

Araştırma Makalesi / Research Article

The Effects of *Coriandrum sativum* L. and *Chaerophyllum macropodum* Boiss. (Apiaceae) on human plasma angiotensin-converting enzyme (ACE) *in vitro*

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Abstract

Hypertension is a very important problem around the world. The inhibition of the Angiotensin-converting enzyme (ACE, EC.3.4.15.1.) is regarded as fundamental of hypertension treatment. However, synthetic ACE inhibitors have several side effects. For this reason, there are lots of studies to improve green ACE inhibitors. Therefore, this study was designed to determine the potential inhibitory effects of two members of Apiaceae, *Coriandrum sativum* and *Chaerophyllum macropodum*, on human plasma ACE. For this purpose, water extracts of the plants were used. ACE inhibition activity was detected spectrophotometrically. Both plant extracts showed an inhibitory effect on ACE activity. The obtained results showed that *Coriandrum sativum* and *Chaerophyllum macropodum* have inhibitory effects on human plasma ACE with an IC₅₀ value of 0.7 mg/mL and 1.14 mg/mL, respectively. Lineweaver-Burk graph was used to determine the inhibition type. The inhibition types were found as reversible noncompetitive. According to the obtained results, *Coriandrum sativum* and *Chaerophyllum macropodum* are valuable functional food with ACE inhibition capacity which may be used to balance blood pressure efficiently.

Keywords: Hypertension, Angiotensin-converting enzyme I, *Coriandrum sativum*, *Chaerophyllum macropodum*, Apiaceae

***Coriandrum sativum* L. ve *Chaerophyllum macropodum* Boiss. (Apiaceae)'nin *in vitro* İnsan Plazma Anjiyotensin Dönüştürücü Enzim Üzerine Etkileri**

Öz

Hipertansiyon dünya çapında çok önemli bir problemdir. Anjiyotensin dönüştürücü enzimin (ACE, EC.3.4.15.1.) inhibisyonu, hipertansiyon tedavisinin temeli olarak kabul edilir. Ancak sentetik ACE inhibitörlerinin bazı yan etkileri vardır. Bu nedenle, doğal ACE inhibitörleri geliştirmek için birçok çalışma yapılmaktadır. Bu sebeple, bu çalışma, Apiaceae'nin iki üyesi olan *Coriandrum sativum* ve *Chaerophyllum macropodum*'un insan plazma ACE'si üzerine potansiyel inhibitör etkilerini belirlemek için tasarlanmıştır. Bu amaçla, bitkilerin su ekstraktları kullanılmıştır. ACE inhibisyon aktivitesi spektrofotometrik olarak tespit edildi. Her iki bitki özütü de ACE aktivitesi üzerinde inhibe edici etki gösterdi. Elde edilen sonuçlar, *Coriandrum sativum* ve *Chaerophyllum macropodum*'un sırasıyla 0,7 mg/mL ve 1,14 mg/mL IC₅₀ değeriyle insan plazma ACE üzerine inhibe edici etkilere sahip olduğunu gösterdi. İnhibisyon tipini belirlemek için Lineweaver-Burk grafiği kullanıldı. İnhibisyon türleri geri dönüşümlü, yarışmasız inhibisyon olarak bulundu. Elde edilen sonuçlara göre, *Coriandrum sativum* ve *Chaerophyllum macropodum*'un ACE inhibisyon kapasitesine sahip, kan basıncını etkin bir şekilde dengelemek için kullanılabilecek, değerli fonksiyonel gıdalardır.

Anahtar kelimeler: Hipertansiyon, Anjiyotensin dönüştürücü enzim I, *Coriandrum sativum*, *Chaerophyllum macropodum*, Apiaceae

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1. Introduction

Hypertension is very important health problem causing death around the World, and it is associated with coronary diseases [1]. Pathogenesis of this disease has indicated that the angiotensin-converting enzyme (ACE) is a powerful regulator for the balance of blood pressure [2]. ACE is a peptidase in the renin-angiotensin system (RAS) which transforms angiotensin I into the angiotensin II [3]. RAS has a central role in the regulation of peripheral electrolyte homeostasis and blood pressure in mammals [4]. Juxtaglomerular cells of the kidney release renin regulating the decrease in blood pressure and volume of the kidney [5]. Renin helps in the formation of angiotensin I [6]. However, the blocking of ACE activity suppresses the angiotensin II production and reduces blood pressure. In this way, ACE inhibitors are used to treat hypertension in medicine [7]. Today, several ACE inhibitors are in use clinically to treat hypertension, which includes captopril, lisinopril, and temocapril. But synthetic ACE inhibitors have several adverse impacts such as coughing, rashes, and taste aversion [8]. For this reason, research interests have focused on ACE inhibitors from natural sources including plants [9,10]. It has been reported that some plant extracts showed the inhibition effect on ACE, such as *Glycine max* [11], *Cassia tora* [12], *Rosa damascene* [13], and *Thymbra sintenisii* [14].

Apiaceae is known as a large plant family which includes 3780 species in 434 genera [15]. Apiaceae family is generally seen in the northern area and Mediterranean countries [16]. Approximately, 101 genera including 451 species of this family have been determined in Turkey [17], and the members of this family are used in cosmetics including perfumery and pharmaceutical industries [16,18].

Chaerophyllum genus of Apiaceae shows distinctive fragrant character, by this way, they are used in preparations of food, such as flavoring in cheese production, and also consumed as an edible vegetable in Turkey and Iran [19-21]. *Chaerophyllum macropodum* (*C. macropodum*) is traditionally mixed into herby cheese which is a famous dairy product for its aroma and flavor in Turkey [21]. But there is limited knowledge about the bioactivity of *C. macropodum*. The studies on *Chaerophyllum* species have shown that it has phenylpropanoids, phenolic acids, flavonoid glycosides, and polyacetylenes [22]. In addition, there are some reports that indicate chemical composition, antioxidant and antimicrobial effects of *C. macropodum* [20-22]. To our best knowledge, there is no report about the inhibitory effect of *C. macropodum* on ACE activity.

Coriandrum sativum L. (*C. sativum*), another member of the family Apiaceae, is a biennial herb. *C. sativum* is cultivated in Asia, Europe, and North Africa and green leaves of *C. sativum* are a rich source of minerals, vitamins and iron [23]. Its seed oil is widely used in cosmetic, soft drink, food, and chocolate industries [24]. *C. sativum* is traditionally used to treat disorders such as respiratory, urinary systems disorders, diabetes, inflammation, and anxiety [25-27]. In addition, it has been stated that *C. sativum* has analgesic [28], anti-insulin resistance activity [29], and antihypertensive properties [30].

As far as we know, there is no study about the inhibition effects of *C. sativum* and *C. macropodum* on human plasma ACE activity *in vitro*. Thus, the present study was designed to investigate the inhibition properties of *C. sativum* and *C. macropodum* on human plasma ACE *in vitro* for the first time.

2. Material and Methods

2.1. Plant Material

Chaerophyllum macropodum Boiss. was collected in Diz Stream of Hakkari Cilo mountain at 1730m. in May. *Coriandrum sativum* L. was collected at 850 m in Siirt Kurtalan in June. Scientific diagnoses of the plants were made by Mehmet FIRAT from Van Yuzuncu Yil University, Faculty of Education, Department of Biology

2.2. Plant Extraction

After the plant samples were dried properly, they were ground into a fine powder with the help of a blender. Then, 90 mL of hot water was added by weighing 10 g of each of the plant samples and kept at room temperature until it cools down. Then, it was used fresh by filtering through filter paper. Stock solutions were stored at +4 °C [31]. Minor modification were made to the method.

2.3. Preparation of the human plasma

Blood samples were taken from the Van Red Crescent Blood Center of Turkey. The samples were added into tubes including EDTA and centrifuged at 1500 rpm for 15 minutes. Obtained plasma was centrifuged again for 1 hour (40 °C, 8500 rpm) to uproot the ghosts and intact cells. Plasma samples were then stored [14]

2.4. Determination of ACE Activity

The ACE activity was determined according to Holmquist et al. (1979). Fifty mM HepesNa buffer, 0.3 M NaCl, 10 µM ZnCl₂, and 1 mM FAPGG were added to the assay cuvette. One unit of activity was defined as the quantity of ACE that produces a ΔA 345/min of 1.0 [32,33].

2.5. ACE Inhibition Assay

The experiments were carried out in the laboratories of the Van YYÜ Chemistry Department. In the test, human plasma was used to evaluate ACE activity. Two experimental tubes were received as blank and sample. Then, 100 µL of plasma containing ACE was added to each tube. After this, 900 µL of HEPES buffer (50 mM HEPES, 0.3 M NaCl, 10 µM ZnCl₂ pH 7.5) was put into the blank tube and stirred. The spectrophotometer (Shimadzu 1800 UV-Vis) was reset with a blank tube. Fifty mM HEPES buffer (pH 7.5), inhibitor (plant extracts), and 1 mM substrate (FAPGG) were added to the sample tube (total volume 1000 µL) and stirred. Different concentrations of *C. sativum* and *C. macropodium* extracts (at 0, 0.25, 0.5, 0.75, 1 mg/mL) were used. The absorbance value was read at 345 nm. The sample tube was incubated for 30 minutes at 35 °C. After the waiting time, the absorbance of the tubes was determined at 345 nm. The reduction in absorbance was calculated.

$$A (\text{ACE Activity}) = (\Delta\text{OD}/0.517) \times (\text{Vc}/\text{Ve}) \times f$$

ΔOD: Difference between optic densities at 345 nm for per minute

Vc: Whole volume

Ve: Volume of enzyme solution (plasma hemolysate)

f: Dilution factor

0.517 mM⁻¹ cm⁻¹: Extinction coefficient of FAPGG

The inhibition activity of ACE was found from the calibration curve and calculated via the following equation:

$$\% \text{ ACE inhibition} = (\text{Uninhibited activity} - \text{Inhibited activity}) / \text{Uninhibited activity} \times 100$$

In this study, the inhibition affects *C. sativum* and *C. macropodium* plants on the ACE enzyme in human plasma was investigated. Extracts of both plants showed a reversible-noncompetitive inhibition effect on ACE. Inhibition type and IC₅₀ values were determined from Lineweaver-Burk and % Activity versus inhibitor concentration graphs for each plant extract.

3. Results and Discussion

Hypertension is identified an important health problem which affects one billion people around the world [34]. Moreover, it is known as a “silent killer” due to its asymptomatic affect in adults [35]. It has been reported that the inhibition of ACE is an important way of hypertension treatment. This enzyme is zinc-dependent metalloproteinase that transforms angiotensin I to angiotensin II and promotes the degradation of vasodilator bradykinin [36]. In addition, it has been stated that hypertension may be prevented by ACE inhibitors [37]. These inhibitors are shown as the first step for the treatment of hypertension, myocardial infarction and heart failure [38]. At this point, ACE inhibitors may effectively reduce blood pressure, but synthetic medications can cause some adverse effects [39,40]. Recently, there is a considerable interest in green components for treatment of hypertension [41].

These plants which are used in folk medicine have been used to treat some illness in all civilizations. These medicinal plants are popular because of their efficiency, cheapness, and few adverse effects. It has been reported that more than two thousand plants have been identified as a medicinal herb for the treatment of hypertension including cardioprotective, cardioactive, cardiostimulant, or circulatory stimulating activities [42]. Moreover, it has been concluded that bioactive components that are available

in foods and medicinal plants prevent cardiovascular health [43]. These components such as phenolic acids, alkaloids, polyphenols, flavonoids, tannins, polysaccharides, and sterol have been shown as ACE inhibitors [44]. These natural components are very important for preventing and treating hypertension. Flavonoids have been documented to inhibit different zinc metalloproteinases such as ACE, and anthocyanins, flavones, flavonols, and flavanols have been reported to have an inhibitory potential more than %50 of ACE. Furthermore, it has been exhibited that flavonoid-rich foods may lower blood pressure and inhibit ACE [45]. In addition, it has been revealed that edible plant components including peptides, flavonoids, and phenolic contents inhibit ACE activity [46,47]. Thus, in this study, two members of Apiaceae which are edible plants and rich in bioactive components were investigated as a potential ACE inhibitor [22,48]. With this aim, water extracts of *C. sativum* and *C. macropodium* were used to find their inhibitor potentials on human plasma ACE activity. To determine their inhibition potentials, the spectrometric method was used. Human plasma samples were treated with different concentrations of extracts. Then, Lineweaver-Burk graph was plotted for the determination of inhibition type with different FAPGG concentrations and different *C. sativum* and *C. macropodium* concentrations. Inhibition types were detected as reversible noncompetitive. The obtained results showed that *C. sativum* and *C. macropodium* have an inhibition potential on ACE activity in a dose-dependent manner with an IC_{50} value of 0.7 mg/mL and 1.14 mg/mL, respectively as shown in Figure 1 and Figure 2. Inhibition types were detected as reversible noncompetitive (Figure 3 and Figure 4).

The obtained data are in accordance with previous reports in the literature. In a study, Hussain et al (2018) reported that *C. sativum* has ACE inhibition potential. In the study, researchers determined that fresh leaves of *C. sativum* have good inhibition potentials on ACE [49]. Moreover, they fractionated four secondary metabolites to find out actual bioactive compounds against the ACE activity. At the end of the study, they concluded that flavonoid-rich fraction has the most powerful ACE inhibitory effect and IC_{50} value was detected as 28.91 μ g/mL. In another work, Ali et al (2019) reported that methanolic extract of whole plants of *Angelica decursiva* has inhibitory effects against ACE [50]. Hyun et al (2013) reported that *A. gigas* and its coumarin constituents have a potential inhibitory effect on ACE [51]. In addition, it has been shown that *Centella asiatica* (Apiaceae) has an inhibition effect on ACE [52]. Simaratanamongkol et al (2014) concluded that methanolic extract of *Apium graveolens*, another member of apiaceae, showed important ACE inhibitory activity. They detected IC_{50} value as 1.7 mg/mL [53]. Suručić et al (2017) reported that essential oil of *S.pallasii* showed dose-dependent inhibition capacity on ACE with an IC_{50} value of 0.33 mg/mL [54]. In contrast to the results from our work, Saleem et al. (2017) stated that ethanol and water extracts of seeds of dill, ajowan, fennel, coriander, and anise from Apiaceae family did not show an inhibition effect on ACE [55]. This difference may be due to the extractions used in the study and bioactive component content. Similarly, Hussain et al (2018) reported that fresh leaves of *C. sativum* have high ACE inhibitory effect while the seeds of the plant did not have any ACE inhibitory affect [49].

In conclusion, the obtained results show that *C. sativum* and *C. macropodium* have an inhibitory affect on human plasma ACE activity *in vitro*. If these plants are used in an appropriate way, they can prevent cardiovascular diseases. But, further studies are needed to use this plant safety for treatment of hypertension.

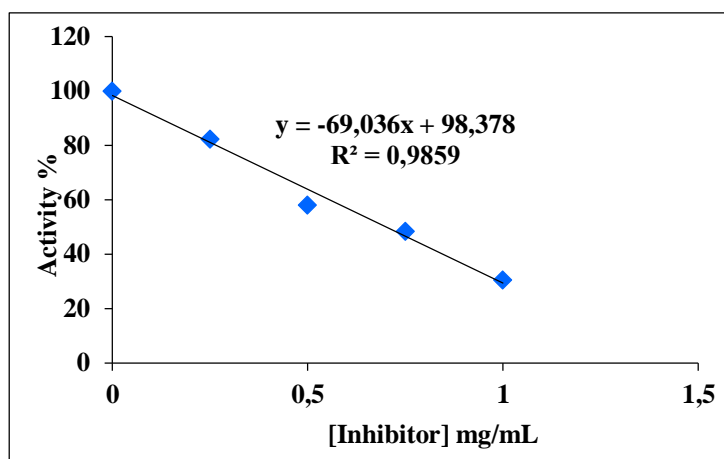


Figure 1. The inhibition effect of *C. sativum* L. extract on the ACE activity

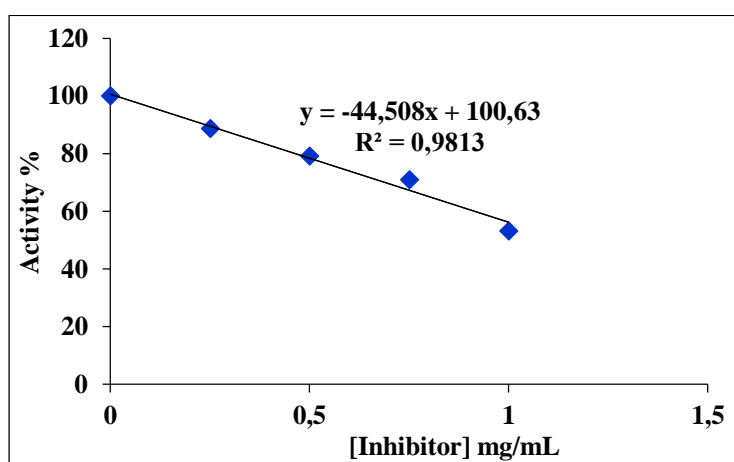


Figure 2. The inhibition effect of *C. macropodium* extract on human plasma ACE activity.

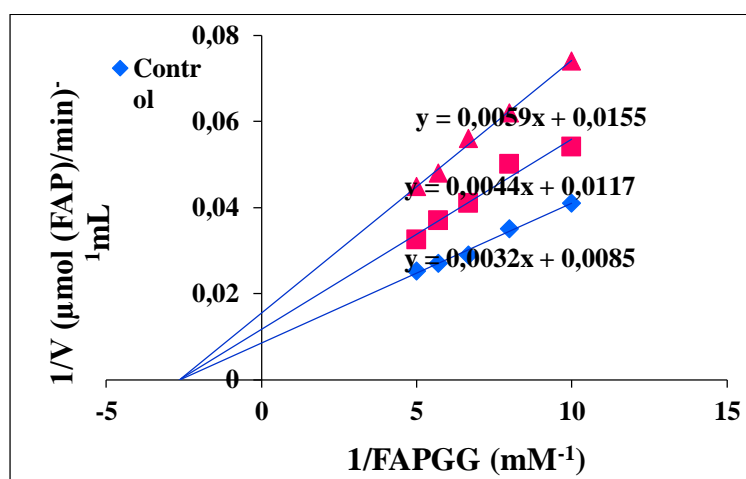


Figure 3. Lineweaver-Burk graph with different FAPGG concentrations. Two different *C. sativum* concentrations were used for the evaluation of inhibition type.

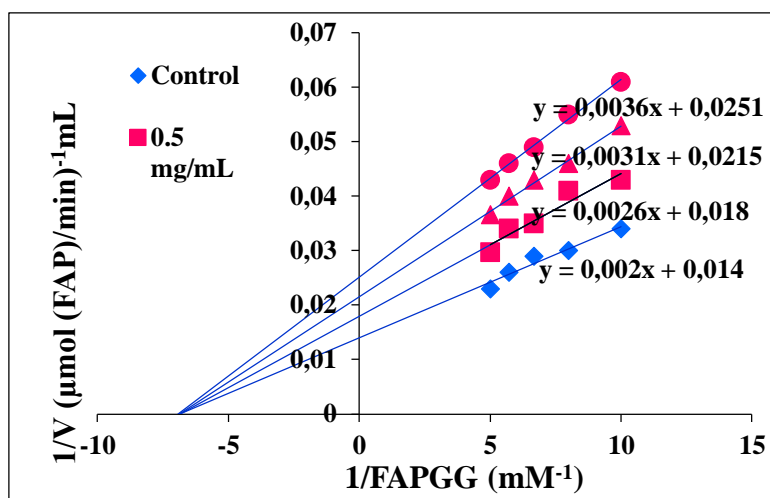


Figure 4. Lineweaver-Burk graph with different FAPGG concentrations and three different *C. macropodum* concentrations were used for the evaluation of inhibition type.

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Author's Contributions

Fatih Çağlar ÇELİKEZEN and Vedat TÜRKÖĞLU contributed to the planning of the study, literature review, experimental studies, writing and evaluation of the study results. Mehmet Fırat took part in the collection and scientific diagnosis of plants. Zehra BAŞ took part in experimental studies and interpretation and writing of the results.

Statement of Conflicts of Interest

There is no conflict of interest among the authors.

Statement of Research and Publication Ethics

The authors declares that this study complies with Research and Publication Ethics.

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