The inhibition profile of sesamol against α-glycosidase and acetylcholinesterase enzymes

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ABSTRACT
Sesamol (1,3-benzodioxol-5-ol) is found in the oilseed product, sesame. In our study, the inhibitory effects of sesamol compound on acetylcholinesterase and α-glycosidase enzymes were evaluated. Another aim of this study was to compare the inhibitory effects of sesamol to acarbose for α-glycosidase enzyme and tacrine for acetylcholinesterase (AChE). Sesamol exhibited non-competitive inhibition for both metabolic enzymes. IC$_{50}$ values for AChE and α-glycosidase enzymes were calculated as 86.63 nM and 99.00 nM, respectively. On the other hand, $K_i$ values were calculated as 46.68 nM and 75.33 nM for AChE and α-glycosidase enzymes, respectively. According to the obtained results showed effective inhibition at low concentrations.

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Introduction
Enzymes are catalyst molecules that are specific to reactions, which accelerate chemical reactions and return to their original state even if they have been physically altered during these reactions.$^{[1–4]}$ Reduce or destroy the enzymes in the event of activity both in vivo and in vitro by certain compounds called enzyme inhibition. Inhibitor is a molecule or ions that binds to an enzyme and decreases its activity.$^{[5–7]}$

Acetylcholinesterase (AChE; E.C.3.1.1.7) is an enzyme in the family of cholinesterases. AChE is a membrane-bound enzyme. Acetylcholinesterase is responsible for the hydrolysis of choline esters.$^{[8–10]}$ AChE is a type of hydrolase that hydrolyzes ACh to choline and acetic acid. In addition, it was found cholinergic, central, peripheral, cholinergic, adrenergic, muscle, nerve, placental tissue and erythrocytes in the body. The decrease in AChE activity causes many health problems including nervous system disorders.$^{[11,12]}$ The most important substrate of acetylcholinesterase is acetylcholine (ACh).$^{[13]}$ A sudden drop in the level of acetylcholine can cause death. Alzheimer’s disease (AD) occurs with gradual decline of this level.$^{[14–16]}$ One of the most important substrates of acetylcholinesterase is acetylcholine (ACh).$^{[13]}$ AChE enzyme was first obtained by the extraction of the electric organ from electric fish of Torpedo marmorata.$^{[27]}$ Many properties of AChE have been discovered as a result of studies on the enzyme purified from electric eel (Electrophorus electricus).$^{[28]}$

Glucose is one of the most important food sources in living organisms and controlled via insulin in the blood.$^{[29,30]}$ Diabetes mellitus (DM) occurs when glucose concentration is above normal level.$^{[31,32]}$ Since insulin hormone cannot be released regularly, it cannot tolerate this glucose. DM is a chronic disease seriously affecting the quality of life.$^{[33–35]}$ Unfortunately, this disease cannot be completely...
treated. Uncontrolled blood sugar is the main problem of diabetes. In Type-2 diabetes, either a decrease in insulin secretion in peripheral tissues or a disorder in insulin secretion is caused. If hyperglycemia is not controlled long term, there may occur with dysfunction or failure of various organs. As an oral antidiabetic drug, α-glycosidase enzyme inhibitors are preferred.

α-Glycosidase (E.C.3.2.1.20) is an enzyme found in the small intestine spicular surface. It is responsible for breaking down complex carbohydrates. α-Glycosidase inhibitors retard the absorption of carbohydrates by inhibiting α-glycosidase enzymes of the small intestine. α-Glycosidase inhibitors not only inhibit carbohydrate absorption but also affect the gastrointestinal hormone axis. α-Glycosidase inhibitors are antihyperglycemic agents. The postprandial plasma glucose lowering in fasting plasma glucose in mildly decreases. It prevents the breakdown of complex carbohydrates.

Sesame (Sesamum indicum L.) is one of the most important seeds used in oil. Protein and fat contents are very high. Sesamol (3,4-methylenedioxyphenol), a component of sesame oil used in our study, is a natural organic compound. Sesamol is a white crystalline solid with a phenol derivative (Figure 1). It is slightly soluble in water but can be miscible with most fats. This compound can be produced by organic synthesis from heliotrope. Sesamol has been found to be an antioxidant and antifungal that can prevent the deterioration of fats.

**Materials and methods**

**Chemicals**

α-Glycosidase from Saccharomyces cerevisiae, α-D-glycopyranoside (p-NPG), p-Nitrophenyl AChE purified from electric eel (Electrophorus electricus), Sesamol was purchased from Sigma-Aldrich (G5003; St. Louis, MO).

**Measurement of acetylcholinesterase activity**

Acetylcholinesterase activity was spectroscopically performed according to Ellman’s method as described previously. In this method, acetylthiocholine is used as substrate. 5,5'-Dithio-bis (2-nitrobenzoic) acid (DTNB) and acetylcholine iodide (AChI) were used as substrates of AChE activities. Tris-HCl buffer (1.0 M, pH 8.0) and sample solutions with different concentrations were dissolved in pure water. The resulting solution 30 μL AChE solution was added. The mixture was incubated for 10 min at 25°C. Then, DTNB (0.5 mM, 100 μL) was supplemented. After this procedure, the reaction mixture was added 100 mL AChI (10 mM) and activity studies was complete. Absorbances at 412 nm were evaluated in the enzyme.

**Measurement of α-glycosidase inhibitory activity**

For determination of α-glycosidase activity, p-NPG was used as the substrate. For this purpose, sesamol was prepared by dissolving ethanol (1 mg mL$^{-1}$). Firstly, 0.2 mL of NaH$_2$PO$_4$ with pH 7.4...
and 20 μL of enzyme solution were mixed. And then, different quantities of sesamol were added into the current solution and these were mixed. After, it was incubated at 35°C for 10 min by adding the p-NPG to initiate the reaction. In addition, 100 μL of p-NPG at pH 7.4, 5 mM of sodium phosphate buffer after preincubation was added and the incubation was again carried out at 35°C. IC₅₀ values were evaluated with the obtained data. Absorbance values were measured at 405 nm.

Results and discussion

Today, enzymes are widely used in medicine, food industry, and environmental industries. The elucidation of metabolic mechanisms of inhibitors is a guide for biochemists.[59,60] The chemical structure of sesamol is given in Figure 1. It was known that sesamol could cross the blood–brain barrier. In this case, sesamol can affect many tissues, especially kidneys, liver, and brain. It was first came the liver by spreading into other tissues such as kidney, lung, and brain.[61] As shown in Figure 2 and Table 1, sesamol had marked inhibition effects against α-glycosidase enzyme at nanomolar level. Agents identified as α-glycosidase inhibitors reduce postprandial plasma glucose and moderate fasting plasma glucose. These agents prevent the breakdown of complex carbohydrates. Malabsorption is not observed with α-glycosidase inhibition. Thus, the agents can reduce glucose levels and postprandial hyperglycemia by 35–45%.[62]

Also, it was determined that sesamol inhibited AChE and α-glycosidase enzymes as noncompetitive (Table 1 and Figure 3). Accordingly, the inhibitor was bound to a different domain than the active site of the enzyme.[63] AD is a neurodegenerative disease that demonstrates behavioral disorders such as loss of cognitive activity, lack of self-care, and neuromuscular damage as a result of synapse and neuron cell damage affecting the central nervous system.[63,64] Today, AChE inhibitors are the most important and the only group of drugs used to treat AD.[65,66] If the activity of the AChE enzyme is reduced or stopped, acetylcholine molecules will be less degraded and thus the acetylcholine concentration will remain high and the solution for the disease may be present.[7,67]

Preferred AChE inhibitors for treating AD are inhibitors that increase the activity of cholinergic neurotransmission by increasing the amount of ACh.[68,69] As the most potent inhibitor, the long-acting tacrine (IC₅₀: 8.18 nM; Kᵢ: 8.59 ± 5.38 nM) compound has a hepatotoxic effect. In particular, it was found

![Figure 2](image-url)  
Figure 2. Determination of IC₅₀ (a) and Kᵢ (b) values of the Sesamol on acetylcholinesterase (AChE) enzyme.

| Enzymes       | IC₅₀(nM) | r²         | Kᵢ (nM)     | Inhibition Type         |
|---------------|---------|------------|-------------|-------------------------|
| AChE          | 86.63   | 0.9871     | 46.68 ± 7.51| Non-competitive          |
| α-Glycosidase | 99.00 nM| 0.9567     | 75.33 ± 31.69| Non-competitive          |
that the liver enzyme increases alanine transaminase level. Because of these reasons, its usage has been restricted. Galantamine, donepezil, and rivastigmine are the current drugs used for the treatment of AD. As can be seen in Figure 1, the sesamol contains benzodioxol and phenolic groups. Both groups are responsible for biological activities. In recent studies, sesamol has been shown to be anticancer and inhibits growth in heart cells. It was thought that there was a relationship between neurodegenerative diseases and monoamine oxidase activity. Sesamol may play a protective role in such diseases. It is thought that the sesamol used in this study can also be used for this purpose. In particular, it has been shown that this compound obtained from the sesame plant may be more effective for our natural metabolism. The IC$_{50}$ of the AChE was calculated as 86.63 nM and the Ki value was 46.68 nM. Sesamol showed non-competitive inhibition. So, the molecule by showing the non-competitive inhibition, it binds to outside active site of the enzyme. In this way, it reduces the catalytic activity of the enzyme and causes non-competitive inhibition. Thus, the amount of ACh is thought to remain in high level.

Comparing current results with previous results, it was found that novel bromphenols (Ki: 159.6–924.2 nM), oxazolidinone (Ki: 16.5–35.6 nM), pyrazolines (Ki: 48.2–84.1 nM), hydrazones (Ki: 66–128 nM), tacrine derivatives (Ki: 68–8480 nM), sulfamides (Ki: 0.027–0.076 nM), olivetol (Ki: 3.40 nM), and benzenesulfonamides (Ki: 22.7–109.1 nM) effectively inhibited AChE enzyme.

As seen in Figure 4, α-glycosidase enzyme, which released from intestine cells, hydrolyzes the oligosaccharides and polysaccharide to monosaccharide units, such as glucose and fructose in small intestine. It is not able to use glucose as a result of a metabolic disorder in Type 2 diabetes mellitus (T2DM). After the meal, cellular glucose uptake increases with insulin secretion. Thus, the production of glucose stops in the liver. As a result, the blood sugar concentration increases. In this way, a condition called hyperglycemia occurs. The osmotic balance in dehydrated cells is impaired and causes symptoms of diabetes. These symptoms include thirst and excessive urination. The treatment of DM includes physical activity, diet, education, and medicine. Oral antidiabetics and insulin therapy are used if other routes are unsuccessful or insufficient to control blood sugar in T2DM. Acarbose and voglibose are α-glycosidase inhibitors and orally used. Highly effective but they can cause adverse effects such as bloating, diarrhea and abdominal distention. As given in Table 1, sesamol showed nanomolar level inhibition against α-glycosidase enzyme. The IC$_{50}$ value was calculated as 99.00 nM (r$^2$: 0.9567). On the other hand, the Ki value was calculated as 75.33 nM. Whereas, IC$_{50}$ value of acarbose, which used as the α-glycosidase inhibitor, was found to be 22.80 μM. It is thought that sesamol obtained from natural product will guide oral diabetic drug groups according to these values.
Conclusion

It is clearly seen that sesamol had efficient inhibition properties on AChE and α-glycosidase enzymes. So this phenolic compound can be considered for treatment of nervous system and T2DM. Besides consumption, it was believed that its biological activity would inspire for drug designers in the treatment of many diseases including myasthenia gravis, postural tachycardia syndrome, AD (as cholinergic enzymes inhibitors) and treatment of T2DM (as α-glycosidase inhibitors).

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