In silico studies on olive oil polyphenolic natural products to identify neuroprotective lead compounds beneficial in the treatment of Alzheimer's disease

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Abstract:

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders. Nearly 44 million people across the globe are living with it. Despite tremendous progress in understanding the pathophysiology of AD, only a few drugs have been approved by the US FDA to date that too provides only symptomatic relief. The current computational study was designed to investigate the potential of phenolic metabolites present in olive oil to identify lead molecule(s) that could help in fighting against AD. A total of 21 phenolic compounds from olive oil were selected, and their simplified molecular input line entry system (SMILES) notations were generated using Chemsketch. Cheminformatics software such as, *Molinspiration* to predict the bioactivity scores and physicochemical properties, prediction of activity spectra for substances (*PASS*) software to predict the acetylcholinesterase (AChE) inhibition, neuroprotective, antioxidant, and anti-inflammatory activities; *Osiris* for pharmacokinetic profile and toxicity; and *Autodock Vina* for molecular docking were used for *in silico* studies. The results were compared with four clinically used AD drugs. All the tested compounds were predicted to possess anti-inflammatory activity (Pa score= 0.357-0.831) and antioxidant activity (Pa score = 0.320-0.903). Luteolin and elenolic acid were identified as the most promising bioactive polyphenolic compounds of olive acting at multiple targets in AD pathogenesis. Luteolin showed better binding to both β-secretase-1 (BACE) and AChE enzymes in comparison to elenolic acid. It is concluded that luteolin and elenolic acid hold promise for the development of anti-Alzheimer's therapy.

Keywords: Alzheimer's disease; Antioxidant; AChE; BACE-1; Neuroprotection; Phenolic compounds.

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1. Introduction:

Dementia is a set of symptoms that are linked to a loss of memory or other mental abilities, limiting a person's capacity to carry out daily tasks. (Gupta et al. 2020). Memory, cognitive, and behavioral impairments are common symptoms of Alzheimer's disease (AD). This neurodegenerative disorder leads to multiple brain functioning defects which are both irreversible and progressive in nature that gradually erodes memory and thinking abilities, as well as the capacity to do even the routine tasks (Kumar et al. 2013). This brain disorder affects approximately 44 million people worldwide which includes mostly elderly population. In the United States of America, AD is the sixth leading cause of death, with over five million people living with it. In Oman, around 3.86% of total deaths are due to dementia, with a prevalence increasing drastically (Alzadjali et al. 2020). It has been predicted by world health organization (WHO) that by 2050, over 135 million people worldwide will have dementia, tripling the number of people who have it now (Association Alzheimer's Society (ASA) 2017). AD usually starts after the age of 65, but it may start at an earlier age, and in this case, it is called “young Alzheimer's” or early- onset AD.

AD was first described by Dr. Alois Alzheimer and since then scientific community has tried to unwind the complexities associated with its diagnosis and treatment. Unfortunately, due to the complexity of disease, very few drugs have been approved by the US FDA. The currently approved anti-AD medications include; donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Razadyne®), aducanumab (Aduhelm®) and memantine (Namenda®) (Figure 1) (Athar et al. 2021). These drugs do not halt the progression of AD and provide only symptomatic treatment. In addition to this, their use is associated with side effects such as vertigo, emesis, appetite loss, increased bowel motions, headache, constipation, and disorientation, etc. Additionally, they only aid in masking the symptoms of AD instead of treating the underlying disease or delay its progression (Gupta et al. 2020; Athar et al. 2021). Thus, to overcome the dark side of AD therapy, it leads us to think of new potential treatments by utilizing the phenolic compounds present in olive oil. We have selected this source based on previous literature data, its historical medical use, in addition to being mentioned in Islamic medicine for their health benefits (Marwat et al. 2009; Saad 2015).

Figure 1. Chemical structures of anti-Alzheimer's drugs used clinically.

Previous research studies have shown that phenolic constituents of olive exhibit great anti-Alzheimer properties with additional anti-inflammatory, antioxidant, and monoamine oxidase (MAO) inhibitory properties (Abdelrahman et al. 2019; Delphine 2017). A meta-analysis study suggested that extra virgin oil could be beneficial in protecting against AD (Román et al. 2019). Abuznait and co-workers demonstrated that oleocanthal, a phenolic component of extra-virgin olive oil, may improve β-amyloid (Aβ) clearance from brain by up-regulating P-glycoprotein (P-gp) and lipoprotein receptor- related protein-1 (LRP1) in *in vivo* and *in vitro* studies (Abuznait et al. 2013). Results of an *in vitro* study have shown that three naturally occurring phenolic compounds found in olives *viz.*, hydroxytyrosol, oleuropein, and oleuropein aglycone are capable in preventing *tau* fibrillization (Daccache et al. 2011). Furthermore, oleuropein has been shown to form non-covalent complex with the Aβ peptide and was accounted for its neuroprotective activity (Omar 2010). Recently, it was shown that oleuropein and other compounds (tyrosol, hydroxytyrosol and oleuropin agylcone) from olive oil inhibit human islet amyloid polypeptide aggregation and cytotoxicity thereby protecting the nerve cells (Chaari 2020).

The current study employed a computer-aided drug design (CADD) approach to identify potential phenolic metabolites present in olive oil as drug candidate(s) for AD therapy.

2. Materials and Methods:

2.1. *Prediction of Molecular Properties, Biological Activities and Toxicity of Phenolic Compounds*

A list of phenolic chemical constituents naturally occurring in olive oil was prepared by a comprehensive literature review using various databases. A total of 21 naturally occurring phenolic compounds in olive oil were selected for computational studies (Figure 2). Chem Draw7 was used to draw 2D chemical structures and to generate simplified molecular input line entry system (SMILES) notation. An online *Molinspiration software* was used to predict bioactivity scores and molecular properties of phenolic compounds (Sharma and Kaur 2022).

A prediction of activity spectra for substances *(PASS) software* was utilized to predict the probability of exhibiting neuroprotective activity. Probability (Pa) score of >0.5 for inhibition of MAO enzymes, anti-inflammatory, antioxidant, acute neurologic disorders treatment, and antineurotic activity, etc., were recorded. The toxicity of compounds was predicted with the

help of *Osiris software*. The *Osiris* prediction results are valued and color coded. Red color indicated toxicity while a compound with drug-like properties is shown with green color.

2.2. Molecular Docking Studies

2.2.1. Preparation of Ligands

Luteolin and elenolic acid were selected for molecular docking studies. Chemical structures of both the ligands in .sdf files were downloaded from the Zinc database and then were subjected to CHARMM energy minimization protocol using discovery studio (DS) before saving as .pdb files. The crystal *Auto Dock Vina 1.1.2* was employed to perform molecular docking while the DS was used for the visualization of poses.

2.2.2 Preparation of Protein (Enzyme) Structures

3D protein structures of *Tc*Acetylcholinesterase (*Tc*AChE) (PDB ID:1w6r) and human beta-secretase-1 (*h*BACE; PDB ID:2qp8) were acquired from the protein data bank (Figure 3). As per the standard protocol, both the crystalline protein structures were cleaned for water and hetero atoms while missing hydrogen atoms were placed on the structures and then energy minimized structures were saved as .pdb files using DS.

2.2.3 Molecular Docking Analysis for Binding Energy and Conformation Poses

PyRx Autodock Vina wizard was used for docking of the prepared ligands onto the protein targets as per the standard experimental protocol (Ali et al. 2016). Binding energy corresponding to the best conformation poses inside the binding pocket of the receptors was noted down.

Figure 2. Chemical structures of 21 phenolic compounds naturally occurring in olive oil.

Figure 3. 3D Protein structures of (A) AChE; & (B) BACE-1 retrieved from the protein data bank.

2. Results and Discussion:

Olive oil is an important part of Mediterranean diet. The low prevalence of AD and other neurodegenerative diseases in this part of the world could be attributed to the consumption of olive oil which is rich in polyphenolic and other secondary plant metabolites (Delphine 2017). We hypothesized that certain polyphenolic compounds occurring naturally in olive oil possess significant biological activities and can be used to develop disease-modifying drugs to treat AD. We further postulated that one or more of these polyphenolics may act at multiple targets to inhibit the activities of MAO-B, BACE, and cholinesterase enzymes, in addition to reducing neuro-inflammation and the oxidative stress which could slow down or curb the progression of AD (Ennacerie et al. 2019). Hence, this computational study was undertaken with an aim to identify the most promising therapeutic agent that could be used to treat AD. Molecular properties, biological activities and toxicity studies were carried out with the help of online computational software to identify one or two potential polyphenolic compounds for molecular docking from the selected library of 21 compounds.

In the first step, *molinspiration software* was used to predict the molecular properties of the phytochemicals of olive oil. Physicochemical properties help in selection of orally active compounds based on Lipinski's rule of 5. Lipinski's rule of 5 is a useful guideline for predicting the oral bioavailability of small-molecules and it states that orally bioactive molecules should have low molecular weight (<500 daltons), lipophilicity (logP <5), no more than 5 OH, NH (hydrogen bond donor) and $\leq$ 10 O and N atoms combined (hydrogen bond acceptors). Any violations in this rule may affect oral bioavailability (Lipinski 2004). The results obtained from the *molinspiration software* are presented in Table 1. Chemical compounds namely, 5-caffeoylquinic acid (1 violation for hydrogen bond donor), hesperidin (3 violations for hydrogen bond donor, hydrogen bond acceptor and molecular weight), homoorientin (1 violation for hydrogen bond donor) and oleuroside (3 violations for hydrogen bond donor, hydrogen bond acceptor and molecular weight) are noted to violate the Lipinski's rule and thus will not be orally active. Hence, these four compounds were excluded from further studies. Rest of the polyphenolics were low molecular weight small molecules (molecular weight = of 138-392) similar to clinically used anti-AD drugs (molecular weight = of 165-379). Moreover, for an orally-

active anti-Alzheimer's drug must meet two more additional requirements; (i) it should have enough metabolic stability in the intestine and liver and, (ii) it should be lipophilic enough to cross the blood brain barrier (BBB) which consists of various overlapping zones contained in an anisotropic lipid layer (Borra and Kuna 2013). Polar surface area (PSA) calculated based on the structural features and partition coefficient (LogP) are the two parameters that can help in evaluation of metabolic stability in intestine and lipophilicity or ability of a molecule to penetrate through the BBB. Orally used drug molecules in brain disorders usually have LogP values between 2 to 4. On the other hand, a compound with a high logP value is expected to undergo a rapid metabolic turnover and most likely it will also suffer from poor gastrointestinal absorption because of low aqueous solubility. A highly lipophilic molecule has high chances to bind to hydrophobic proteins other than the desired target that could lead to increased toxicity. Nevertheless, as it can be seen from the data given in table 1, some compounds have a LogP value lower than the range of 2-4 such as galantamine (1.54), hence we, also considered phenolic compounds around 1.5 LogP value for short listing to the next step. The *molinspiration* predicted milogP values (-0.55-2.46) of the polyphenolic compounds was lower than the four clinically used AD drugs (1.54-4.10). The excluded polyphenolics were having miLogP values below zero indicating them to be highly water soluble, highly susceptible to metabolism and unsuitable to cross the BBB. Amongst all the compounds, apigenin is predicted to have the highest LogP value (2.46) followed by luteolin (1.97), cinnamic acid (1.91), oleuropein aglycone (1.86), *o*-coumaric acid (1.67), 4-hydroxy benzoic acid (1.37), and so on. PSA values are also used to predict BBB penetrability as well as overall transportation of drug *in vivo*. Therefore, PSA is of paramount importance in early phase screening of drug libraries (Österberg and Norinder 2000). In general, drugs designed to treat neurological disorders tend to have lower PSA which is around 60–70Å^2 and usually should not exceed 120 Å^2 (Kelder et al. 1999). Therefore, compounds having desirable PSA values (50-120 Å^2) were selected for further bioactivity prediction. One compound namely ellagic acid (141.3 Å^2) was excluded as exceeds the maximum PSA value required to cross the BBB. Almost all the tested compounds were having higher PSA values than the reference compounds (26.02-41.93).

Table 1. Predicted molecular properties of olive oil polyphenolics by *molinspiration* software

Bioactivity score of the phenolic compounds was also generated by the *molinspiration*. Possible mechanism of action of the potentially drug-like phenolic compounds in terms of bioactivity scores to act as G-protein-coupled receptor (GPCR) ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor is given in Table 2.

Table 2. Predicted bioactivity scores of polyphenolic compounds and four anti-AD drugs by *molinspiration* software

GPCRs or transmembrane receptors are located on the membrane of proteins and are targeted by almost half of the existing drug molecules. These are essentially used by cells to transform extracellular signals into intracellular responses. Previous studies demonstrated that these are implicated in AD pathophysiology. GPCRs may bind to β and γ secretase enzymes which are fundamental enzymes in the formation of amyloid plaques in the brain by the breakdown process of amyloid protein precursor (APP) (Zhao et al. 2016). The data presented in table 2 indicated that galantamine (Pa score=0.93) is a GPCR ligand followed by donepezil. The predicted bioactivity score of phenolics (-0.98 to 0.05) is much lower than the reference compounds (-0.41 to 0.93). Elenolic acid (0.05), luteolin (-0.02), and apigenin (-0.07), and were identified as the most likely GPCR ligands. Furthermore, according to the widely accepted cholinergic hypothesis, low level of neurotransmitter acetylcholine (ACh) plays a role in the cognitive decline as seen in AD. Therefore, enhancing the release of ACh in the brain is one way of increasing neuronal activity and ameliorating attention and cognition. ACh release is regulated by both ligand-gated and voltage-gated ion channels (Li et al. 2018). Additionally, aggregation of Aβ protein and *tau* protein have been shown to produce chronic neuro-inflammation (Thei et al. 2018). Based on the previous literature data highlighting the importance of ion channel modulators, three phenolic compounds *viz.*, apigenin (-0.09), elenolic acid (0.33) and luteolin (-0.07) with the highest ion channel modulator activity scores were selected. Another key pathophysiological factor leading to the development of AD is the hyperphosphorylation of *tau* protein which can result in aggregation, misfolding and formation of neurofibrillary tangles (NFT). This process is regulated by specific protein

kinases such as GSK-3β, CDK5, etc (Medda et al. 2013). Apigenin (0.18) and luteolin (0.26) were noted to have the highest kinase inhibitor bioactivity.

In the next step, phenolics that were selected based on molecular properties, were subjected to prediction of activities such as MAO inhibition, anti-inflammatory activity, reduction in oxidative stress and neuroprotection by *PASS software*. We wanted to investigate the ability of olive oil phenolics to act on multiple targets involved in the pathogenesis of AD. AD lesions are distinguished by the presence of various inflammatory proteins which suggested the potential use of anti-inflammatory drugs as a possible treatment and as protective agents for AD therapy. This prompted us to consider the anti-inflammatory property exhibited by the selected polyphenolic metabolites and choose the ones with the highest activity (Zouhri et al. 2022). The biological activity spectrum of chemical compounds and clinically used anti-AD drugs predicted with the help of a *PASS software* are presented in Tables 3 and 4.

Table 3. Predicted biological activity scores of polyphenolics using *PASS software*.

Table 4. Predicted biological activity spectrum of four Anti-Alzheimer's' drugs by using *PASS software*.

Elenolic acid with a Pa score of 0.831 is expected to possess excellent anti-inflammatory activity and thus was short listed. Additionally, substantial data confirms that oxidative stress is a key factor that could led to the late-onset sporadic types of AD. A reduction in antioxidant defenses, toxicity related to Aβ, and altered metal metabolism in the brain and peripheral tissues, mitochondrial abnormalities, inadequate energy supply and inflammation may all contribute to this pro-oxidative imbalance (Chang et al. 2014). Several epidemiological studies have linked consumption of antioxidant diet or supplement such as vitamin E and *Ginkgo biloba* extract to a lower prevalence of dementia, AD and cognitive decline in elderly people (Grundman and Delaney 2002). Among the tested polyphenolic metabolites, apigenin (0.740), elenolic acid (0.903) and luteolin (0.775) are found to possess the highest Pa score for the antioxidant activity.

Cholinergic and MAO also play important functions in cognition. AD patients show a decrease level of both MAO and ACh (Tariot et al. 1987b). A double-blind, placebo-controlled interventional study evaluated the potential of administration of L-deprenyl, a selective MAO-B inhibitor, via serial treatment in AD patients. It was found that patients who took L-deprenyl had a significant decrease in total Brief Psychiatric Rating Scale (BPRS) scores. They also displayed lower measures of anxiety, depression, tension, and excitement. Clinically, the patients' conditions improved as well, with more exercise and social contact (Tariot et al. 1987a). Compounds with the highest MAO inhibition score were noted to be apigenin (0.500), luteolin (0.584) and gallic acid (0.568) (Figure 4).

Thus based on the Pa values for MAO inhibition, anti-inflammatory and antioxidant activities, apigenin, elenolic acid and luteolin were selected as multi-target directed ligands for toxicity studies. Gallic acid was excluded because it showed the lowest Pa score for three most common molecular targets of AD.

Figure 4. Chart representing the phenolic compounds with the highest Pa score for various activities

In silico toxicity of the three most promising compounds selected based on *PASS software* score and *molinspiration* was predicted using *Osiris property explorer*. This is a very crucial step in drug design it ensures the safety of compounds. *Osiris software* predicts the possible drug toxicity of the compounds based on the structural fragments. This *in silico* technique is a better alternative to animal models which are limited by time, ethical concerns, and budgetary constraints. This step helps in decreasing late-stage failures in drug design (Raies and Bajic 2016). The *Osiris* toxicity data for the three selected phenolic metabolites are shown in Table 5. As it can be seen, apigenin is potentially mutagenic and hence was excluded from molecular docking studies. Elenolic acid and luteolin were found to be safe as these are least likely to be mutagenic, tumorigenic and will have not toxicity on reproductive organs.

Table 5. *Osiris property explorer* predicted toxicity of three phenolic compounds.

Elenolic acid and luteolin, the two most potent and safest phenolic compounds, were docked onto the BACE-1 and AChE to analyze their binding energy. BACE-1 was selected for docking studies because several studies have indicated BACE inhibition as emerging molecular target to treat AD. This enzyme endoproteolyzes the large type-I membrane protein APP to free Aβ protein (Mancini et al. 2011). Both luteolin and elenolic acid showed high stability upon binding to BACE-1 (table 6). AChE has been shown to bind through its peripheral anionic site (PAS) with senile plaque components forming a stable complex. Furthermore, amyloid formations also increase the chances of altered glycosylation of AChE (Talesa 2001). Both olive oil phenolic compounds were found to bind to the active sites on AChE in a stable manner. Luteolin showed better binding affinity to AChE (-10.5 kcal/mol) than elenolic acid (-7.6 kcal/mol) and therefore will have a pronounced inhibitory effect (Table 6).

Table 6. Binding energies of the best poses of polyphenolic compounds with BACE- 1 and AChE.

Figure 5 (A-D) displays a hydrogen bond surface of luteolin and elenolic acid in the binding pocket of the ligands with the target proteins BACE-1 and AChE. The phenolics fit well in to the active pocket of the enzyme and seen to form various non-covalent interactions mainly hydrogen bond and π-π stacking with the amino residues of chain A of the receptors. Hydrogen bonding is important as it seems to affect the affinity, molecular recognition and orientation of the drug molecule in the active binding site. However, the binding affinity is influenced by hydrophobic interactions between the lipophilic surfaces of a molecule and the hydrophobic zones of the binding cavity. Binding pattern graphics (Figure 6A-B) reveals that selected polyphenolic compounds interacted with BACE-1 and formed hydrogen bonds. Luteolin formed three hydrogen bonds with BACE-1 amino acid residues *viz.*, Gly221, Thr 315 and Tyr189 while elenolic acid was able to form only one hydrogen bond with Thr76. It could be inferred that luteolin bind more strongly to inhibit BACE than elenolic acid. 2D interactions between luteolin and target enzymes are shown in Figure 6. However, elenolic acid was noted to form two π-π bonds with Phe327 and Trp81 residues of BACE-1 in comparison to one π-π bond of luteolin with Asp219. These results are in agreement with the binding energies of luteolin and elenolic acid on to the BACE-1 (Table 6). Surprisingly, luteolin showed only two hydrogen bonds with the amino acid residues of AChE (Glu196 and

Gly138) though its binding energy to AChE was higher than BACE-1. Based on the molecular docking results, it can be concluded that Luteolin inhibits both BACE-1 and AChE and thus could be a potential candidate for the further development and optimization in drug discovery.

Figure 5. Pictures illustrating hydrogen bond surface of; A: elenolic acid with AChE; B: elenolic acid with BACE-1; C: luteolin with AChE and D: luteolin with BACE-1.

Figure 6. Picture showing 2D interactions of luteolin with (A) AChE and (B) BACE-1.

3.Conclusion:

The current study investigated the potential of polyphenolic compounds present in olive oil to identify potential anti-AD agents using several cheminformatics software. A library of 21 polyphenolic phytochemicals was subjected to evaluation of molecular properties, prediction of biological activities and toxicity to identify the potent and safe drug candidates. Luteolin and elenolic acid emerged as promising lead molecules for molecular docking studies. These compounds were docked onto the BACE-1 and AChE enzymes which are key players in the pathogenesis of AD. Luteolin showed the better binding affinity to both enzymes than elenolic acid. However, *in vitro* and *in vivo* experimental studies must be carried out to corroborate the findings of this study.

Our research presents a starting point and opens up a window for further scientific exploration that may focus on investigating the chemical tailoring and modification of the final selected compounds in order to improve their structural, pharmacokinetic and biological properties. Additional modifications can also aim to improve drug distribution and in turn, boost the therapeutic outcomes and decrease side effects. The strategies to develop these compounds into new chemical entities include chemical structure alteration and/or developing vectors capable of reaching the target cells in the brain via specific recognition mechanisms. Based on the computational studies, it is suggested that luteolin and elenolic acid, the two most potent polyphenolic compounds of olive oil, act at multiple targets such as BACE, AChE, MAO, neuroinflammation and oxidative stress in AD pathogenesis and

therefore hold the promise for the further discovery and development of lead compounds for possible anti-Alzheimer's therapy.

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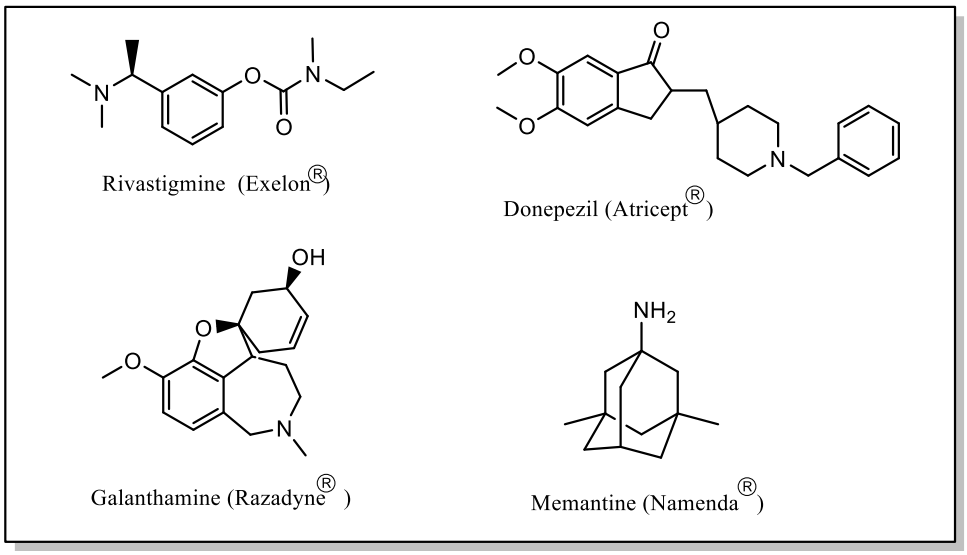

Figure 1. Chemical structures of anti-Alzheimer's drugs used clinically.

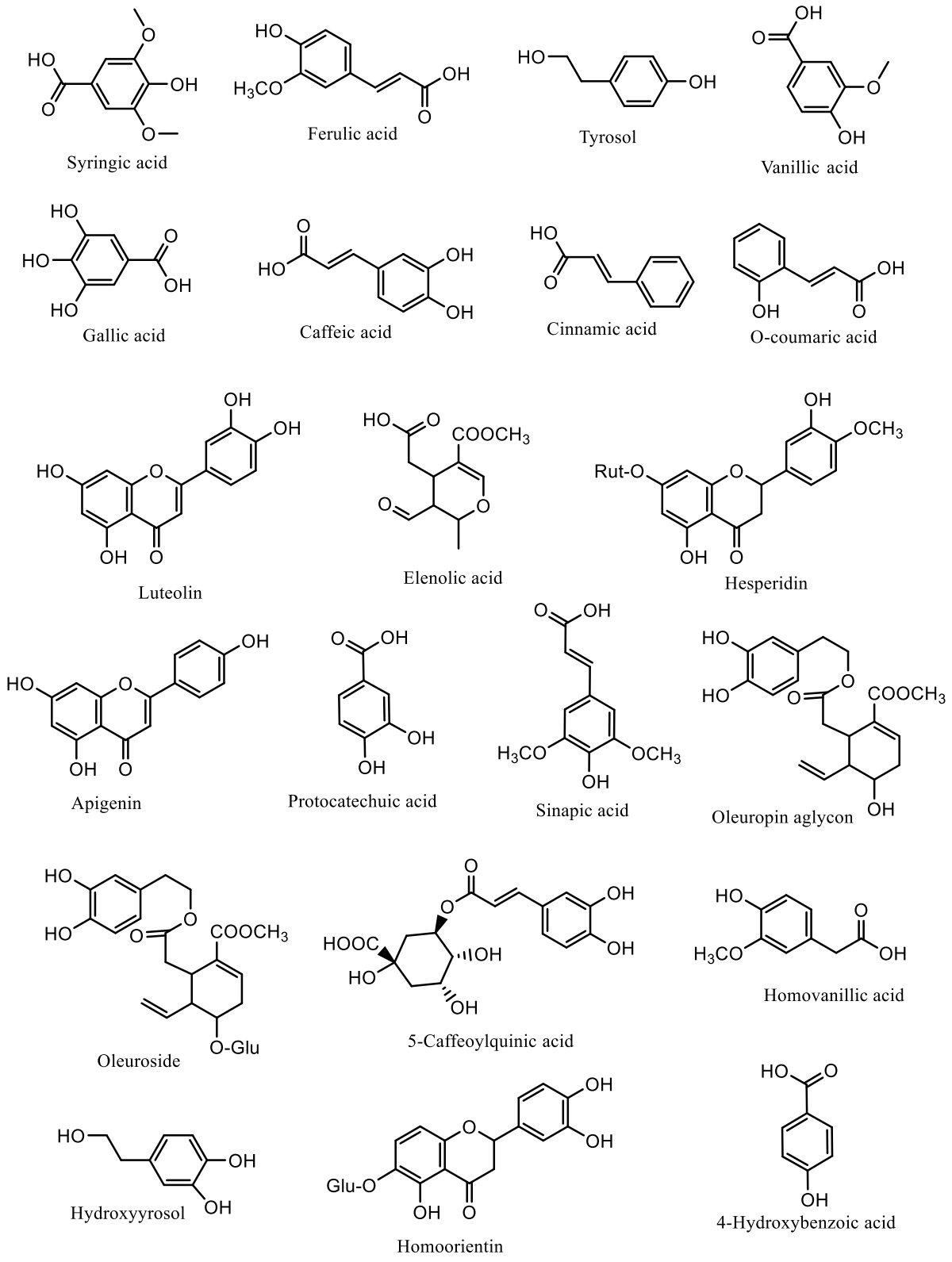

Figure 2. Chemical structures of 21 phenolic compounds naturally occurring in olive oil.

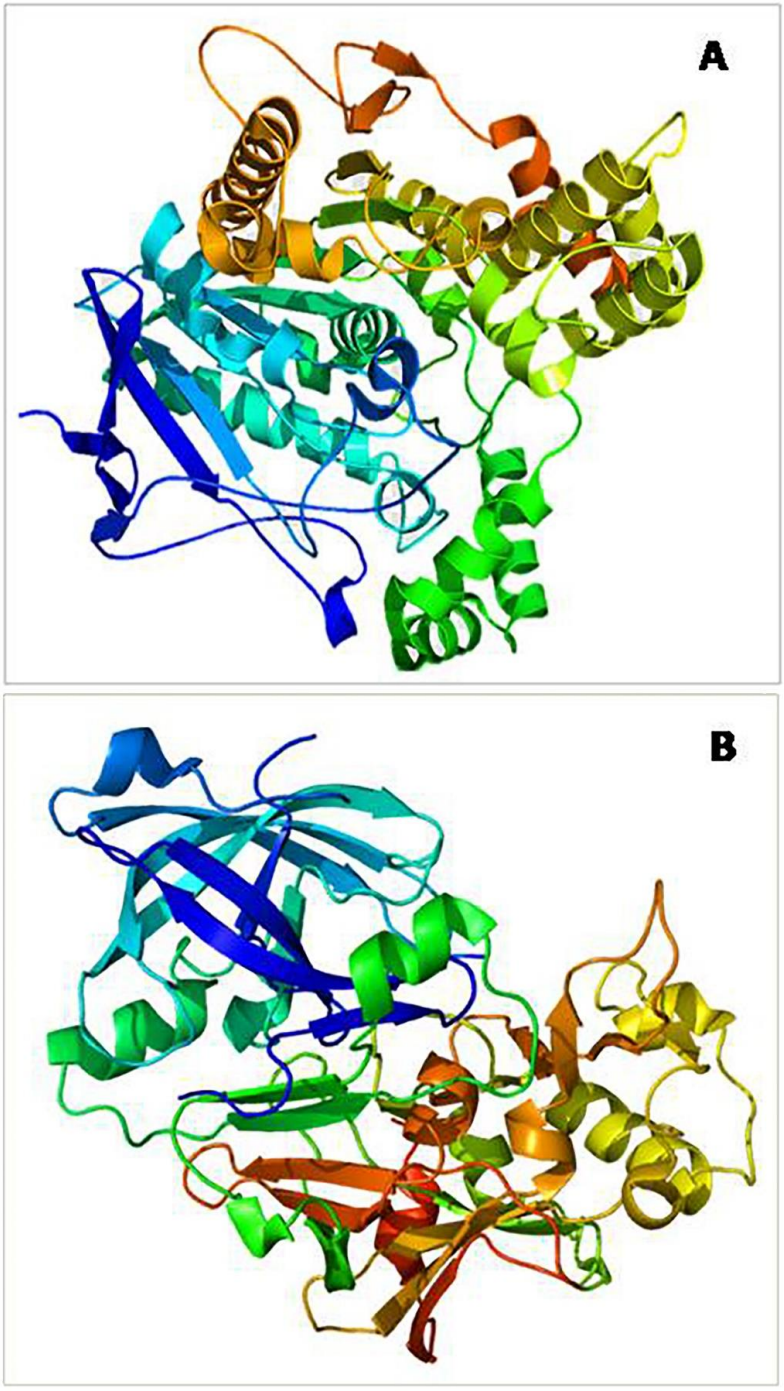

Figure 3. 3D Protein structures of (A) AChE; & (B) BACE-1 retrieved from the protein data bank.

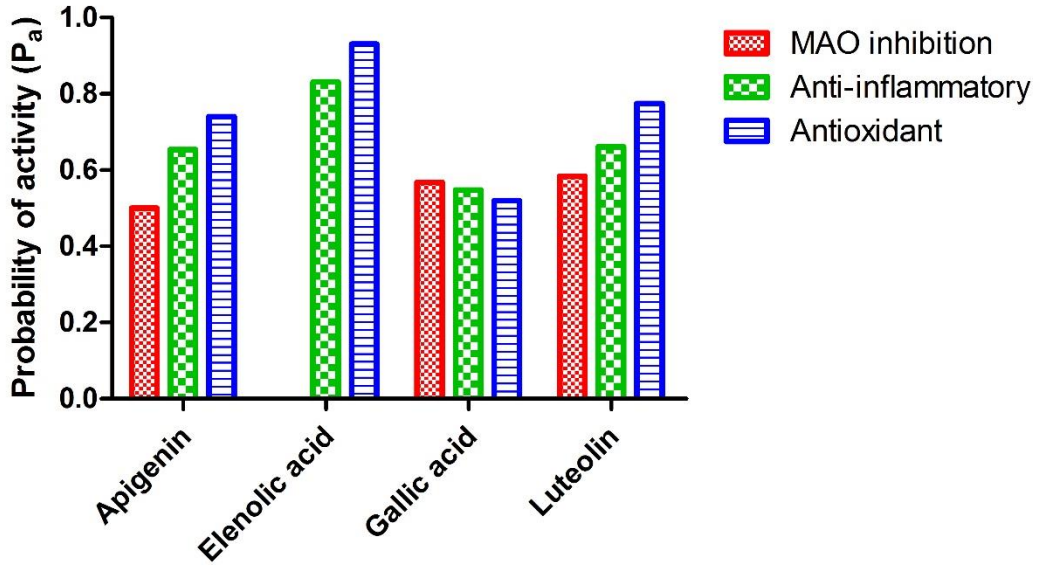

Figure 4. Chart representing the phenolic compounds with the highest Pa score for various activities

Figure 5. Pictures illustrating hydrogen bond surface of; A: elenolic acid with AChE; B: elenolic acid with BACE-1; C: luteolin with AChE and D: luteolin with BACE-1.

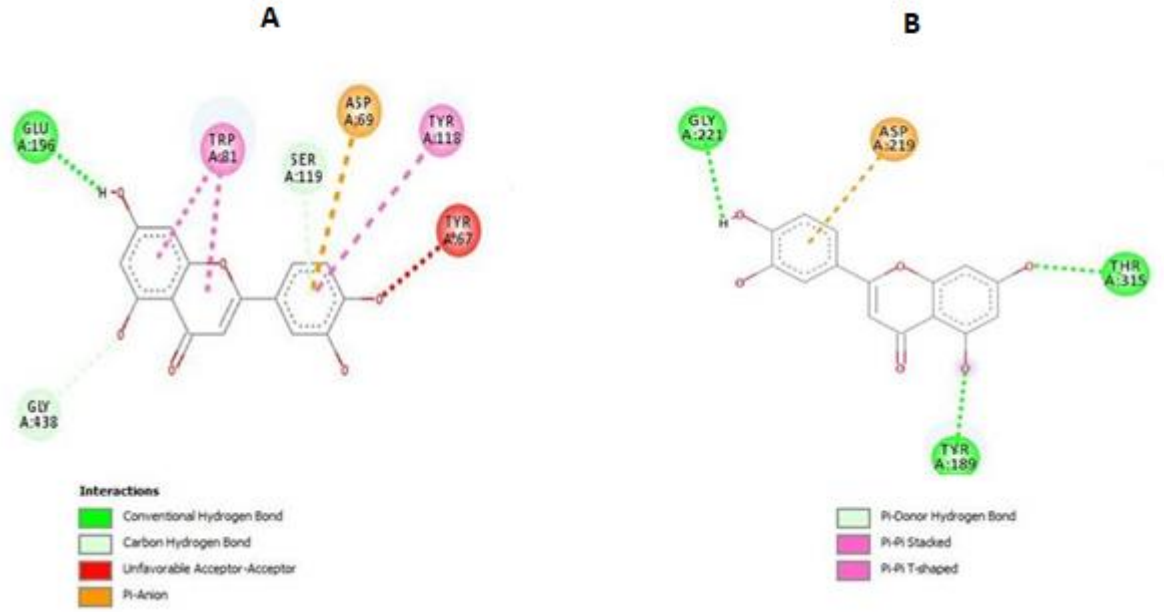

Figure 6. Picture showing 2D interactions of luteolin with (A) AChE and (B) BACE-1.

Table 1. Predicted molecular properties of olive oil polyphenolics by *molinspiration* software

Compound	miLogP	TPSA	natoms	MW	nON	nOHNH	nviolations	nrotb	volume
Apigenin	2.46	90.89	20	270.24	5	3	0	1	224.05
5-Caffeoylquinic acid	-0.45	164.74	25	354.31	9	6	1	5	296.27
Cinnamic acid	1.91	37.30	11	148.16	2	1	0	2	138.46
O-coumaric acid	1.67	57.53	12	164.16	3	2	0	2	146.48
Elenolic acid	0.20	93.07	17	242.23	6	2	0	4	212.18
Ferulic acid	1.25	66.76	14	194.19	4	2	0	3	172.03
Hesperidin	-0.55	234.30	43	610.57	15	8	3	7	511.79
Homoorientin	-0.31	176.62	30	417.37	10	6	1	7	346.95
Homovanillic acid	0.70	66.76	13	182.18	4	2	0	3	161.41
4-Hydroxybenzoic acid	1.37	57.53	10	138.12	3	2	0	1	119.06
Hydroxytyrosol	0.52	60.68	11	154.16	3	3	0	2	141.70
Luteolin	1.97	111.12	21	286.24	6	4	0	1	232.07
Oleuropein aglycone	1.86	122.53	28	392.40	8	3	0	9	350.99
Protocatechuic acid	0.88	77.75	11	154.12	4	3	0	1	128.08
Oleuroside	0.15	201.68	39	554.54	13	6	3	12	483.12
Sinapic acid	1.26	76	16	224.21	5	2	0	4	197.57
Syringic acid	1.20	76.00	14	198.17	5	2	0	3	170.15
Tyrosol	1	40.46	10	138.17	2	2	0	2	133.68
Vanillic acid	1.19	66.76	12	168.15	4	2	0	2	144.61
Gallic acid	0.59	97.98	12	170.1	5	4	0	1	135.10
Caffeic acid	0.94	77.75	13	180.16	4	3	0	2	154.50
Donepezil	4.10	38.78	28	379.50	4	0	0	6	367.89
Galanthamine	1.54	41.93	21	287.36	4	1	0	1	268.19
Rivastigmine	2.28	32.78	18	250.34	4	0	0	5	250.34
Memantine	2.32	26.02	12	165.28	1	2	0	0	174.87

miLogP: Octanol/Water partition coefficient; TPSA: total polar surface area; natoms: number of atoms; nON: number of hydrogen bond on acceptors; nOHNH: number of hydrogon bond donor; nrotb: number of rotational bonds.

Table 2. Predicted bioactivity scores of polyphenolic compounds and four anti-AD drugs by *molinspiration* software

Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Apigenin	-0.07	-0.09	0.18	0.34	-0.25	0.26
Cinnamic acid	-0.74	-0.40	-1.14	-0.47	-0.98	-0.30
O-coumaric acid	-0.64	-0.37	-0.97	-0.25	-0.90	-0.21
Elenolic acid	0.05	0.33	-0.87	-0.04	-0.20	0.24
Ferulic acid	-0.47	-0.30	-0.72	-0.14	-0.81	-0.12
Homovanillic acid	-0.46	-0.15	-0.82	-0.22	-0.68	-0.07
4-Hydroxybenzoic acid	-0.98	-0.39	-1.21	-0.62	-1.19	-0.41
Hydroxytyrosol	-0.71	-0.12	-0.79	-0.61	-0.90	-0.16
Luteolin	-0.02	-0.07	0.26	0.39	-0.22	0.28
Protocatechuic acid	-0.88	-0.35	-1.10	-0.58	-1.09	-0.34
Sinapic acid	-0.32	-0.20	-0.47	-0.03	-0.56	0.03
Syringic acid	-0.65	-0.28	-0.69	-0.44	-0.82	-0.15
Tyrosol	-0.80	-0.13	-0.87	-0.65	-0.97	-0.21
Gallic acid	-0.77	-0.26	-0.88	-0.52	-0.94	-0.17
Caffeic acid	-0.48	-0.23	-0.81	-0.10	-0.79	-0.09
Donepezil	0.22	-0.14	-0.16	0.03	0.03	0.25
Galantamine	0.93	0.26	-0.15	0.20	0.01	1.02
Rivastigmine	-0.05	0.06	-0.38	-0.35	-0.18	-0.01
Memantine	-0.41	0.01	-1.14	-0.93	-0.26	-0.18

Table 3. Predicted biological activity scores of polyphenolics using *PASS software*.

Compound name	MAO inhibition		Anti-inflammatory		Antioxidant		Acute neurologic disorders treatment		Antineurotic	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	**Pi**
Apigenin	0.500	0.003	0.654	0,022	0,740	0.004	0.519	0.072	0.337	0.211
Cinnamic acid	0.114	0.064	0.655	0.022	0.489	0.007	---	---	0.302	0.245
O-coumaric acid	0.100	0.080	0.686	0.018	0.523	0.006	0.524	0.069	---	---
Elenolic acid	---	---	0.831	0.005	0.903	0.003	---	---	---	---
Ferulic acid	0.138	0.043	0.610	0.029	0.547	0.005	0.398	0.145	---	---
Homovanillic acid	0.067	0.051	0.633	0.025	0.321	0.020	0.462	0.104	0.407	0.158
4-Hydroxybenzoic acid	0.102	0.077	0.503	0.056	0.320	0.020	0.594	0.040	0.380	0.176
Hydroxytyrosol	0.171	0.029	0.401	0.095	0.411	0.011	0.521	0.071	0.456	0.131
Luteolin	0.584	0.003	0.661	0.021	0.775	0.004	0.499	0.083	0.297	0.250
protocatechuic acid	0.098	0.083	0.538	0.046	0.401	0.012	0.574	0.046	0.319	0.227
Sinapic acid	0.111	0.066	0.612	0.029	0.576	0.005	0.323	0.207		
Syringic acid	0.090	0.086	0.498	0.058	0.403	0.012	0.400	0.143	0.363	0.189
Tyrosol	0.178	0.026	0.357	0.118	0.341	0.018	0.538	0.062	0.534	0.096
Vanillic acid	0.103	0.076	0.505	0.055	0.374	0.014	0.479	0.094	0.360	0.191
Gallic acid	0.568	0.004	0.548	0.044	0.520	0.006	0.510	0.077	0.274	0.274
Caffeic acid	0.131	0.048	0.661	0.021	0.611	0.004	0.512	0.076	---	---

Pa= probability of being active; Pi= probability of being inactive

Table 4. Predicted biological activity spectrum of four Anti-Alzheimer's' drugs by using *PASS software*.

	Antioxidant		Butyrylcholinesterase inhibitor		Acute Neurologic disorders treatment		Neurotrophic factor enhancer		Antineurotic	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	**Pi**
Donepezil	-	-	0.135	0.009	-	-	-	-	0.356	0.195
Galantamine	0.173	0.076	0.586	0.002	-	-	0.176	0.102	-	-
Rivastigmine	-	-	0.581	0.002	-	-	-	-	-	-
Memantine	-	-	-	-	0.476	0.096	0.232	0.040	-	-

Table 5. *Osiris property explorer* predicted toxicity of three phenolic compounds.

Compound	**Mutagenic**	**Tumorigenic**	**Reproductive effectiveness**
Apigenin	Unsafe (red)	Safe(green)	Safe(green)
Elenolic acid	Safe (green)	Safe(green)	Safe(green)
Luteolin	Safe(green)	Safe(green)	Safe(green)

Table 6. Binding energies of the best poses of polyphenolic compounds with BACE- 1 and AChE.

Compound	Binding energy (kcal/mol) of the best pose	
	BACE- 1	*Tc*AChE
Elenolic acid	-6.7	-7.6
Luteolin	-7.9	-10.5

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