

Effects of Pennyroyal (*Mentha pulegium* L.) on Angiotensin Converting Enzyme-2 (ACE-2) and Antioxidant Parameters in Rabbits

Mustafa Makav^{1a}Mükremin Ölmez^{2b}

ABSTRACT

Many studies have been conducted on medicinal aromatic plants in recent years. Alternative medicine particularly comes to the fore as an alternative to the use of synthetic agents. The antioxidant, anti-inflammatory, antimicrobial and antiviral effects of phenolic compounds, especially in the structure of aromatic plants, are known. Among those well-known aromatic plants, Pennyroyal (*Mentha pulegium* L.) is known to contain a large amount of phenolic compounds. In our study, by taking these effects of phenolic compounds into consideration, the effectiveness of pennyroyal on antioxidant parameters and Angiotensin-converting enzyme 2 (ACE2), and that has many important functions in the organism, was evaluated. A total of 15 New Zealand rabbits were used in the study. The animals were divided into three experimental groups with 5 rabbits in each group. While no Pennyroyal was added to the control group, 0,1% and 0,2% were added to the diets for the other groups. All groups were fed ad-libitum. On the 14th day of the experiment, serum ACE2, GSH and MDA levels were determined with blood taken from the ears of the rabbits. According to the analysis results, while a decrease in ACE2 and MDA levels was determined in the groups which were given 0,1% and 0,2% Pennyroyal compared to the control group, a significant increase was observed in the GSH level. As a result, determined the antioxidant effect of Pennyroyal as well as the effect of decreasing the serum ACE2 level.

Keywords: Angiotensin-converting enzyme 2, Pennyroyal, GSH, MDA, Covid-19

INTRODUCTION

In recent years, with the increased interest in medicinal and aromatic plants and the active ingredients derived from these plants, studies that reveal the effects of these plants on humans and animals have been brought to the agenda (Baytop, 1999). The secondary metabolites of these plants have found widespread use in traditional medicine due to their potential for pharmaceutical and biological properties. Secondary metabolites have shown several biological and pharmaceutical effects in plants, including antioxidant, anti-inflammatory, and antimicrobial activities (Zengin et al., 2018). Some of the nearly 300 plant families that grow in nature have an important place. Among those, Labiatae (Lamiaceae) family has been widely used in the world for many purposes (Ishtiaq et al., 2014). It is the genus *Mentha*, which is a large member of this family and spreads from the Mediterranean to Central Asia (Ceylan, 1997).

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¹Department of Physiology,
Faculty of Veterinary
Medicine, Kafkas University,
Kars, Turkey

²Department of Animal
Nutrition and Nutritional
Diseases, Faculty of
Veterinary Medicine, Kafkas
University, Kars, Turkey

ORCID-

[*0000-0003-1879-8180](https://orcid.org/0000-0003-1879-8180)[b0000-0002-5003-3383](https://orcid.org/0000-0002-5003-3383)

Correspondence

Mustafa Makav

mustafamakav@gmail.com

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This genus has more than twenty species. *Mentha* plants have been used extensively in medicine, food and cosmetics for many years (Karadoğan et al., 2003; Villaverde et al., 2016). Additionally, *Mentha* plants exhibit antioxidant, anti-inflammatory, antimicrobial and antiviral effects due to their rich flavonoid and phenolic compounds (Baratta et al., 1998; Kasrati et al., 2015; Lee & Shibamoto, 2002).

Pennyroyal (*Mentha pulegium*) is a perennial aromatic herbaceous plant belonging to the genus *Mentha* that can grow up to half a meter in height (Gruenwald et al., 2000). The dried parts and the essential oil obtained from them are widely used in traditional medicine (respiratory system disorders, digestion, liver and gall bladder disorders), gastronomy (spices, snacks), aromatherapy and cosmetics (Agnihotri et al., 2005; Ahmed et al., 2018; Gruenwald et al., 2000; Rodrigues et al., 2013).

Free radicals are molecules with unpaired electrons in their outer orbits. Free radicals occur naturally in the body and are important intermediates in natural processes involving the control of vascular tone, cytotoxicity, and neurotransmission. However, the presence of free radicals in high concentrations can damage all cell structures including DNA, proteins and cell membranes that cause many diseases in humans and animals such as atherosclerosis, cancer, diabetes, rheumatoid arthritis, cardiovascular diseases, genital track infection, inflammation, aging and other degenerative diseases. The antioxidant defense system contains antioxidant components and antioxidant enzymes and plays an important role in delaying and preventing the oxidation of biomolecules such as DNA and protein. Aromatic plants are classified as natural antioxidants because they contain phenolic compounds that reduce the formation of free radicals and have antioxidant activity, and many studies have indicated that they can be used as a replacement for synthetic antioxidants with side

effects (Grimsrud et al., 2008; Keller, 2006; Kuru et al., 2016).

Angiotensin converting enzyme 2 (ACE2) is a homologue of an Angiotensin converting enzyme (ACE) discovered in 2000 (Donoghue et al., 2000). Although there is a similarity between ACE and ACE2, their functions are completely different. Although ACE2 is widely found in the heart, kidney, lung and testis, a small amount is also found in the circulation (Serfozo et al., 2020; Tipnis et al., 2000). In the last months of 2019, it has been reported that ACE2 enzyme is one of the primary receptors in the entry and attachment of the coronavirus in the human body, which is described as a new type of coronavirus infection (SARS-CoV-2,) which appeared in Wuhan, China, and caused a pandemic (H. Cheng et al., 2020; Lu et al., 2020).

In this study, the effects of Pennyroyal added to rabbits' feed on serum ACE2 levels and antioxidant parameters were investigated.

MATERIALS and METHODS

Animals and experiment design

In the study, 15 female New Zealand rabbits weighing 1500-2500 g were used. Rabbits were obtained from Atatürk University Experimental Animal Breeding Unit, which is officially authorized to breed and sell test animals. The animals were housed in cages specially designed for their species and were fed ad-libitum. The temperature of the room where the animals were housed was set to 25°C, and the lighting was set to be 12 hours light and 12 hours dark. The rabbits were fed a basal ration containing 24% crude protein, 3,2% crude fat, 5,90% crude fiber and 3300 kcal / kg metabolic energy (NRC, 1995). Experiment Groups;

Group I: Control group (C) fed ad-libitum without any intervention,

Group II: The group in which 0.1% Pennyroyal powder (P1) was added to the feed for 14 days,

Group III: The group in which 0.2% Pennyroyal powder (P2) was added to the feed for 14 days,

Pennyroyal (*M. pulegium*)

Pennyroyal used in the study was collected in the season from Bogatepe village (40 ° 48'21.2 "N 42 ° 53'37.8" E / Turkey) of Kars province, dried and ground. The GC/MS analysis of Pennyroyal (*M. pulegium* L.) was performed by obtaining essential oil through water vapor distillation method. The results of the analysis showed that the major compounds of the Pennyroyal were Linalool (13,61%) and Menthone (10,56%).

Sampling and analysis

At the end of the study (14th day), blood samples were taken from the ear vena of the animals into anticoagulated tubes. The blood samples taken were centrifuged at 3000 rpm for 5 minutes, and their plasma was stored at -20°C until the day of analysis. Plasma ACE2 levels were determined according to the kit procedure using commercial kits of Enzyme-Linked ImmunoSorbent Assay (ELISA- Elabscience® USA). While GSH analysis was determined according to the Beutler (1963) method, Yoshioka et al. (1979) method was used in MDA analysis.

Statistical analyses

Analysis of variance (ANOVA) was conducted for all the biochemical parameters to test if there is a difference among the three groups. The mean separation among groups was performed utilizing Tukey's test. An experiment-wise p-value of $\leq 0,05$ was deemed to be statistically significant throughout the study. All the analyses were conducted using GraphPad 8.1 (San Diego, CA, USA).

RESULTS

The efficacy of Pennyroyal addition on blood plasma ACE2, GSH and MDA levels in rabbits is presented in Figure 1. There was a decrease in plasma ACE-2 levels in the diet of the P1 and P2 groups compared to the C group ($P < 0,0001$). There was a significant increase in the GSH level in the P2 group compared to the C group ($P < 0,001$). There was no difference in the P1 group compared to the C group ($P > 0,05$). When the P1 and P2 groups were evaluated, a significant increase was found in the P2 group compared to the P1 group ($P < 0,05$). There was a significant decrease in the MDA level in the P2 group compared to the C group ($P < 0,0001$). It was determined that there was no difference between the P1 group and C group ($P > 0,05$). However, when the P1 and P2 groups were evaluated, a significant decrease was found in MDA levels in the P2 group compared to the P1 group ($P < 0,001$).

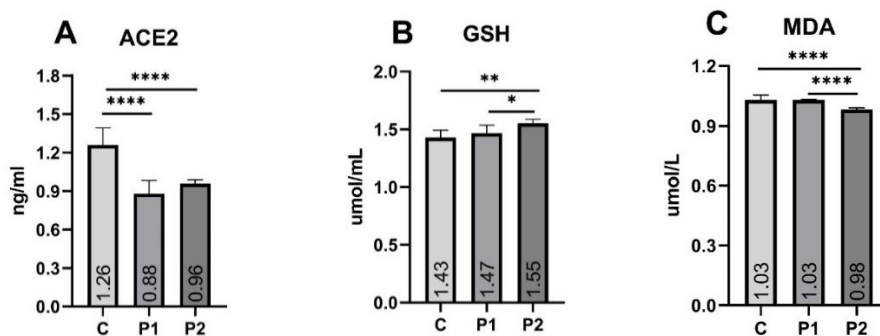


Figure 1. Means and Std. Errors of the three groups for (A, B, C) for biochemical parameters. * p < 0.05, ** p < 0.01, **** p < 0.0001

DISCUSSION

Aromatic plants and their products have been used by researchers as an alternative method in combating many diseases since the first days of the disease (Asdadi et al., 2020; Hansen Chen & Du, 2020; Senthil Kumar et al., 2020). In the present study, were determined the effectiveness of the dietary intake of Pennyroyal from aromatic plants on circulating ACE2 levels. Similar to the results of the study, it was determined that essential oils bind and inhibit ACE2 by in vitro and molecular docking methods. The researchers have reported that by decreasing ACE2 expression, the attachment of the virus to host cells can be reduced or prevented, however, this mechanism is an issue that needs to be clarified (H Chen & Du 2020; L. Cheng et al., 2020; da Silva et al., 2020; Senthil Kumar et al., 2020; Thuy et al., 2020). However, experiments do not show the efficacy of Pennyroyal and aromatic plants on ACE2 in in vivo settings, and intensive in vivo studies are needed in this area (Andrew M. South et al., 2020). ACE2 provides a vasodilator effect by inhibiting ACE (Vickers et al., 2002).

ACE2 is the binding receptor of the coronavirus. Especially, it plays the primary role in the penetration of the coronavirus into the lungs in the respiratory system (Batlle et al., 2008). During the Covid-19 pandemic process, emphasis has been placed on studies on ACE2, and according to the studies, it has been concluded that it may be more effective to prevent the entry of infection into the organism. Studies conducted in this context have focused on therapeutic approaches to prevent infection, especially by decreasing the ACE2 level (Andrew M South et al., 2020). In addition, the present study was performed in healthy rabbits to determine the effects on protection from infection before exposure to possible Covid-19 infection. However, it is important to carry out intensive studies in order to determine how Pennyroyal will affect the ACE2 levels in

humans and the daily dose to be consumed for protection.

Oxidative stress occurs when reactive oxygen species (ROS) production exceeds the capacity that natural antioxidant defense mechanisms of organism can cope with. It damages macromolecules such as DNA, proteins and lipids (Bartsch and Nair, 2000; Macdonald et al., 2010). This is generally characterized by increases in malondialdehyde (MDA) and GST activities and decreases in GSH production. Increased MDA is a marker of lipid peroxidation caused by oxidative damage. Reduced glutathione (GSH) is an endogenous antioxidant which plays a vital role in detoxification of xenobiotics and clearance of free radicals or ROS in cells (Albano et al., 1998; Macdonald et al., 2010; Kuru et al.).

Many studies have detected the antioxidant activity of Pennyroyal (Cherrat et al., 2014; Kamkar et al., 2010; Ölmez, 2018; Teixeira et al., 2012). Similarly, in the present study, the increase in the level of GSH, which shows antioxidant activity, and the decrease in the level of MDA used in determining lipid peroxidation with the effects of Pennyroyal reveal that Pennyroyal may have a good antioxidant characteristic. There are also studies reporting that the antioxidant activity of Pennyroyal is not important (Marzouk et al., 2008). It is known that the difference in antioxidant activity is due to the chemical composition of the Pennyroyal used, which varies depending on the geography. It has also been reported that the use of the plant itself may produce different results with the use of essential oil (Kamkar et al., 2010; Teixeira et al., 2012). An increase in the number of animal trials is needed to determine the antioxidant activity of Pennyroyal.

As a result, in addition to being a good antioxidant substance, Pennyroyal has an important ACE2 receptor reducing effect. In this context, it is seen that the use of Pennyroyal

can be particularly effective on some infections. In addition, considering the hypertensive patients, it is important to pay attention to its use in these patients due to its ACE2 reducing effect. However, since there are not many studies on the subject, more similar studies need to be conducted.

CONCLUSION

As a result, in addition to being a good antioxidant substance, Pennyroyal has an important ACE2 receptor reducing effect. In this context, it is seen that the use of Pennyroyal can be particularly effective on some infections. In addition, considering the hypertensive patients, it is important to pay attention to its use in these patients due to its ACE2 reducing effect. However, since there are not many studies on the subject, more similar studies need to be conducted.

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Ethical approval: The ethics committee report of this study was obtained from Kafkas University Animal Experimental Local Ethics Committee (Authorization number: KAU-HADYEK / 2020-124)

Conflict of interest: The authors declare that there is no conflict of interest for this study.

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