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Biological effects and molecular docking studies of Catechin 5-O-gallate: antioxidant, anticholinergics, antiepileptic and antidiabetic potentials

Parham Taslimi[a], Umit M. Kocyigit[b], Burak Tüzün[c] and Mahinur Kirici[d]

[a]Department of Biotechnology, Faculty of Science, Bartin University, Bartin, Turkey; [b]Department of Basic Pharmaceutical Sciences, Division of Biochemistry, Faculty of Pharmacy, Sivas Cumhuriyet University, Sivas, Turkey; [c]Department of Chemistry, Faculty of Science, Sivas Cumhuriyet University, Sivas, Turkey; [d]Department of Chemistry, Faculty of Arts and Sciences, Bingol University, Turkey

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ABSTRACT

Gallocatechin gallate is a form of catechin and an ester of gallocatechin and gallic acid. This is an epimer of the gallate epigallocatechin. In this study, the effect of this molecule, containing a biologically active group, was investigated in terms of important metabolic enzymes (carbonic anhydrase isoenzymes I and II (hCA I and II), achethylcholinesterase (AChE) and α-glycosidase (α-Gly) enzymes). The molecular docking method used to compare the biological activities of the Catechin 5-O-gallate molecule against enzymes was used. Afterwards, the ADME/T analysis was performed to investigate the drug availability of the Catechin 5-O-gallate molecule and the parameters obtained from ADME/T analysis were examined. Continuation of this study, for evaluating antioxidant and radical scavenging capacity Catechin 5-O-gallate, cupric ion (Cu^{2+}) reduction capacity by CUPRAC method, Fe^{3+}-Fe^{2+} reducing capacity, DPPH free radical clarifying ($DPPH^{\cdot}$), ABTS radical clarifying ($ABTS^{\bullet+}$) were performed separately and during the study, trolox, α-tocopherol BHT and BHA were used as the reference antioxidant compound. Comparisons were applied with the four standard substances.

Abbreviations: ADME: absorption, distribution, metabolism and excretion; ACR: acarbose; AZA: acetazolamide; AChE: achethylcholinesterase; ABTS: 2, 2′-azino-Bis-3-ethylbenzothiazoline-6-sulfonic acid (biochemical reagent); α-Gly: α-glycosidase; BHA: butylated hydroxyanisole; BHT: butylated hydroxytoluene; BChE: butyrylcholinesterase; CA: carbonic anhydrase; CUPRAC: cupric reducing antioxidant capacity; DPPH: 2,2-diphenyl-1-picrylhydrazyl; EGCG: gallate epigallocatechin; GA: gallic acid; GCG: gallocatechin gallate

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1. Introduction

Catechins are a group of polyphenolic compounds most commonly found in foods and drinks as a natural product, such as cacao products, grapes, red wine and green tea. According to the gallic acid ester in the C3 position of the catechins, two major forms of catechins make up about 80% of the polyphenolic compounds present in green tea: non-gallate catechins such as gallate epigallocatechin (Figure 1) (Chen et al., 2014; Huang et al., 2019).

Glaucoma with high intraocular pressure is one of the most important eye diseases. It causes 15–20% blindness. hCA II is the primary cause of the formation of intraocular pressure in the eye retina. The most significant method of eliminating this disease is to inhibit the activity of hCA II. Several years ago acetazolamide (AZA) and heteroaromatic sulfonamides were used as inhibitors for this purpose (Topal & Gülcin, 2014).

Acetyl CoA is a compound derived from pyruvate that occurs in glycolysis as a metabolic drug. Alzheimer's disease is caused by reduced neurotransmitters in the brain. The most reduced neurotransmitter in this disease is widespread dementia and neurodegenerative disease. Alzheimer's illness has been found to be associated with memory dysfunction. The greater biochemical factor of this disease is the decrease in the level of acetylcholine in the brain (Göçer et al., 2013). This disease is currently incurable. Today's therapies aim to alleviate the symptoms of this disease. To this end, AChE inhibitors such as Rivastigmin and Donepezil are widely used (Göcer et al., 2017; Koçyiğit, 2018). Butyrylcholinesterase and acetylcholinesterase are both inhibited by rivastigmine and tacrine. Their use is, however, limited as they cause damage to the liver (Alaşehirli, 2005).

α-Glycosidase enzymes are found on the brushy surface of the small intestine. And they are responsible for the breakdown of complex carbohydrates. It is quickly absorbed from the intestinal wall in monosaccharides and passes into the blood. Glucoamylase, sucrase, maltase, isomaltase and lactase are among the well-known alpha glucosidase enzymes. The effects of alpha-glucosidase enzyme inhibitors on these enzymes are different. In the absorption of carbohydrates with enzyme, inhibition slowdown happens (Mai et al., 2007). Acarbose, miglitol and vogliboz are used in the treatment of

CONTACT Umit M. Kocyigit ukocyigit@cumhuriyet.edu.tr Department of Basic Pharmaceutical Sciences, Division of Biochemistry, Faculty of Pharmacy, Sivas Cumhuriyet University, Sivas 58140, Turkey.

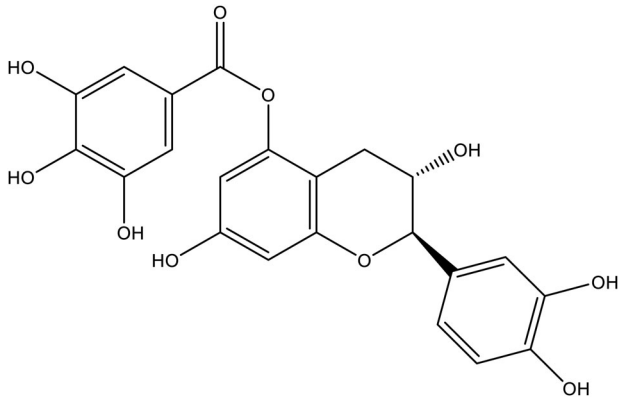

Figure 1. Structure of Catechin 5-O-gallate.

diabetes today. Gastrointestinal tract is a part of the body parts where the most important side effects of these drugs take place. In the small intestine, undigested carbohydrates are metabolized by bacteria located in the colon. The fermentation of the undigested carbohydrates is causing symptoms of bloating, stomach pain and air (Rahim et al., 2020).

Reactive oxygen species occurs in the organism in the normal process and with its accumulation, it causes much damage to the organism. It is known that free oxygen radicals may cause many diseases, especially cancer. Thanks to exogenous and endogenous antioxidants, the risk of diseases caused by free oxygen radicals is reduced. Today, natural antioxidants are preferred over synthetic antioxidants. Interest in them has increased in recent years with the preference of natural and food-borne antioxidant sources, especially plant ones (Eruygur et al., 2019; Gulcin, 2020).

The molecular docking method used to compare the biological activities of the Catechin 5-O-gallate molecule against enzymes was used. The enzymes used in this study are human alpha-galactosidase (α-Gly) (PDB ID: 1R47), human acetylcholinesterase (AChE) (PDB ID: 4M0E), human Carbonic Anhydrase I (hCA I) (PDB ID: 3LXE), human carbonic anhydrase II (hCA II) (PDB ID: 5AML). Afterwards, the ADME/T analysis was performed to investigate the drug availability of the Catechin 5-O-gallate molecule, and the parameters obtained were examined. With this ADME/T analysis, the effects and reactions of this molecule on human metabolism were examined.

In this study, the inhibition properties of Catechin 5-O-gallate with fluvonoid structure were investigated. The effect of Catechin 5-O-gallate on hCA I, hCA II, AChE and alpha glucosidase enzymes purified from human blood would be studied. In addition, antioxidant activities of Catechin 5-O-gallate were investigated in this article. Fe^{3+} reducing, CUPRAC, iron reduction, DPPH and ABTS, methods. We think that the results obtained in the studies will contribute to the pharmacological applications and design of the drugs to be used for therapeutic purposes.

2. Experimental

2.1. Antioxidant studies

2.1.1. DPPH• activity

DPPH radical removal activity measurement was performed in accordance with Blois method (Blois, 1958). As a free radical, 1 mM solution of DPPH was used. Stock solutions of 1 mg/mL concentrations prepared previously were used as samples. Stock solutions adjusted in different concentrations were added to the test tubes and ethanol was used to complete their total volume to 3 mL. Then, stock 1 mL of DPPH solution was added to each tube. Tubes were mixed thoroughly with Vortex. Tubes to be used as a control were placed with 1 mL of DPPH solution and 3 mL of ethanol. Ethanol was used as a blind. It was kept in the dark and room temperature for half an hour. Then, the absorbance values at 517 nm were measured against the corner. Decreased absorbance values were read according to increasing concentrations. Reduced absorbance gave free radical removal activity.

2.1.2. CUPRAC activity

Cu^{2+} reduction activities of Catechin 5-O-gallate were performed by light modification of copper ions reduction method (Apak, 2019). Pure water, 250 µL $CuCl_2$ solution (10 mM), 250 µL ethanolic neocuprin (7.5 mM) and 250 µL CH_3COONH_4 buffer (1 M) were added to the tubes containing Catechin 5-O-gallate in different concentrations. The amount of distilled water varies according to the sample amounts added, respectively. The amount of pure water varies according to the amount of sample. Distilled water was used as a blind, after 450 min at 450 nm, absorbance values were measured against the blind (Durmaz, 2019).

2.1.3. $Fe3^{+}$ reducing method

Fe^{3+}-Fe^{2+} reduction measurement was done according to Oyaizu method (1986). For this, a stock solution of 1 mg/mL was prepared. The stock solution was added to the test tubes at different concentrations and their volumes were completed to 1 mL with distilled water. Then, 2.5 mL of phosphate buffer (0.2 M, pH 6.6) and 2.5 mL of 1% potassium ferricyanide [$K_3Fe(CN)_6$] were added to the tubes. The mixture was incubated at 50 °C for 20 min. Then, 2.5 mL of TCA (10%) solution was added to the reaction mixture. 2.5 mL was taken from the upper phase of the solution. Thereto, 2.5 mL of distilled water and 0.5 mL of $FeCl_3$ (0.1%) were added. As control, distilled water was used instead of sample. Distilled water was used as a blind. Absorbance values were measured against the corner at 700 nm.

2.1.4. ABTS radical scavenging assay

ABTS radical removal activity measurement was performed in accordance with the method of Re et al. (1999). First, ABTS 7.0 mM solution was prepared. ABTS radicals were produced by adding 2450 mM persulfate solution to this solution. Before the ABTS radical solution was used, the absorbance of the control solution at 734 nm was adjusted to 0.700 ± 0.025 with a 0.1 M phosphate buffer with a pH of 7.4. One mL of ABTS radical solution was added to different concentrations (10–30 µg/mL) of Rutinhydrate, where the ABTS radical removal activity would be measured. Tubes were mixed thoroughly with vortex and after half an hour of incubation,

Table 1. Determination of reducing power of same concentration of Catechin 5-O-gallate and standard compounds by ferric ions (Fe^{3+}) reducing and cupric ions (Cu^{2+}) reducing capacity by CUPRAC method.

	Fe^{3+}-Fe^{2+}reducing		Cu^{2+}-Cu^{+} reducing	
Antioxidants	λ_{700}	r^2	λ_{450}	r^2
BHA	2.234 ± 0.008	0.9732	2.181 ± 0.020	0.9868
BHT	2.013 ± 0.003	0.9242	2.249 ± 0.021	0.9472
α-Tocopherol	1.013 ± 0.015	0.9380	0.879 ± 0.012	0.9889
Trolox	1.761 ± 0.007	0.9816	0.941 ± 0.027	0.9236
Catechin 5-O-gallate	1.865 ± 0.018	0.9851	1.432 ± 0.034	0.9467

absorbance values at 734 nm were read and recorded against the blend of ethanol (Rajurkar & Hande, 2011).

2.2. Enzymes studies

For the determination of the activities of CA izoenzymes, improvements in absorbance were calculated and performed during 3 min at 348 nm using PNA as a substrate According to Verpoorte et al. (1967) as previously defined (Tutar et al., 2019; Verpoorte et al., 1967). AChI was used as reaction substrate molecules and as a previous study, DTNB was used to determine anticholinesterase activity and conducted in accordance with the Ellman method (Ellman et al., 1961; Kocyigit et al., 2017).

The inhibition effect of glycosidase of Catechin 5-O-gallate was assessed using Tao et al. process (Köse et al., 2015). First, the phosphate buffer (pH 7.4, 75 µL) was combined with 5 µL of the sample and 20 µL of the α-glycosidase enzyme solution prepared in the phosphate buffer (0.15 U/mL, pH 7.4). After pre-incubation, 50 µL of *p*-Nitrophenyl-D glycopyranoside (*p*-NPG) was applied to the phosphate buffer (5 mM, pH 7.4) and re-incubated at 37 °C. At 405 nm, the absorbance of mixtures was reported. Three separate concentrations of Catechin 5-O-gallate were used to determinate the K_i values. The graphs were then drawn from Lineweaver & Burk (1934).

2.3. Molecular docking studies

Theoretical calculations are one of the easiest methods to compare the biological activities of molecules (Genç Bilgiçli et al., 2020; Ojha et al., 2020; Tüzün & Saripinar, 2020; Tüzün et al., 2018). This is because, when it is first made to compare the biological activities of molecules with theoretical calculations, it provided both preliminary information about the results and great convenience in cost and time. With the results found, it is possible to synthesize more effective and active molecules. The most widely used method among the theoretical calculations is the molecular docking method, which makes the comparison of the biological activities of molecules possible (Bytyqi-Damoni et al., 2020; Taslimi et al., 2020; Türkan et al., 2020). The enzymes used in this study are human alpha-galactosidase (PDB ID: 1R47) (Garman & Garboczi, 2004), human acetylcholinesterase (PDB ID: 4M0E) human Carbonic Anhydrase I (PDB ID: 3LXE) (Alterio et al., 2010) and human carbonic anhydrase II (PDB ID: 5AML) (Ivanova et al., 2015). The biological activities of the Catechin 5-O-gallate molecule against these enzymes were investigated. For this examination, Gaussian software program (Frisch et al., 2009) was used to find the optimized structures of molecules at first. Files with the *.sdf extension were created using these optimized structures. Using these files, calculations were made on Maestro Molecular modeling platform (version 12.2) by Schrödinger, LLC (Schrodinger, 2019). Maestro Molecular modeling platform consists of many sections. In the first part, the protein preparation module (Friesner et al., 2006; Schrödinger, 2019b) was used for the preparation of proteins. The crystal structures of the studied enzymes, consisting of many proteins, were downloaded from the protein data bank site. These enzymes were initially minimized and the water molecules in the structure were removed. In the next step, the active sites of the enzymes were determined, in which the proteins in this active zone were given freedom of movement. Therefore, these proteins interacted more easily with molecules. In the next step, the molecule was prepared for calculations, and the LigPrep module (Sastry et al., 2013; Schrödinger, 2019a) was used for this process. Three dimensional structures and the correct protonation conditions were calculated at the physiological pH values of the high energy isomers of the Catechin 5-O-gallate molecule. Calculations of the molecule and proteins were done using the OPLS3e method. In the next step, the prepared protein and molecule were interacted with each other. The Glide ligand docking module (Du et al., 2020) was used for this step. Molecule and enzymes were interacted with this module. Following this interaction, ADME/T analysis (absorption, distribution, metabolism, excretion and toxicity) was performed to examine the ability of the molecule to be used as a drug in the future. The Qikprop module (Schrödinger, 2020) of the Schrödinger software was used in the calculations of ADME/T analysis.

3. Result and discussion

3.1. Antioxidant results

Natural phenolic molecules are distributed extensively in nature. Their natural antioxidant potential depends on the structure and quantity of the structural conjugation and hydroxyl groups (Bursal et al., 2013). In this article, several antioxidant activity methods based on different reactions were used to detect the strong antioxidant action of Catechin 5-O-gallate.

i. The capacity of Catechin 5-O-gallate to reduce Fe^{3+} ions was found by measuring the absorbance values of solutions of different concentrations at 700 nm. In this method, the yellow test solution turns into a green color due to the reducing effects of antioxidant substances in the experimental environment. The color change of the compounds is seen as a marker of antioxidant activity (Gülçin, 2006). The reduction capacity of routine hydrate increases proportionally with increasing concentration (Table 1). The activities of reducing the ferric ions of the routine hydrate and standard antioxidants to the ferrous ions were compared.

Table 2. Determination of half maximal concentrations (IC_{50}) of Catechin 5-O-gallate and standards for DPPH· and $ABTS^{\bullet+}$ activities.

Antioxidant compounds	DPPH· scavenging	r^2	$ABTS^{\bullet+}$ scavenging	r^2
BHA	13.35	0.9848	9.57	0.9462
BHT	14.51	0.9430	8.77	0.9635
α-Tocopherol	21.31	0.9814	15.16	0.9789
Trolox	8.43	0.9127	7.51	0.9512
Catechin 5-O-gallate	15.23	0.9637	10.83	0.9807

BHA (2.234 ± 0.008, r^2:0.9732) > BHT (2.013 ± 0.003, r^2:0.9242) > Catechin 5-O-gallate (1.865 ± 0.018, r^2:0.9851) > Trolox(1.761 ± 0.007, r^2:0.9816) > α-Tocopherol (1.013 ± 0.015, r^2:0.9380)

i. Cu^{2+} reduction capacity of routine hydrate was determined by measuring the absorbance values of solutions of different concentrations at 450 nm. With the same method, the absorbance values of the solutions of different concentrations for the standard antioxidant α-Tocopherol, Trolox, BHA and BHT were also examined. It was observed that the capacity of the routine hydrate to reduce the cupric ions (Cu^{2+}) increased proportionally with the concentration (Table 1). The capacities of Catechin 5-O-gallate and standard antioxidants to reduce Cu^{2+} ions to Cu^{+} ions were compared. The results were determined as follows. BHT (2.249 ± 0.021, r^2:0.9472) > BHA (2.181 ± 0.020, r^2:0.9868) > Catechin 5-O-gallate (1.432 ± 0.0034, r^2:0.9467) > Trolox (0.941 ± 0.027, r^2:0.9236) > α-Tocopherol (0.879 ± 0.012, r^2:0.9889)

ii. DPPH assay is based on the determination of the reducing ability of natural antioxidant compounds toward DPPH radicals (Göçer & Gülçin, 2011). Table 2 show IC_{50} values of Catechin 5-O-gallate and the reference radical scavenger agents like a-tocopherol, BHA, trolox and BHT. IC_{50} values were 8.43 mg/mL (r^2: 0.9127) for Trolox, 13.35 mg/mL (r^2: 0.9848) for BHA, 14.51 mg/mL (r^2: 0.9430) for BHT 15.23 mg/mL (r^2: 0.9637) for Catechin 5-O-gallate and 21.32 mg/mL (r^2: 0.9814) for α-Tocopherol.

iii. Another improved assay for the determination of radical scavenging is $ABTS^{\bullet+}$ scavenging activity (Gülçin, 2010). A lower IC_{50} values indicate higher $ABTS^{\bullet+}$ scavenging activity. ABTS radicals were generated in an ABTS/$K_2S_2O_8$ system. IC_{50} values for Catechin 5-O-gallate and the reference radical scavenger agents like α-tocopherol, trolox, BHA and BHT were 7.51 mg/mL (r^2: 0.9512) for Trolox, 8.77 mg/mL (r^2: 0.9635) for BHT, 9.57 mg/mL (r^2: 0.9462) for BHA, 10.83 mg/mL (r^2: 0.9807) for Catechin 5-O-gallate and 15.16 mg/mL (r^2: 0.9789) for α-Tocopherol (Table 2).

3.2. Enzymes results

Inhibition of metabolic enzymes was investigated, and their results were reported as follows.

i. Catechin 5-O-gallate had a K_i value of 135.13 ± 22.36 nM for the hCA I enzyme, and 94.37 nM for the IC_{50} value (Table 3). Catechin 5-O-gallate had a K_i value of 143.71 ± 17.02 nM for the hCA II isoform and 105.37 nM for the IC_{50} (Table 3). In this article the molecule of AZA was used as an inhibitor of CA. It is used in glaucoma treatment, epileptic seizures, idiopathic, intracranial hypertension and dural ectasia (Burmaoglu et al., 2019). K_i values for both isoforms are 145.47 ± 36.03 and 162.53 ± 34.38 nM, respectively. IC_{50} values of Catechin 5-O-gallate and standard (AZA) molecules were: Catechin 5-O-gallate (94.37 nM, r^2: 0.9915)<AZA (107.31 nM, r^2: 0.9973) for hCA I, while the values exhibited for hCA II isoform by these compounds are given in the following order: Catechin 5-O-gallate (105.37 nM, r^2: 0.9790)<AZA (124.34 nM, r^2: 0.9805). The CAI compounds were used in treatment of antiglaucoma, antiepileptics, altitude sickness and diuretics (Taslimi et al., 2017). AD in elderly people is an outcome of the malfunctioning of several biological metabolisms.

ii. Catechin 5-O-gallate was effective inhibiting AChE as metabolic enzyme. K_i values for AChE were obtained to be 22.34 ± 2.10 nM (Table 3). Also, the Tacrine (TAC) molecule was used as AChE enzyme control molecule; it had K_i values of 24.41 ± 5.23 nM. Catechin 5-O-Gallate and TAC values IC_{50} were: Catechin 5-O-gallate (27.27 nM, r^2: 0.9631) < TAC (31.03 nM, r^2: 0.9218) for AChE. AChE inhibitor compound is a neurotoxic molecule capable of causing central, peripheral or both peripheral and central cholinergic crises. The molecule investigated in the present study can record application as medicinal products developed to treat myasthenia gravis and AD.

iii. Conversely, Catechin 5-O-gallate shown as IC_{50} and K_i values are 69.26 nM, r^2:0.9441 and 85.18 ± 20.50 (Table 3). For the α-glycosidase present on cells lining, and the intestine, hydrolyzing monosaccharides are absorbed through the intestine. The results of the α-glycosidase assay showed that Catechin 5-O-gallate has an effective α-glycosidase inhibition profile compared to that of acarbose (IC_{50}: 148.82 nM, K_i:155.22 ± 19.90) as a standard α-glycosidase inhibitor (Tao et al., 2013). The inhibition of α-glycosidase digestive enzyme was of great importance for the treatment and prevention of diabetes, postprandial glucose levels and hyperglycemia (Taslimi et al., 2017).

3.3. Molecular docking results

Molecular docking is a method used to estimate the chemical and biological activities of molecules through theoretical calculations before experimental processes. Many parameters found in calculations through molecular docking method are shown in Table 4. Numerical values of these parameters are used to compare the biological activities of molecules. A well-known fact is that the most important factor affecting the biological activities of molecules is the interactions between molecules and enzymes (Figures 2–5).

These interactions have many variations such as hydrogen bonds, polar and hydrophobic interactions, π-π and halogen bonds (Jayarajan et al., 2020; Sayin & Karakaş, 2017, 2018a, 2018b; Sayin & Üngördü, 2019a, 2019b, 2019c). The

Table 3. The enzyme inhibition results of Catechin 5-O-gallate against human carbonic anhydrase isoenzymes I and II (hCA I and II), achethylcholinesterase (AChE) and α-glycosidase (α-Gly) enzymes.

	IC_{50} (nM)								K_i (nM)			
Compounds	hCA I	r^2	hCA II	r^2	AChE	r^2	α-Gly	r^2	hCA I	hCA II	AChE	α-Gly
Catechin 5-O-gallate	94.37	0.9915	105.37	0.9790	27.27	0.9631	69.26	0.9441	135.13 ± 22.36	143.71 ± 17.02	22.34 ± 2.10	85.18 ± 20.50
AZA[a]	107.31	0.9973	124.34	0.9805	–	–	–	–	145.47 ± 36.03	162.53 ± 34.38	–	–
TAC[b]	–	–	–	–	31.03	0.9218	–	–	–	–	24.41 ± 5.23	–
ACR[c]	–	–	–	–	–	–	148.82	0.9263	–	–	–	155.22 ± 19.90

[a]Acetazolamide (AZA) was used as a control for hCA I and II.
[b]Tacrine (TAC) was used as a control for AChE and BChE enzymes.
[c]Acarbose (ACR) was used as a control for α-glycosidase enzyme.

Table 4. Numerical values of the parameters obtained from interactions of molecule with enzymes.

	α-Gly	hCA I	hCA II	AChE
Docking score (kcal/mol)	−5.95	−5.69	−6.12	−7.51
Glide ligand efficiency (kcal/mol)	−0.19	−0.18	−0.19	−0.23
Glide Hbond (kcal/mol)	−0.16	−0.47	−0.26	−0.04
Glide Evdw (kcal/mol)	−24.10	−29.85	−26.36	−35.26
Glide Ecoul (kcal/mol)	−27.70	−16.92	−23.00	−19.67
Glide Emodel (kcal/mol)	−67.43	−66.01	−69.75	−72.36
Glide energy (kcal/mol)	−51.81	−46.76	−49.35	−54.92
Glide Einternal (kcal/mol)	11.52	1.74	4.28	10.56

parameters obtained as a result of the calculations were given in Table 4. This table compares the biological activities of molecules according to the numerical value of each parameter. The most important parameter among the parameters obtained as a result of the calculations is the docking score (Subhani et al., 2015), which has the lowest biological activity of the molecule whose numerical value is the most positive. However, another parameter is Glide Ligand Efficiency (Sever et al., 2019), which is a numerical value of the effectiveness of molecules. The parameters consisting of Glide Hbond, Glide Evdw and Glide Ecoul (Wang et al., 2019) are interaction related parameters. Another parameter is Glide Energy, which is a numerical value of the interaction energy. Glide Emodel and Glide Einternal (Atmaca et al., 2019; Türe et al., 2019) parameters are the numerical value of the interaction pose.

After molecular docking calculations, ADME/T analysis was performed to examine the drug's availability properties. As a result of this analysis, many parameters showing the numerical value of the molecule's effects and reactions in human metabolism were obtained. By interpreting these parameters, it is possible to design more effective and more active molecules.

The parameter obtained as a result of ADME/T analysis predicts the movements of the molecule in human metabolism. The effect of the drug molecule to be delivered to organs is theoretically examined. The first parameter among the obtained ones is Solute Molecular Weight (Mermer et al., 2019), which tells how much the molecular weight should be for a certain human metabolism. Another parameter is Solute Hydrophobic SASA (Bayindir et al., 2019), which is the Hydrophobic component of the SASA (saturated carbon and attached hydrogen). Another parameter is QPlogHERG (Acar et al., 2019), which is the predicted IC_{50} value for blockage of HERG K channels. Another parameter is QPPCaco (Menteşe et al., 2019), which is the predicted apparent Caco-2 cell permeability in nm/s. Caco-2 cells are a model for the gut-blood barrier. QikProp predictions are for non-active transport. The numerical value of this parameter should be <25 poor,> 500 great (in Table 5 '*'). Another parameter is QPlogBB (Turkan et al., 2019), which is Predicted brain/blood partition coefficient. Another parameter is QPPMDCK (Sağlık et al., 2019), which is the predicted apparent MDCK cell permeability in nm/s. MDCK cells are considered as a good mimic for the blood/brain barrier. QikProp predictions are for nonactive transport. The numerical value of this parameter should be <25 poor,> 500 great (in table '*').

Two parameters shown among the most important parameters obtained as a result of ADME/T analysis are RuleOfFive (Lipinski et al., 1997) and RuleOfThree (Jorgensen & Duffy, 2002) These parameters are more important than the others. When the numerical conditions of this parameter are not met, it can be stated that the molecule will not be a drug. RuleOfFive is Lipinski Rule of 5 which are known as the Pfizer 5 rule. This is number of violations of Lipinski's rule of five. The rules are: mol MW <500, QPlogPo/w < 5, donorHB ≤ 5, accptHB ≤ 10. Compounds that satisfy these rules are considered druglike (The 'five' refers to the limits, which are multiples of 5.). RuleOfThree is Jorgensen Rule of 3. This is Number of violations of Jorgensen's rule of three. The three rules are: QPlogS> −5.7, QP PCaco> 22 nm/s, # Primary Metabolites <7. Compounds with fewer (and preferably no) violations of these rules are more likely to be orally available.

4. Conclusions

Natural phenolic molecules can neutralize free radicals with their useful efficacy. Researchers have also concentrated on the pathological role of free radicals in a variety of diseases including cancer and atherosclerosis. In this study, Catechin 5-O-gallate's antioxidant activity has been compared with BHT, BHA, a-Tocopherol and Trolox. AChEIs are classified as substances linked to medicines and toxins. Catechin 5-O-gallate, which exhibited effective antioxidant activity, has potent effects inhibiting CA enzymes such as AZA. AZA, a well-known CA receptor, is a positive regulation agent, such as topiramate, zonisamide, methazolamide, which has been approved for epilepsy treatment and epileptic disorder. Digestive enzyme inhibition of α-glycosidase was of great importance for the treatment and prevention of diabetes and postprandial glucose amounts in hyperglycemia.

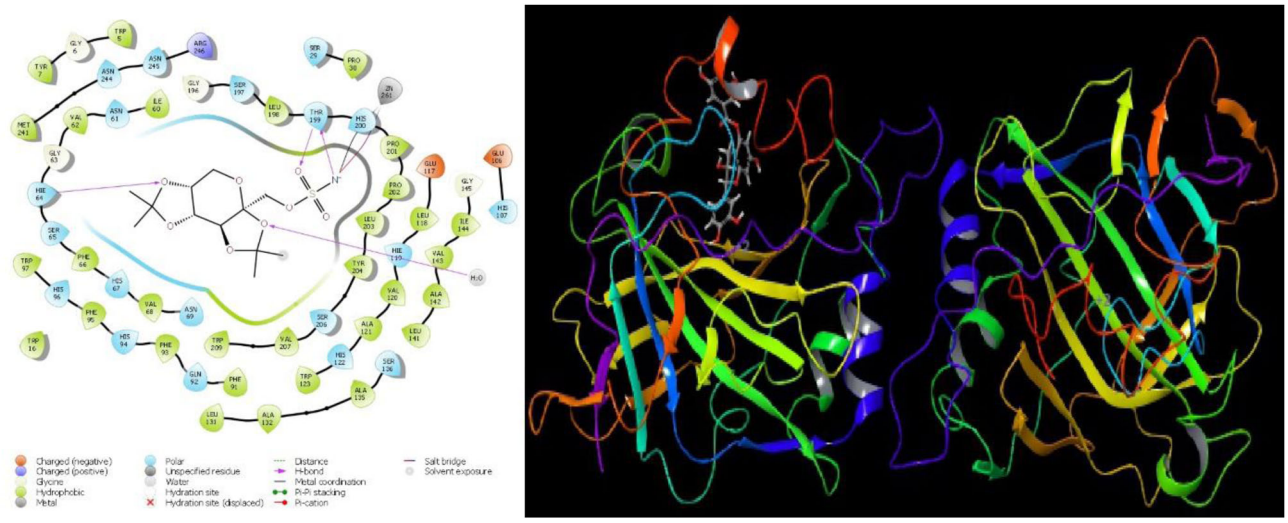

Figure 2. Demonstration of interactions of the molecule with α-Gly enzyme.

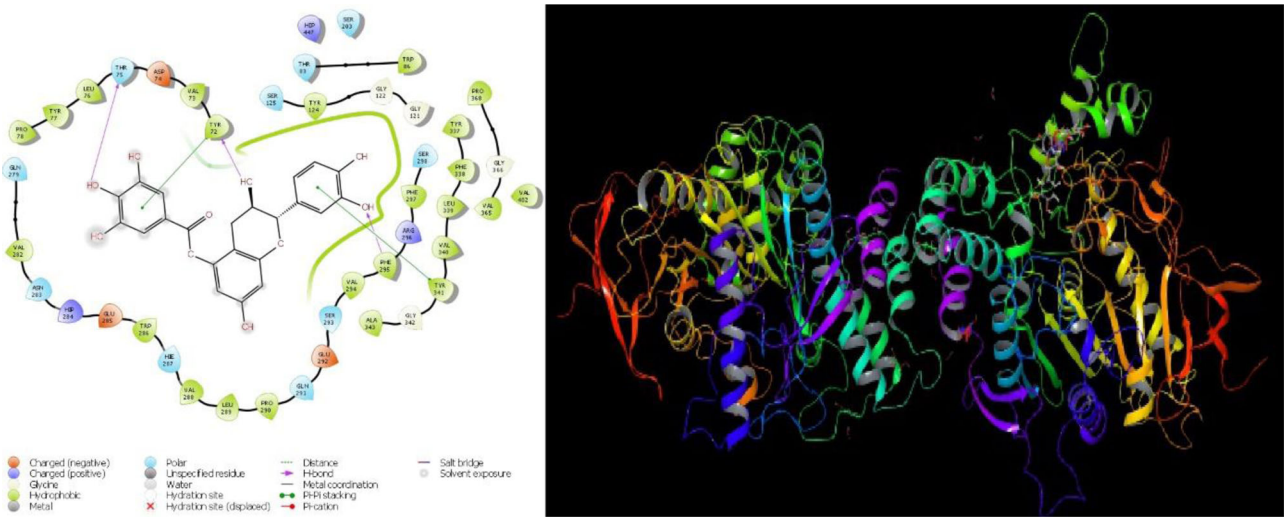

Figure 3. Demonstration of interactions of molecule with AChE enzyme.

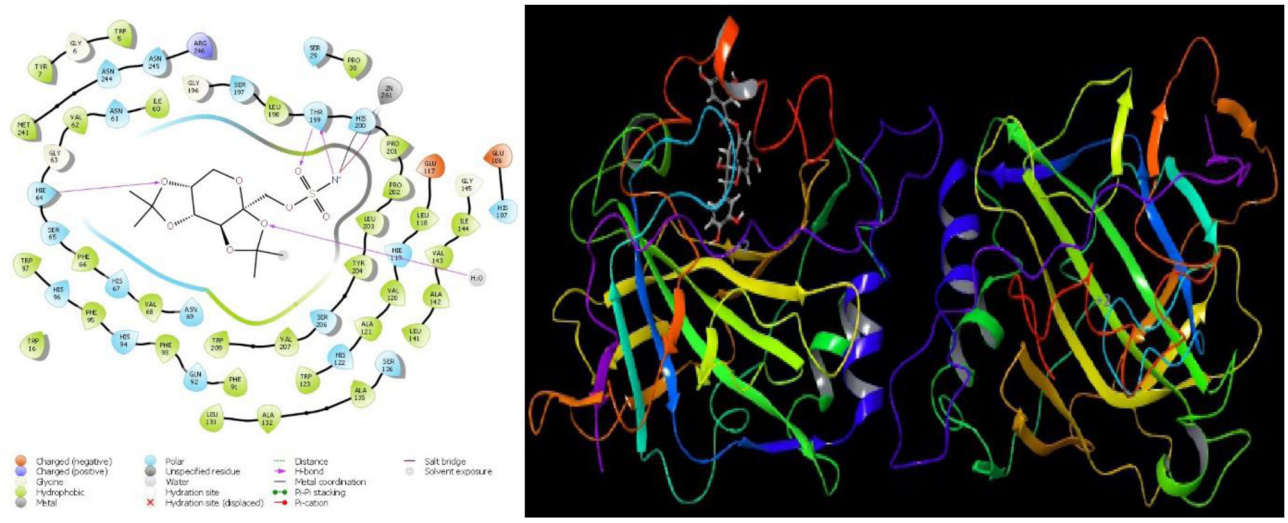

Figure 4. Demonstration of interactions of molecule with hCA I enzyme.

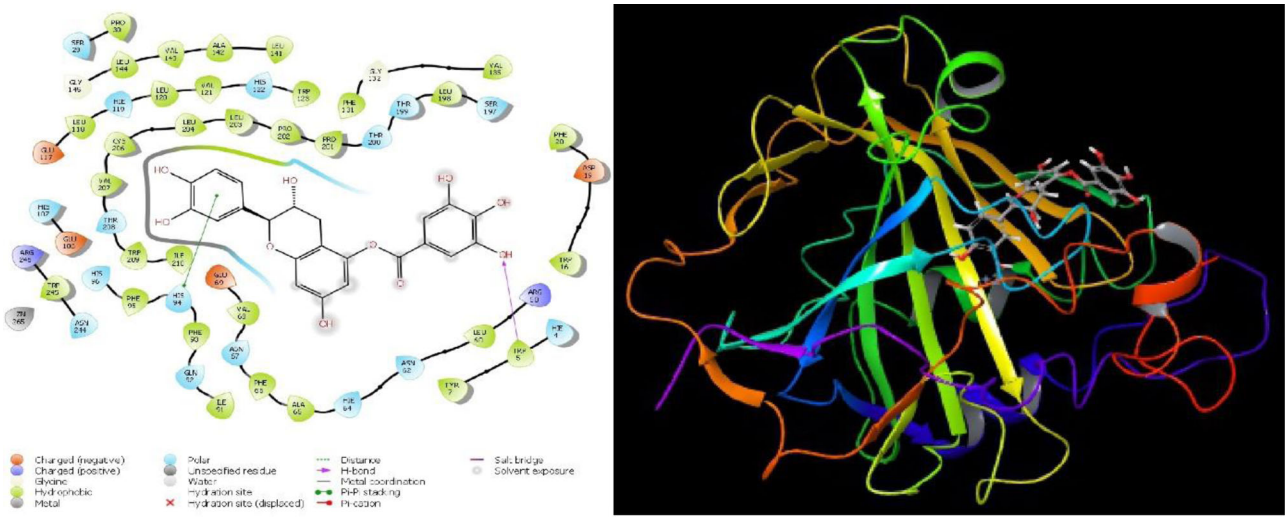

Figure 5. Demonstration of interactions of molecule 2 with α-Gly enzyme.

Table 5. ADME properties of molecules.

	Molecule	Referance range
Solute molecular weight	442	130–725
Solute dipole moment (*D*)	7.97	1.0–12.5
Solute total SASA	721	300.0–1000.0
Solute hydrophobic SASA	57	0.0–750.0
Solute hydrophilic SASA	393	7.0–330.0
Solute carbom Pi SASA	272	0.0–450.0
Solute weakly polar SASA	0	0.0–175.0
Solute molecular volume (A^3)	1266	500.0–2000.0
Solute as donor-hyrogen bonds	7	0.0–6.0
Solute as acceptor-hyrogen bonds	9.45	2.0–20.0
Solute globularity (Sphere = 1)	0.78	0.75–0.95
QP polarizability (Angtroms ^3)	41	13.0–70.0
QP log p for hexadecane/gas	16	4.0–18.0
QP log p for octanol/gas	31	8.0–35.0
QP log p for water/gas	24	4.0–45.0
QP log p for octanol/water	−0.01	−2.0–6.5
QP log S aqueous solubility	−4.13	−6.5–0.5
QP log S-conformation indepent	−5.15	−6.5–0.5
QPlogHERG	−6.32	(corcern below −5)
QPPCaco (nm/s)	1.88	*
QPlogBB	−4.23	−3.0–1.2
QPPMDCK (nm/s)	0.56	*
QPlogKp	−6.93	Kp in cm/h
IP (ev)	9.41	7.9–10.5
EA (eV)	0.47	−0.9–1.7
#metab	9	1.0–8.0
QPlogKhsa	−0.41	−1.5–1.5
Human oral absorption	1	–
Percent human oral absorption	19	**
PSA	192	7.0–200.0
RuleOfFive	1	Maximum is 4
RuleOfThree	2	Maximum is 3
Jm	0.00	$K_p \times MW \times S$ ($\mu g.cm^{-2}.h^{-1}$)

*<25 is poor and >500 is great.
**<25% is poor and >80% is high.

As a result of molecular docking calculations, the interactions of the molecule with enzymes were examined. The calculations showed that the most important factor determining the biological activity of molecules is interaction. Therefore, it has been found that as the interactions of molecules with enzymes increase, the biological activities of molecules can be increased. As a result of ADME/T analysis, it is possible to use this molecule as a medicine in the future.

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ORCID

Parham Taslimi http://orcid.org/0000-0002-3171-0633
Umit M. Kocyigit http://orcid.org/0000-0001-8710-2912

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