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Research Article

Antioxidant, anti-acetylcholinesterase potentials, ADME estimations and molecular docking studies of green algae extracts

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ABSTRACT

Algae have become the center of attention due to their strong antioxidants and enzyme-inhibitory activities. In this study, green algae (*Enteromorpha linza*) extracts obtained using acetone, hexane and methanol were investigated. In the study, antioxidant properties, anti-acetylcholinesterase (AChE) potential, ADME estimations and molecular docking analyses of green algae extracts were investigated. The best binding position was obtained by docking sirsimaritin, daidzein, kaempferol, morin and myricetin to the active site of acetylcholinesterase receptor. Docking score values were calculated as -10.0, -10.3, -9.9, -9.8 and -9.8 kcal/mol, respectively. Experimental analysis revealed that the extracts showed inhibitory activity against acetylcholinesterase enzyme. Acetone and hexane extract showed good inhibition performance with IC_{50} values of 0.0379 mg/ml and 0.0414 mg/ml, respectively. The IC_{50} value for methanol extract was determined as 0.997 mg/ml. When the antioxidant activity results of the extracts were evaluated in terms of both DPPH and ABTS radical scavenging capacities, it was revealed that the acetone-based extract had a higher radical scavenging capacity (DPPH: 17.48%, ABTS: 83.58%) compared to the extracts obtained with other solvents. In general, the obtained results revealed that the green algae examined can be used as a source of natural agents beneficial for human health.

Keywords: AChE, Algae, Antioxidant, Inhibition, Molecular docking

1. INTRODUCTION

In recent years, interest in bioactive compounds from marine resources has increased significantly due to their positive effects on health. Macroalgae (seaweeds) in particular stand out as a rich source of various bioactive substances. The cell walls of these algae contain different types of sulfated polysaccharides, and these compounds show a wide range of biological activities such as anti-coagulant, antiviral, antioxidant, anticancer and immunomodulatory effects. Therefore, they offer significant potential for the nutraceutical, pharmaceutical and cosmeceutical industries [1].

Algae are diverse photosynthetic organisms that live in water and encompass thousands of species. In general, seaweeds are divided into two main classes: microalgae and macroalgae (often called seaweeds). Macroalgae are further divided into three subgroups: green algae (Chlorophyta), brown algae (Phaeophyta), and red algae (Rhodophyta). These

groups differ in species diversity and chemical composition [2]. Green algae, one of the three main groups of macroalgae, are widespread in the marine environment and are distributed worldwide [3]. The genus *Enteromorpha* (also known as *Ulva*), a group of green algae, is an important macroalgae causing green tides. *Enteromorpha* species are notable for their high tolerance to environmental stresses and rapid growth rates [4,5]. *Enteromorpha* species are therefore seen as a promising source of biomass for various industrial applications [6,7]. *Enteromorpha* species contain a variety of nutrients such as carbohydrates, proteins, fats, minerals and vitamins. Studies on *Enteromorpha* extracts and isolates have shown that these algae have antioxidant, antimicrobial, anti-ageing, anti-radiation and moisturizing properties [5,8].

Alzheimer's disease (AD) is a neurodegenerative disease characterized by atypical behavioral symptoms, memory impairment, cognitive decline, and intellectual disability, frequently seen in the ageing population [9,10]. Alzheimer's disease (AD) is pathologically defined by neuronal degeneration, the presence of senile plaques located interstitially between neurons, and changes in synaptic architecture [11]. The aetiology of AD highlights the critical function of acetylcholinesterase (AChE) within the central nervous system. The primary role of AChE involves the enzymatic hydrolysis of acetylcholine (ACh) into acetate ($CH3COO^-$) and choline (Ch) [12,13]. When AChE content is high and its activity is strong, ACh content decreases rapidly. In this case, neuronal damage occurs, and AD occurs. Therefore, oral drugs that can inhibit the existing AChE content in the brain can easily alleviate the symptoms of AD patients [14]. Therefore, the use of AChE inhibitors (AChEIs) for cholinergic degradation of ACh offers a promising and effective approach in the treatment of Alzheimer's disease (AD) [15].

Molecular Docking is a computational method widely used in drug design. This technique helps to introduce new molecules into the field by assessing the strength of interactions between the molecules under study and biological systems such as enzymes, while providing mechanistic insights into chemical interactions [16,17].

During normal cellular metabolism in living organisms, reactive oxygen species (ROS) are produced, which can be detrimental to essential biomolecules such as lipids, carbohydrates, nucleic acids, and proteins [18–20]. Additionally, ROS serve as a primary immune defence mechanism in all living beings and are implicated in numerous diseases [21,22]. Studies have revealed that oxidative stress and reactive oxygen species (ROS) are key determinants contributing to numerous chronic conditions, including cancer, immunodeficiency syndrome, age-related pathologies, cardiovascular diseases, arteriosclerosis, diabetes, and obesity [23,24]. Consequently, inhibiting the formation of ROS may be crucial in reducing the incidence of chronic diseases [25].

Nowadays, the development of natural and reliable treatment strategies for neurodegenerative diseases and oxidative stress-related pathologies has been receiving increasing attention in the literature. In this context, the rich bioactive compound portfolio of marine-derived natural products draws attention with their potential that has not yet been fully explored. In light of current studies, it is thought that a comprehensive evaluation of molecular interactions and pharmacokinetic properties of green algae extracts will better determine the place of natural agents in therapeutic applications. This study aims to provide new perspectives on the biological activities of this natural resource by examining the antioxidant and acetylcholinesterase inhibition potentials of green algae extracts through the integration of experimental analyses and computational methods.

2. MATERIALS AND METHODS

2.1. Preparation of Extracts

The green algae (*Enteromorpha linza)* were collected from Izmir, Türkiye. The collected sample was brought to the laboratory in plastic bags containing seawater to prevent evaporation. The algae were washed thoroughly with tap water and distilled water to remove surface particles and epiphytes and dried in the shade for 5 days. They were dried in an oven at 50 °C until constant weight was achieved. The dried algae were ground into fine powder using an electric mixer. They were mixed with acetone (E-

A), hexane (E-H) and methanol (E-M) (solid/liquid ratio 1:10 w/v) as solvents. The mixture was placed on a magnetic stirrer and stirred for 2 h. Then, it was filtered using a Whatman No. 1 filter. The filtrate obtained was dried and stored at 4 °C until needed [26,27].

2.2. Molecular Docking Studies

Molecular docking studies were carried out using the AutoDock Vina tool and UCSF Chimera software [28–30]. Cholinesterase and bioactive phytochemicals (cirsimaritin, daidzein, kaempferol, morin and myricetin) were evaluated for molecular docking studies. Acetylcholinesterase (PDB:4M0E) Structure of human acetylcholinesterase in complex with dihydrotanshinone I Method: X-RAY diffraction resolution: 2.00 Å) receptor was retrieved from the RCSB (https://www.rcsb.org/) protein data bank. After minimization, the grid box resolution for docking along the x, y and z axes was set to the binding region. Results were recorded after docking analysis [31,32]. Protein-ligand interactions were evaluated in the https://proteins.plus/ and amino acids were labelled. Finally, both 2D and 3D structures of the protein-ligand interface were shown. The PoseEdit system employs the PoseView algorithm and the InteractionDrawer JavaScript library (https://github.com/rareylab/InteractionDrawer) to automatically generate highly detailed 2D and 3D diagrams illustrating ligand interactions. The structural representations adhere to IUPAC guidelines. The system visualizes various computed interactions between the ligand and nucleic acids, amino acids, and metals, including hydrogen bonds, cation-pi interactions, pi-stackings, ionic interactions, and metal interactions, using colored dashed lines. Additionally, hydrophobic contacts are represented by green splines with labels [33].

2.3. ADME Analysis

Swiss ADME online web tool (http://www.swissadme.ch/) was used to perform ADME analysis of cirsimaritin, daidzein, kaempferol, morin and myricetin compounds [34]. ChemDraw was utilized to generate SMILES data for these compounds. Subsequently, various physicochemical properties were evaluated, including lipophilicity, drug-likeness, pharmacokinetics, topological polar surface area (TPSA), the number of rotatable bonds, and any violations of Lipinski's rule of five.

2.4. Acetylcholinesterase (AChE) Inhibition Activity

The inhibitory effect of green algae on acetylcholinesterase (AChE) was evaluated [35]. Briefly, 100 µL of 1 M Tris-HCl buffer (pH 8.0) was combined with 10 µL AChE solution and 10 µL extract and the total volume was brought to 900 mL with distilled water. It was then incubated at 25 °C for 5 min. Then, 50 µL of acetylthiocholine iodide (AChI) and 50 µL of 5,5'-dithio-bis-(2-nitrobenzoic acid) (DTNB) were added to the reaction medium. The resulting mixture was incubated for another 5 min at 25 °C. A control reaction was performed using an equivalent volume of dimethyl sulfoxide (DMSO) instead of the sample. Absorbance measurement was carried out at 405 nm in a spectrophotometer. The percentage of inhibition was determined according to the following formula (1):

$$Inhibiton\ (\%) = \frac{(A_c - A_s)}{A_c}\ X\ 100 \qquad (1)$$

Where A_c is the absorbance value of the control and A_s is the absorbance value of the sample.

2.5. DPPH Radical Scavenging Activity

To study the antioxidant potential of the crude extract of green algae, 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity (RSA) was performed with slight modifications to the previously reported method [36]. The experiment was carried out by adding 100 µL (1 mg/mL) of algae extract to 900 µL of DPPH (0.1 mM) mixture. The reaction mixture was then incubated at room temperature for 30 min in the dark to record absorbance (517 nm) readings on a spectrophotometer. 1 mL of DPPH was used as control. DPPH radical scavenging activity was calculated according to the following formula (2):

$$Radical\ scavenging\ activity(\%) = \frac{(A_c - A_s)}{A_c}\ X\ 100 \qquad (2)$$

Where A_c is the absorbance value of the control and A_s is the absorbance value of the extracts.

2.6. ABTS Radical Scavenging Activity

2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging activity of green algae was determined according to the previously described method with minor revisions [5]. Briefly, ABTS (7 mM) was mixed with potassium persulfate (2.45 mM) in the dark at room temperature for 16 h to form ABTS radicals. The solution was then diluted with phosphate buffer (pH = 7.4) until the absorbance at 734 nm was 0.70 ± 0.02. 5 µL of sample solution prepared at a concentration of 1 mg/ml was reacted with 995 µL of ABTS solution and the absorbance of the mixture was measured at 734 nm.

3. RESULTS AND DISCUSSION

3.1. Extraction Yield (Ey)

To determine the extraction yield (Ey), the percentage of the ratio between the extracted mass and the dry sample mass was calculated. Acetone-extract (E-A), hexane-extract (E-H) and methanol-extract (E-M) had values of 13.5, 11.4, 14.7%, respectively. These values revealed that the methanol extract had a higher yield.

3.2. Molecular Docking

A crucial computational technique for examining the structural and dynamic characteristics of biomolecular systems is molecular docking. This method, extensively utilized in drug discovery and biotechnology research, enables the investigation of how small molecules, known as ligands, interact with the active sites of target proteins and the potential impacts of these interactions on biological systems [37]. Molecular docking analyses evaluate ligand-protein interactions in terms of binding energies, with the lowest docking score indicating the highest binding affinity [38]. The composition of the extract was determined based on previously published data [39–41]. The best binding pose was obtained by docking cirsimaritin, daidzein, kaempferol, morin and myricetin into the active site of acetylcholinesterase (PDB: 4M0E) receptor. Docking score values were calculated as -10.0, -10.3, -9.9, -9.8 and -9.8 kcal/mol, respectively.

Chemical interactions between molecules and proteins typically involve conventional hydrogen bonds, pi-pi-shaped bonds, pi-alkyl bonds, pi-anion bonds, carbon-hydrogen bonds, pi-pi stacked bonds, and pi-sulfur bonds. The 2D-3D structures of hydrogen bonds, Pi-pi interaction, ionic interaction, cation-pi interaction and hydrophobic interactions are shown in Figure 1. 4M0E protein formed 1 hydrogen bond with Cirsimaritin, 3 with Daidzein, 2 with Kaempferol, 2 with Morin and 3 with Myricetin. These bonds formed are Phe287, Ser822, Tyr866, Tyr870, Phe287, Tyr329, Phe824, Arg825, Tyr1030, Arg 1061 and Ala 1053, respectively. All other interactions are given in Figure 1. Hydrogen bonds provide specific and directional interactions between the ligand and the protein. This facilitates the localization of the ligand to the correct binding site (active site, binding pocket, etc.) on the protein. The aromatic rings of the ligand can contribute to binding stability by forming π-π interactions with aromatic amino acids in the protein. Specific binding is critical for accuracy in biological processes. The colored spirals in the protein represent α-helix regions. These regions often provide structural stability and can be important in ligand binding [42].

Several compounds, including cirsimaritin, daidzein, kaempferol, morin, and myricetin, demonstrated inhibitory effects on various enzymes such as CYP1A2, CYP2C9, CYP2D6, CYP2C19, and CYP3A4. The BOILED-Egg graph, a predictive model based on molecular lipophilicity and polarity, was utilized to assess the likelihood of gastrointestinal absorption and blood-brain barrier (BBB) penetration. This graph is divided into three distinct areas. As illustrated in Figure 2, the white section of the BOILED-Egg graph (albumin) signifies molecules with high potential for gastrointestinal (GI) absorption, while the yellow area represents possible BBB permeability. Molecules with low GI absorption and minimal brain penetration are depicted in the gray region. The presence of cirsimaritin, kaempferol, and morin in the white area suggests a high likelihood of GI absorption, indicating that these compounds may have increased bioavailability when taken orally.

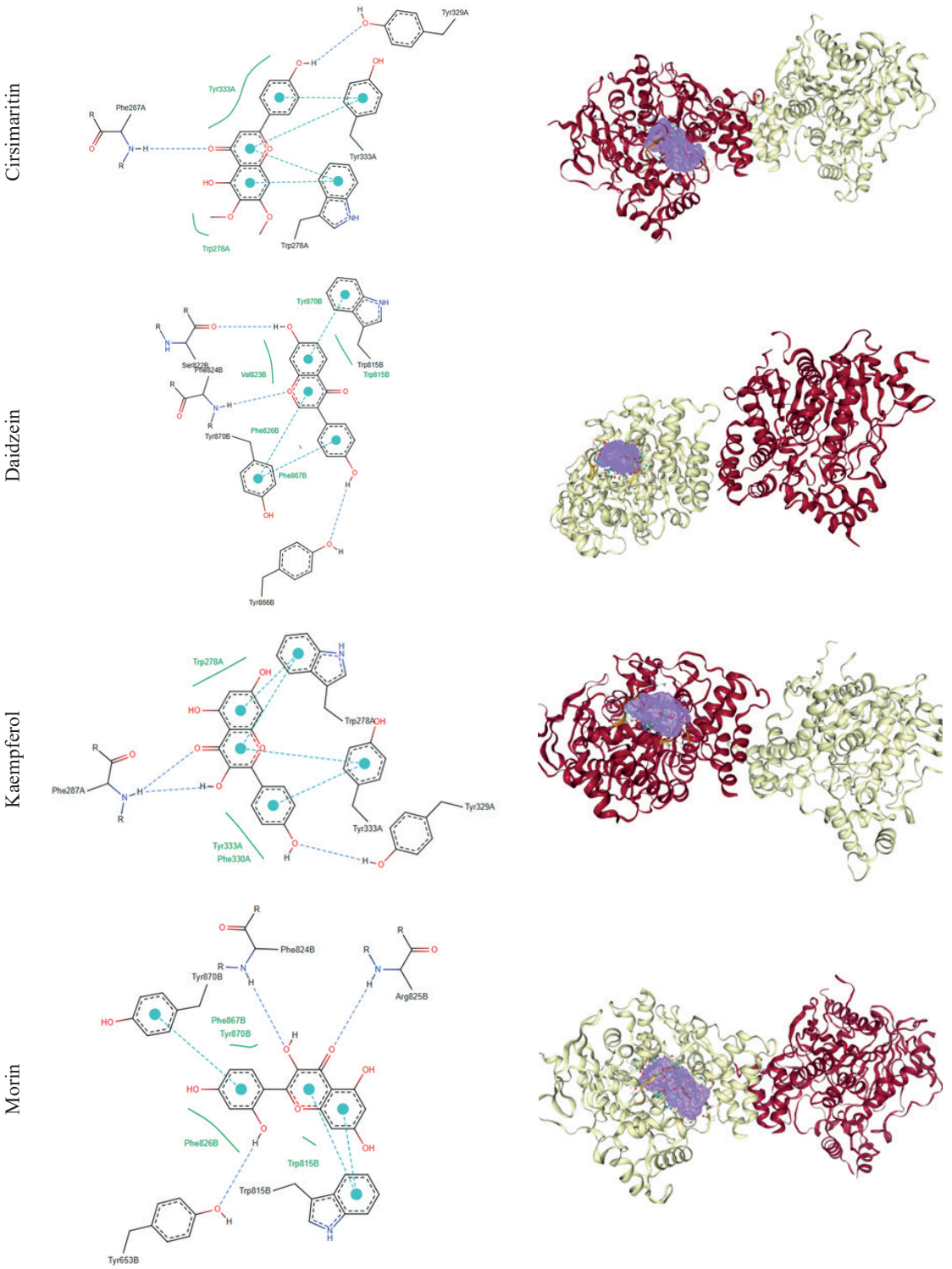

Figure 1. The 2D and 3D binding mode of Cirsimaritin, Daidzein, Kaempferol, Morin and Myricetin ligands with AChE (4M0E)

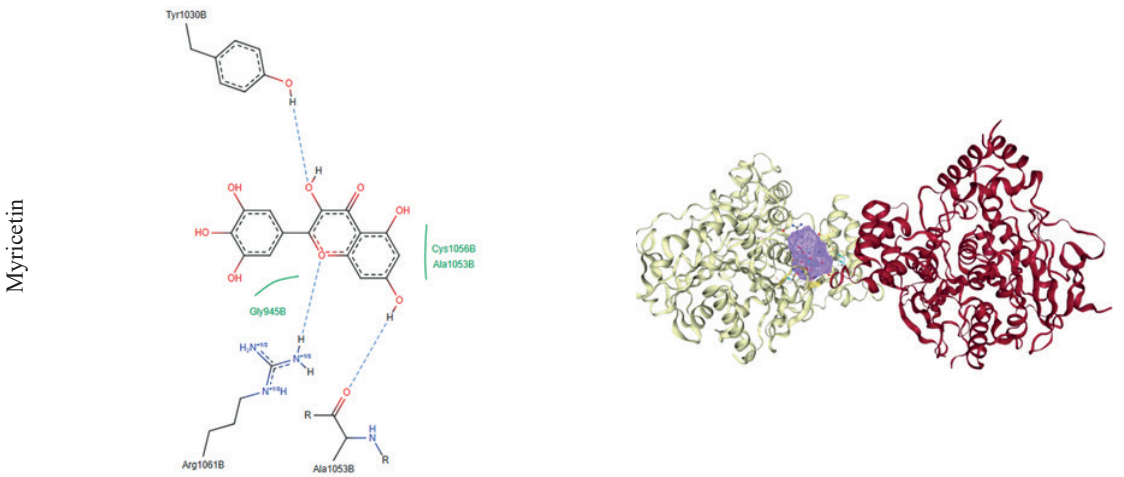

Figure 1. The 2D and 3D binding mode of Cirsimaritin, Daidzein, Kaempferol, Morin and Myricetin ligands with AChE (4M0E) (Continued)

ADME calculations are performed for the use of molecules as drugs in human metabolism. According to chemical parameters such as molar masses of molecules, dipole moment of molecules, hydrogen bonds given and taken by molecules and biological parameters such as absorption of molecules through intestinal and blood barriers, absorption through the skin or numerical values of oral absorption, it is seen that there is no harm in using them as drugs. The presence of different groups in cirsimaritin, daidzein, kaempferol, morin and myricetin suggests that their activity can be enhanced by changing their physicochemical properties and pharmacokinetic parameters to increase their bioavailability and metabolic stability as well as their binding affinity to receptors.

The ADME properties of selected flavonoids provide insights into their pharmacokinetic potential (Table 1). Gastrointestinal (GI) absorption is high for all compounds except for myricetin, which exhibits lower absorption likely due to its high total polar surface area (TPSA = 151.59 Å). In terms of blood-brain barrier (BBB) permeability, only daidzein shows the ability to penetrate the central nervous system, which can be attributed to its lower TPSA (70.67 Å) and moderate lipophilicity (iLOGP = 1.77, XLOGP3 = 2.47).

Regarding metabolism, all flavonoids inhibit CYP1A2 and CYP3A4, suggesting potential drug-drug interactions. However, only cirsimaritin inhibits CYP2C9, which is involved in the metabolism of several anti-inflammatory drugs. Furthermore, all flavonoids except myricetin inhibit CYP2D6, which is responsible for metabolizing numerous psychoactive drugs.

Lipophilicity indices (iLOGP, XLOGP3, and WLOGP) suggest that cirsimaritin is the most lipophilic compound, while myricetin is the least. This is consistent with their respective skin permeation coefficients (Log Kp), where cirsimaritin exhibits the highest permeability (-5.86 cm/s) and myricetin the lowest (-7.40 cm/s). These results indicate that cirsimaritin might be better suited for transdermal delivery systems.

All compounds comply with Lipinski's rule of five, indicating good oral bioavailability. However, myricetin does not satisfy Veber, Egan, or Muegge rules, which may imply limitations in its bioavailability and drug-likeness.

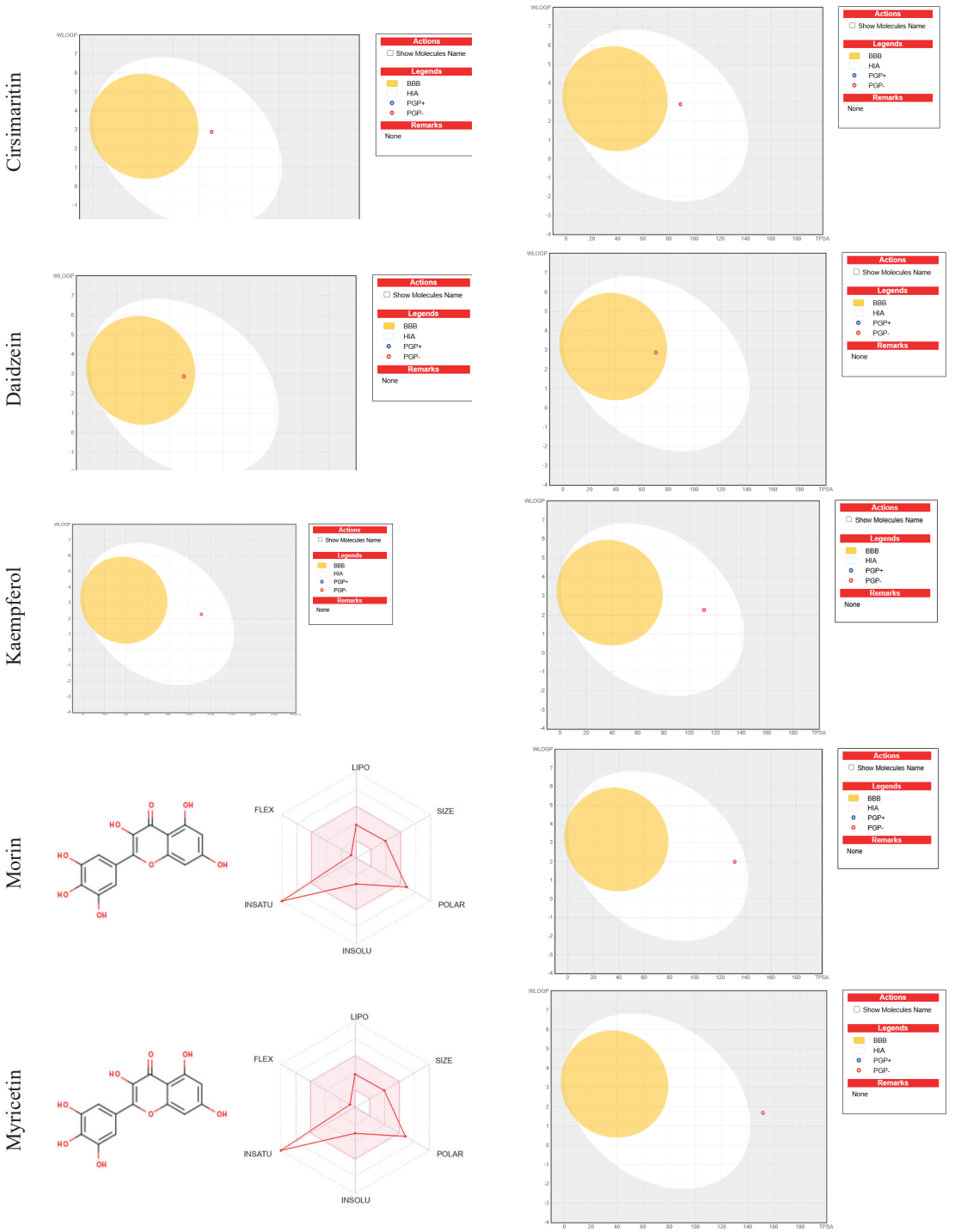

Figure 2. BOILED-Egg chart

Table 1. Physicochemical and ADME properties of cirsimaritin, daidzein, kaempferol, morin, and myricetin

	Cirsimaritin	Daidzein	Kaempferol	Morin	Myricetin
Molecular weight	314.29 g/mol	254.24 g/mol	286.24 g/mol	302.24 g/mol	318.24 g/mol
Num. H-bond acceptors	6	4	6	7	8
TPSA	89.13 Å	70.67 Å	111.13 Å	131.36 Å	151.59 Å
iLOGP	2.56	1.77	1.70	1.47	1.08
(XLOGP3)	3.32	2.47	1.90	1.54	1.18
WLOGP	2.89	2.87	2.28	1.99	1.69
MLOGP	0.47	1.08	-0.03	-0.56	-1.08
SILICOS-IT	3.07	3.02	2.03	1.54	1.06
ESOL	-4.20	-3.53	-3.31	-3.16	-3.01
GI absorption	High	High	High	High	Low
BBB permeant	No	Yes	No	No	No
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	No	No	No	No	No
CYP2C9 inhibitor	Yes	No	No	No	No
CYP2D6 inhibitor	Yes	Yes	Yes	Yes	No
CYP3A4 inhibitor	Yes	Yes	Yes	Yes	Yes
Log K_p (skin permeation)	-5.86 cm/s	-6.10 cm/s	-6.70 cm/s	-7.05 cm/s	-7.40 cm/s
Lipinski	Yes	Yes	Yes	Yes	Yes
Ghose	Yes	Yes	Yes	Yes	Yes
Veber	Yes	Yes	Yes	Yes	No
Egan	Yes	Yes	Yes	Yes	No
Muegge	Yes	Yes	Yes	Yes	No
Bioavailability Score	0.55	0.55	0.55	0.55	0.55

3.3. Acetylcholinesterase (AChE) Inhibition Activity

Acetylcholinesterase is an enzyme found in nerve synapses. Its primary function is to break down the neurotransmitter acetylcholine [43]. In the present study, the acetone-based green algae *(Enteromorpha linza*) extract obtained showed the highest AChE inhibition with an IC_{50} value equal to 0.0379 mg/mL (Figure 3). The hexane extract showed inhibition close to the acetone extract and had an IC_{50} value of 0.0414 mg/mL (Figure 4). Methanol-based extract had the lowest inhibition value and IC_{50} value was calculated as 0.997 mg/mL (Figure 5).

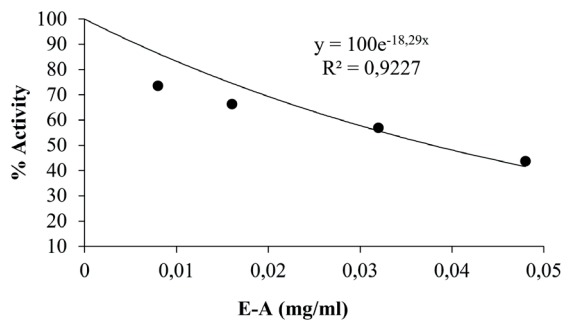

Figure 3. Effect of acetone-based extract (E-A) concentration on the activity of the AChE

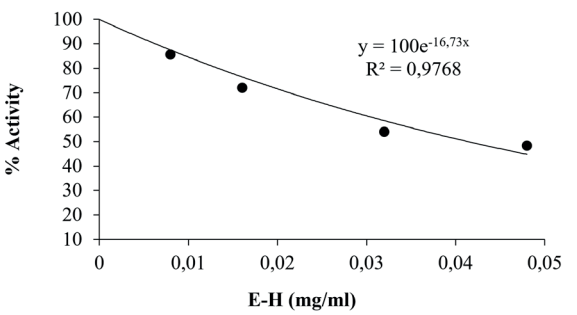

Figure 4. Effect of hexane-based extract (E-H) concentration on the activity of the AChE

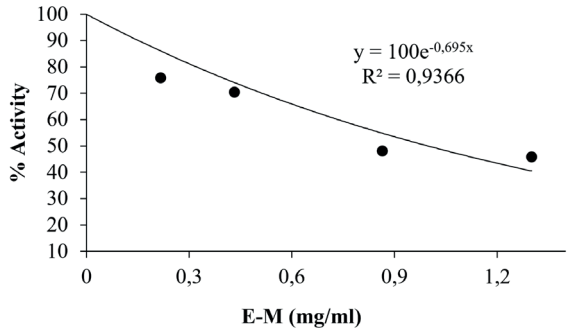

Figure 5. Effect of methanol-based extract (E-M) concentration on the activity of the AChE

3.4. Antioxidant Test

Studying the antioxidant properties of natural substances is an important first step in evaluating potential new therapeutic drugs and understanding their various functions in different diseases [44]. Table 2 summarizes the radical scavenging capacities of green algae extracts. It was found that the algae extracts showed variable radical scavenging abilities on DPPH and ABTS. The DPPH radical scavenging capacity of extracts with 100 µg/mL concentration showed the highest antioxidant property with 17.48 % for acetone extract. The hexane and methanol extracts showed similar radical scavenging capacity (11.89 and 11.48 %, respectively). When the extracts with 5 µg/mL concentration were evaluated in terms of ABTS radical scavenging capacity, acetone extract showed the highest antioxidant capacity with 83.58 % radical scavenging. Then methanol extract showed 78.38 % and hexane extract showed 25.78 % ABTS radical scavenging capacity.

In a previous study, it was reported that the extracts obtained using different solvents such as acetone, hexane and methanol showed different DPPH and ABTS radical scavenging activities, as in our study [45]. DPPH and ABTS radical scavenging capacities were evaluated by calculating IC_{50} (µg/mL) values. The highest radical scavenging for DPPH was achieved by methanol: 35.1 ± 0.27, acetone: 38.3 ± 0.58, hexane: 66.0 ± 3.81. The highest radical removal for ABTS was methanol: 43.2 ± 0.24, acetone: 43.4 ± 0.39, hexane: 91.4 ± 0.39, respectively. Unlike our study, the highest radical scavenging capacity was found in methanol extract. The differences between the antioxidant activities of the extracts may be due to differences in the composition or amounts of antioxidant components in the extracts.

Table 2. DPPH and ABTS free radical-scavenging activity (inhibition %) of extracts

Extracts	DPPH	ABTS
Aceton Extract (E-A)	17.48	83.58
Hexane Extract (H-A)	11.89	25.78
Methanol Extract (M-A)	11.48	78.38

4. CONCLUSION

The present study determined that green algae extract exhibited significant biological activities such as anti-acetylcholinesterase and antioxidant properties. In particular, acetone (IC_{50}: 0.0379 mg/mL) and hexane (IC_{50}: 0.0414 mg/mL) based extracts were determined to have inhibitory potential on acetylcholinesterase enzyme. Molecular docking analyses supported these findings by showing interactions between bioactive compounds and AChE. Furthermore, ADME evaluations revealed that the identified bioactive compounds exhibited promising pharmacokinetic properties, enhancing their potential for drug development. Among the selected flavonoids, daidzein appears to have the best central nervous system accessibility, while cirsimaritin demonstrates the highest permeability and lipophilicity. The strong CYP enzyme inhibition across all compounds suggests that these flavonoids could interact with other drugs metabolized by these pathways. Further experimental studies are required to validate these predictions and explore their pharmacological potential. As a result of DPPH and ABTS radical scavenging analyses, acetone extract was determined to have higher antioxidant capacity (DPPH: 17.48%, ABTS: 83.58%) than hexane and methanol extracts. Overall, the obtained results indicate that green algae extract can be used for human benefit due to its promising biological activities.

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Ethical approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Author contribution

Conceptualization, A.N., M.I. and Ş.B.; Methodology, A.N., M.I. and Ş.B.; Software, A.N.; Validation, A.N. and M.I.; Formal analysis, O.Ç., A.N. and M.I.; Investigation, O.Ç., A.N. and M.I.; Data curation, O.Ç., A.N. and M.I.; Writing—original draft preparation, O.Ç., A.N. and M.I.; Writing—review and editing, O.Ç., A.N. and M.I.; Visualization, O.Ç., A.N. and M.I.; Supervision, Ş.B. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declared that there is no conflict of interest.

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