Wen Goh:** Writing – original draft, Validation, Project administration, Methodology. **Pakhrur Razi:** Writing – review & editing, Visualization, Resources, Methodology. **Amar Daud Iskandar Abdullah:** Writing – review & editing, Validation, Software. **Mahmoud Dahab:** Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Conceptualization, Software, Resources, Data curation, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors want to thank the Faculty of Pure and Applied Sciences, International University of Africa, Sudan, Medicinal and Aromatic Plants and Traditional Medicine Research Institute, National Centre for Research, Sudan, and Department of Medical Sciences, School of Medical and Life Sciences, Sunway University, Malaysia for their valuable technical support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35943.

References

[1] W. Bai, P. Chen, H. Cai, Q. Zhang, Z. Su, T. Cheung, et al., Worldwide prevalence of mild cognitive impairment among community dwellers aged 50 years and older: a meta-analysis and systematic review of epidemiology studies, Age Ageing 51 (2022) afac173.
[2] D. Kaur, T. Behl, A. Sehgal, S. Singh, N. Sharma, V.N. Badavath, et al., Unravelling the potential neuroprotective facets of erythropoietin for the treatment of Alzheimer's disease, Metab. Brain Dis. 37 (2021) 1–16.
[3] Y.Y. Fathy, L.E. Jonkman, J.J. Bol, E. Timmermans, A.J. Jonker, A.J.M. Rozemuller, et al., Axonal degeneration in the anterior insular cortex is associated with Alzheimer's Co-pathology in Parkinson's disease and dementia with lewy bodies, Transl. Neurodegener. 11 (2022) 52.
[4] K. Sharma, Cholinesterase inhibitors as Alzheimer's therapeutics (Review), Mol. Med. Rep. 20 (2019) 1479–1487, https://doi.org/10.3892/mmr.2019.10374. Epub 2019 Jun 11. PMID: 31257471; PMCID: PMC6625431.
[5] M.M. Ibrahim, M.T. Gabr, Multitarget therapeutic strategies for Alzheimer's disease, Neural Regen Res 14 (2019) 437–440.
[6] P. Mcgeer, E. Mcgeer, J. Rogers, J. Sibley, Anti-inflammatory Drugs and Alzheimer Disease, vol. 335, Orig Publ, 1990, p. 1037.
[7] A.C. Cuello, Early and late CNS inflammation in Alzheimer's disease: two extremes of a continuum? Trends Pharmacol. Sci. 38 (2017) 956–966.
[8] L. Bäckman, S. Jones, A.K. Berger, E.J. Laukka, B.J. Small, Multiple cognitive deficits during the transition to Alzheimer's disease, Int. J. Intern. Med. 256 (2004) 195–204.
[9] S.A. Sehgal, M.A. Hammad, R.A. Tahir, H.N. Akram, F. Ahmad, Current therapeutic molecules and targets in neurodegenerative diseases based on in silico drug design, Curr. Neuropharmacol. 16 (2018) 649–663.
[10] C. Ferrari, S. Sorbi, The complexity of Alzheimer's disease: an evolving puzzle, Physiol. Rev. 101 (2021) 1047–1081.
[11] M.B. Čolović, D.Z. Krstić, T.D. Lazarević-Pašti, A.M. Bondžić, V.M. Vasić, Acetylcholinesterase inhibitors: pharmacology and toxicology, Curr. Neuropharmacol. 11 (2013) 315–335.
[12] M.B. Abubakar, K.O. Sanusi, A. Ugusman, W. Mohamed, H. Kamal, N.H. Ibrahim, C.S. Khoo, J. Kumar, Alzheimer's disease: an update and insights into pathophysiology, Front. Aging Neurosci. 14 (2022) 742408.
[13] M. Verma, B.N. Lizama, C.T. Chu, Excitotoxicity, calcium and mitochondria: a triad in synaptic neurodegeneration, Transl. Neurodegener. 11 (2022) 3.
[14] H.P. Wang, H.Y. Wu, Effect of Xiaoyao Powder on the ethology, morphology, and activities of neurotransmitters of Alzheimer's disease model mice, Chin. J. Integr. Tradit. West. Med. 34 (2014) 471–474.
[15] M.H. Mahnashi, O.M. Alshehri, Isolation, in vitro and in silico anti-alzheimer and anti-inflammatory studies on phytosteroids from aerial parts of Fragaria× ananassa, Duch Biomol. 12 (2022) 1430.
[16] P. Riederer, W. Danielczyk, E. Grunblatt, Monoamine oxidase-B inhibition in Alzheimer's disease, Neurotoxicology 25 (2004) 271–277.
[17] T. Lashley, J.M. Schott, P. Weston, C.E. Murray, H. Wellington, A. Keshavan, H. Zetterberg, Molecular biomarkers of Alzheimer's disease: progress and prospects, Model Mech 8 (2018) 11.
[18] M.A. DeTure, D.W. Dickson, The neuropathological diagnosis of Alzheimer's disease, Mol. Neurodegener. 14 (2019) 32.
[19] J.S. Lin, Brain structures and mechanisms involved in the control of cortical activation and wakefulness, with emphasis on the posterior hypothalamus and histaminergic neurons, Sleep Med. Rev. 4 (2000) 471–503.
[20] N.B. Chauhan, Effect of aged garlic extract on APP processing and tau phosphorylation in Alzheimer's transgenic model Tg2576, Ethnopharmacol 108 (2006) 385–394.
[21] K. Santacruz, J. Lewis, T. Spires, J. Paulson, L. Kotilinek, M. Ingelsson, et al., Tau suppression in a neurodegenerative mouse model improves memory function, Science. 309 (2005) 476–481.
[22] E.D. Roberson, K. Scearce-Levie, J.J. Palop, F. Yan, I.H. Cheng, T. Wu, et al., Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model, Science. 316 (2007) 750–754.
[23] I. Zanoni, F. Granucci, Role of CD14 in host protection against infections and in metabolism regulation, Front. Cell. Infect. Microbiol. 24 (2013) 32.

[24] R. Zhang, R.G. Miller, C. Madison, X. Jin, R. Honrada, W. Harris, et al., Systemic immune system alterations in early stages of Alzheimer's disease, J. Neuroimmunol. 256 (2013) 38–42.
[25] P. Venkatraman, Specificity in the interaction of natural products with their target proteins–a biochemical and structural insight, Mini Rev. Med. Chem. 10 (2010) 540–549.
[26] A. Das, G. Shanker, C. Nath, R. Pal, S. Singh, H.A. Singh, Comparative study in rodents of standardized extracts of Bacopa monniera and Ginkgo biloba: anticholinesterase and cognitive enhancing activities, Pharmacol. Biochem. Behav. 73 (2002) 893–900.
[27] N. Singh, B. Pandey, P. Verma, An overview of phytotherapeutic approach in prevention and treatment of Alzheimer's syndrome & dementia, Int. J. Pharmaceut. Sci. Drug Res. 3 (2011) 162–172.
[28] C.S. Chanotiya, A. Yadav, Enantioenriched (3S)-(+)-Linalool in the Leaf Oil of Cinnamomum tamala Nees et Eberm. from Kumaon, J. Essent. Oil Res. 22 (6) (2010) 593–596.
[29] S. Akhondzadeh, M. Noroozian, M. Mohammadi, S. Ohadinia, A.H. Jamshidi, M. Khani, Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial, J. Clin. Pharm. Therapeut. 28 (2003) 53–59.
[30] A. Ferreira, C. Proenca, M. Serralheiro, M. Araujo, The in vitro screening for acetyl cholinesterase inhibition and antioxidant activity of medicinal plants from Portugal, J. Ethnopharmacol. 108 (2006) 31–37.
[31] T. Bakirel, U. Bakirel, O.U. Keleş, S.G. Ulgen, H. Yardibi, In vivo assessment of antidiabetic and antioxidant activities of rosemary (Rosmarinus officinalis) in alloxan-diabetic rabbits, J. Ethnopharmacol. 28 (2008) 64–73.
[32] D.O. Kennedy, A.B. Scholey, The psychopharmacology of European herbs with cognition-enhancing properties, Curr. Pharmaceut. Des. 12 (2006) 4613–4623.
[33] S. Habtemariam, Natural products in Alzheimer's disease therapy: would old therapeutic approaches fix the broken promise of modern medicines? Molecules 24 (2019) 1519.
[34] H. Yu, L. Yao, H. Zhou, S. Qu, X. Zeng, D. Zhou, Y. Zhou, X. Li, Z. Liu, Neuroprotection against Aβ25-35-induced apoptosis by Salvia miltiorrhiza extract in SH-SY5Y cells, Neurochem. Int. 75 (2014) 89–95.
[35] T. Iuvone, D. De Filippis, G. Esposito, A. D'Amico, A.A. Izzo, The spice sage and its active ingredient rosmarinic acid protect PC12 cells from amyloid-beta peptide-induced neurotoxicity, J. Pharmacol. Exp. Therapeut. 317 (2006) 1143–1149.
[36] A. Espargaró, T. Ginex, M.D. Vadell, M.A. Busquets, J. Estelrich, D. Muñoz-Torrero, F.J. Luque, R. Sabate, Combined in vitro cell-based/in silico screening of naturally occurring flavonoids and phenolic compounds as potential anti-Alzheimer drugs, J. Nat. Prod. 80 (2017) 278–289.
[37] N. Perry, C. Bollen, E. Perry, C. Ballard, Salvia for dementia therapy: review of pharmacologyical activity and pilot tolerability clinical trial, Pharmacol. Biochem. Behav. 75 (2003) 651–659.
[38] M. Eidi, A. Eidi, M. Bahar, Effects of Salvia officinalis L. (sage) leaves on memory retention and its interaction with the cholinergic system in rats, Nutrition 22 (2006) 321–326.
[39] N. Tildesley, D. Kennedy, E. Perry, C. Ballard, K. Wesnes, A. Scholey, Positive modulation of mood and cognitive performance following administration of acute doses of Salvia lavandulaefolia essential oil to healthy young volunteers, Physiol. Behav. 83 (2005) 699–709.
[40] D. Hernandez-Saavedra, I.F. Perez-Ramirez, M. Ramos-Gomez, S. Mendoza-Diaz, G. Loarca-Pina, Phytochemical characterization and effect of Calendula officinalis, Hypericum perforatum, and Salvia officinalis infusions on obesity associated cardiovascular risk, Med. Chem. Res. 25 (2016) 163–172.
[41] S. Chowdhury, S. Kumar, Alpha-terpinyl acetate: a natural monoterpenoid from Elettaria cardamomum as multi-target directed ligand in Alzheimer's disease, J. Funct.Foods 68 (2020) 103892.
[42] X. Yu, J. Wang, J. Zhang, L. Wang, Z. Wang, F. Xiong, Physicochemical properties of starch isolated from bracken (Pteridium aquilinim) rhizome, J. Food Sci. 80 (2015) 2717–2724.
[43] C.C. Guimarães, D.D. Oliveira, M. Valdevite, A.L. Saltoratto, S.I. Pereira, França, C. Sde, et al., The glycosylated flavonoids vitexin, isovitexin, and quercetrin isolated from Serjania erecta Radlk (Sapindaceae) leaves protect PC12 cells against amyloid-β25-35 peptide-induced toxicity, Food Chem. Toxicol. 86 (2015) 88–94.
[44] G.K. Jayaprakasha, L.J. Rao, Chemistry, biogenesis, and biological activities of Cinnamomum zeylanicum, Crit. Rev. Food Sci. Nutr. 51 (2011) 547–562.
[45] P.V. Rao, S.H. Gan, Cinnamon: a multifaceted medicinal plant, Evid Based Complement Altern Med 2014 (2014) 642942.
[46] do NascimentoL. Diniz, A.A.B. Moraes, K.S.D. Costa, GalúcioJ.M. Pereira, P.S. Taube, C.M.L. Costa, et al., Bioactive natural compounds and antioxidant activity of essential oils from spice plants: new findings and potential applications, Biomolecules 10 (2020) 988.
[47] M. Ozarowski, P.L. Mikolajczak, A. Bogacz, A. Gryszczynska, M. Kujawska, J.T. Jodynis-Liebert, et al., Rosmarinus officinalis L. leaf extract improves memory impairment and affects acetylcholinesterase and butyrylcholinesterase activities in rat brain, Fitoterapia 91 (2013) 261–271.
[48] L.M. de Macedo, É.M.D. Santos, L. Militão, L.L. Tundisi, J.A. Ataide, E.B. Souto, P.G. Rosemary Mazzola, Rosmarinus officinalis L., syn Salvia rosmarinus spenn.) and its topical applications: a review, Plants Basel. 21 (2020) 651.
[49] P. Russo, A. Frustaci, A. Del Bufalo, M. Fini, A. Cesario, From traditional European medicine to discovery of new drug candidates for the treatment of dementia and Alzheimer's disease: acetylcholinesterase inhibitors, Curr. Med. Chem. 20 (2013) 976–983.
[50] D.O. Kennedy, S. Pace, C. Haskell, E.J. Okello, A. Milne, A.B. Scholey, Effects of cholinesterase inhibiting sage (Salvia officinalis) on mood, anxiety and performance on a psychological stressor battery, Neuropsychopharmacology 31 (2006) 845–852.
[51] A.C. Figueiredo, Biological properties of essential oils and volatiles: sources of variability, Nat Volatiles Essent Oils 4 (2017) 1–13.
[52] D. Chandra, P. Chaubey, A. Parki, O. Prakash, R. Kumar, A. Pant, Study on chemical diversity among plant parts of Zingiber chrysanthum and their antioxidant assay, J Biol Act Prod Nat 7 (2017) 107–117.
[53] N.T. Mir, U. Saleem, F. Anwar, B. Ahmad, I. Ullah, S. Hira, et al., Lawsonia Inermis markedly improves cognitive functions in animal models and modulate oxidative stress markers in the brain, Medicina (Mex) 55 (2019) 192.
[54] M. Ayaz, A. Sadiql, M. Junaid, F. Ullah, M. Ovais, I. Ullah, Flavonoids as prospective neuroprotectants and their therapeutic propensity in aging associated neurological disorders, Front. Aging Neurosci. 11 (2019) 155.
[55] C. Mountaki, I. Dafnis, E.A. Panagopoulou, P.B. Vasilakopoulou, M. Karvelas, A. Chiou, et al., Mechanistic insight into the capacity of natural polar phenolic compounds to abolish Alzheimer's disease-associated pathogenic effects of apoE4 forms, Free Radic. Biol. Med. 171 (2021) 284–301.
[56] M.H. Mahnashi, B.A. Alyami, Y.S. Alqahtani, A.O. Alqarni, M.S. Jan, M. Ayaz, et al., Neuroprotective potentials of selected natural edible oils using enzyme inhibitory, kinetic and simulation approaches, BMC Complement Med Ther 21 (2021) 248.
[57] H. Manev, H. Chen, S. Dzitoyeva, R. Manev, Cyclooxygenases and 5-lipoxygenase in Alzheimer's disease, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35 (2011) 315–319.
[58] Q. Hou, J. Huang, X. Xiong, Y. Guo, B. Zhang, Role of nutrient-sensing receptor GPRC6A in regulating colonic group 3 innate lymphoid cells and inflamed mucosal healing, J Crohn's Colitis 16 (2022) 1293–1305.
[59] M. Matsuyama, T. Nakatani, T. Hase, Y. Kawahito, H. Sano, M. Kawamura, R. Yoshimura, The expression of cyclooxygenases and lipoxygenases in renal ischemia-reperfusion injury, Transplant. Proc. 36 (2004) 1939–1942.
[60] M.H. Mahnashi, B.A. Alyami, Y.S. Alqahtani, A.O. Alqarni, M.S. Jan, F. Hussain, et al., Antioxidant molecules isolated from edible prostrate knotweed: rational derivatization to produce more potent molecules, Oxid. Med. Cell. Longev. 2022 (2022) 3127480.
[61] M.H. Mahnashi, M.A. Alshahrani, M.H. Nahari, S.S.U. Hassan, M.S. Jan, M. Ayaz, et al., In-vitro, in-vivo, molecular docking and ADMET studies of 2-substituted 3,7-dihydroxy-4H-chromen-4-one for oxidative stress, inflammation and alzheimer's disease, Metabolites 12 (2022) 1055.
[62] S.M. Shah, A. Sadiq, S.M. Shah, F. Ullah, Antioxidant, total phenolic contents and antinociceptive potential of Teucrium stocksianum methanolic extract in different animal models, BMC Compl. Alternative Med. 14 (2014) 181.
[63] J.S. Choi, M.N. Islam, M.Y. Ali, Y.M. Kim, H.J. Park, H.S. Sohn, H.A. Jung, The effects of C-glycosylation of luteolin on its antioxidant, anti-Alzheimer's disease, anti-diabetic, and anti-inflammatory activities, Arch Pharm. Res. (Seoul) 37 (2014) 1354–1363.
[64] A. Rauk, The chemistry of alzheimer's disease, Chem. Soc. Rev. 38 (2009) 2698–2715.

[65] J.R. Cirrito, R. Deane, A.M. Fagan, M.L. Spinner, M. Parsadanian, M.B. Finn, P-glycoprotein deficiency at the blood-brain barrier increases amyloid-β deposition in an Alzheimer disease mouse model, J. Clin. Invest. 115 (2005) 3285–3290.
[66] A.M. Hartz, D.S. Miller, B. Bauer, Restoring blood-brain barrier p-glycoprotein reduces brain amyloid-β in a mouse model of Alzheimer's disease, Mol. Pharmacol. 77 (2010) 715–723.
[67] S. Vogelgesang, I. Cascorbi, E. Schroeder, J. Pahnke, H.K. Kroemer, W. Siegmund, Deposition of Alzheimer's beta-amyloid is inversely correlated with P-glycoprotein expression in the brains of elderly non-demented humans, Pharmacogenetics 12 (2002) 535–541.
[68] F.C. Lam, R. Liu, P. Lu, A.B. Shapiro, J.M. Renoir, F.J. Sharom, Beta-Amyloid efflux mediated by p-glycoprotein, J. Neurochem. 76 (2001) 1121–1128.
[69] Alejandro R. Roda, Gabriel Serra-Mir, Laia Montoliu-Gaya, Lidia Tiessler, Villegas, Sandra PhD, Amyloid-beta peptide and tau protein crosstalk in Alzheimer's disease, Neural Regen. Res. 17 (2022) 1666–1674.
[70] L.M. Ittner, J. Götz, Amyloid-β and tau—a toxic pas de deux in Alzheimer's disease, Nat. Rev. Neurosci. 12 (2011) 67–72.
[71] P. Thériault, A. ElAli, S. Rivest, The dynamics of monocytes and microglia in Alzheimer's disease, Alzheimer's Res. Ther. 7 (2015) 41.
[72] T. Malm, M. Koistinaho, A. Muona, J. Magga, J. Koistinaho, The role and therapeutic potential of monocytic cells in Alzheimer's disease, Glia 58 (2010) 889–900.
[73] M. Saresella, I. Marventano, E. Calabrese, F. Piancone, V. Rainone, A. Gatti, et al., A complex proinflammatory role for peripheral monocytes in alzheimer's disease, J. Alzheim. Dis. 38 (2014) 403–413.
[74] E.G. Reed-Geaghan, Q.W. Reed, P.E. Cramer, G.E. Landreth, Deletion of CD14 attenuates alzheimer's disease pathology by influencing the brain's inflammatory milieu, J. Neurosci. 30 (2010) 15369–15373.
[75] K. Wolfe, X. Wu, R.H. Liu, Antioxidant activity of apple peels, J. Agric. Food Chem. 51 (2003) 609–614.
[76] Chun OK. Do, Y.J. Kim, H.Y. Moon, C.Y. Lee, Quantification of polyphenolics and their antioxidant capacity in fresh plums, J. Agric. Food Chem. 516 (2003) 509–615.
[77] G.L. Ellman, D.K. Courtney, V. Andreas, R.M. Featherstone, A new and rapid colorimetric determination of acetylcholinesterase activity, Biochem. Pharmacol. 7 (1961) 88–95.