SELÇUK TIP DERGİSİ / SELCUK MEDICAL JOURNAL

Araştırma Makalesi / Research Article

Selcuk Med J 2018;34(1): 18-22

DOI: 10.30733/std.2018.00992

Effect of Geraniol on Brain Cholesterol, Vitamin A and E Levels in The Hydrogen Peroxide-Treated Rats

Hidrojen Peroksit Uygulanan Sıçanlarda Beyin Kolesterol, A ve E Vitamini Düzeyine Geraniolün Etkisi

Zafer Şahin[1],
Ahmet Özkaya[2],
Ökkeş Yılmaz[3],
Ahmet Orhan Görgülü[4]

[1]Karadeniz Teknik Üniversitesi, Tıp Fakültesi, Fizyoloji Anabilim Dalı, Trabzon
[2]Adıyaman Üniversitesi, Fen Edebiyat Fakültesi, Kimya Anabilim Dalı, Adıyaman
[3]Fırat Üniversitesi, Fen Edebiyat Fakültesi, Biyoloji Anabilim Dalı, Elazığ
[4]Fırat Üniversitesi, Fen Edebiyat Fakültesi, Kimya Anabilim Dalı, Elazığ

Geliş Tarihi/Received: *19 May 2017*
Kabul Tarihi/Accepted: *18 January 2018*

Özet

Amaç: Bir monoterpen olan geraniol, bazı bitkilerde yer alan doğal bir antioksidandır. Hidrojen peroksit (H_2O_2) ise reaktif oksijen türlerinin (ROS) bir üyesidir. Bu çalışmada, H_2O_2 uygulanan sıçanlarda geraniolün beyin kolesterolü ve yağda çözünen A (retinol) ve E (alfa (α)-tokoferol ve α-tokoferol asetat) vitaminlerine etkisinin belirlenmesi amaçlanmıştır.
Gereçler ve Yöntem: Çalışmada yetişkin erkek Wistar sıçanlar rastgele dört gruba ayrılarak (n=7), geraniol (50mg/kg) ve H_2O_2 (16mg/kg), intraperitoneal olarak, 30 gün süresince gün aşırı uygulandı. Beyin numuneleri homojenize edildikten sonra kolesterol, α-tokoferol, α-tokoferol asetat ve retinol düzeyleri yağ ekstraktlarından HPLC ile analiz edildi.
Bulgular: Beyin kolesterol düzeyinin H_2O_2 grubunda kontrol grubuna kıyasla daha fazla olduğu belirlendi. H_2O_2 ve geraniol+ H_2O_2 gruplarında, beyin α-tokoferol asetat düzeylerinin kontrole kıyasla daha yüksek olduğu bulundu. Beyin retinol seviyesi bakımından grupların hiçbirisinde istatistiksel olarak anlamlı bir değişiklik mevcut değildi.
Sonuç: Elde ettiğimiz veriler, beyinde kolesterol ve α-tokoferol asetat düzeylerinin H_2O_2 ile oluşturulan oksidatif stresten etkilendiğini göstermektedir. Geraniolün erkek sıçanlarda H_2O_2'nin etkilerini azaltma potansiyeli olduğu söylenebilir.

Anahtar kelimeler: Geraniol, hidrojen peroksit, beyin, kolesterol, α-tokoferol

Abstract

Aim: Geraniol, a monoterpene, is a plant-derived natural antioxidant. Hydrogen peroxide (H_2O_2) is a member of reactive oxygen species (ROS). The objective of this study is to de-termine the effect of geraniol on brain cholesterol and lipophilic vitamins such as vitamin A (retinol) and vitamin E (alpha (α)-tocopherol and α-tocopherol acetate) in H_2O_2-administrated male rats.
Materials and Methods: Adult male Wistar rats were randomly divided into four groups (n=7). Geraniol (50 mg/kg) and H_2O_2 (16 mg/kg) were administered by an intraperitoneal injection for 30 days with a 1-day interval. Brain samples were homogenized and cholesterol, α-tocopherol, α-tocopherol acetate, and retinol levels analyzed from lipid extracts by HPLC.
Results: Brain cholesterol level was found to be significantly higher in the H_2O_2 group than the control group. Brain α-tocopherol acetate levels were found to be significantly higher in the H_2O_2 and the geraniol+H_2O_2 groups than the control group. There was no difference in retinol levels between any groups.
Conclusion: In conclusion, our results indicate that brain cholesterol and α-tocopherol acetate levels are affected by H_2O_2-induced oxidative stress. Moreover, we suggest that geraniol has the potential to reduce the effect of H_2O_2 in male rats.

Keywords: Geraniol, hydrogen peroxide, brain, cholesterol, α-tocopherol

INTRODUCTION

Geraniol, the main component of rose and palmarosa oils, is a natural molecule belonging to the class of monoterpenes. It is found in the composition of essential oils of some plants such as ginger, lemon, lime, lavender, coconut, and orange in small quantities (1). Terpenes, including geraniol, have biological functions to protect plants against microorganisms and insects as well as to generate aromatic flavor and fragrance (2). Nowadays, natural or synthetic products of these molecules are used as taste and fragrance components in foods as well as in perfumery and cosmetic products (3). In addition, geraniol has a potential as the pharmacological agent. It was reported that geraniol has an anticarcinogenic effect because it could conduct the cell cycle to reduce uncontrolled proliferation in the human pancreatic adenocarcinoma cells (4). In our previous study, we observed that this monoterpene has antioxidant activity and, it improves liver fatty acid changes due to hydrogen peroxide (H_2O_2)-induced oxidative stress in rats (5).

Approximately 23% of total cholesterol in the body is present in the central nervous system (CNS) structures. Therefore, the brain is one of the richest organs in terms of cholesterol content (6). As long as

Address correspondence to: Zafer Şahin, Karadeniz Teknik Üniversitesi, Tıp Fakültesi, Fizyoloji Anabilim Dalı, Trabzon
e-mail: zafersahin55@yahoo.com
Cite this article as: Şahin Z, Özkaya A, Yılmaz Ö, Görgülü AO. Effect of Geraniol on Brain Cholesterol, Vitamin A and E Levels in The Hydrogen Peroxide-Treated Rats. Selcuk Med J 2018;34(1): 18-22.

Disclosure: *None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. All authors have agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

the blood-brain barrier is intact, the transition of the cholesterol from the plasma to the brain is unlikely. This indicates that the high-cholesterol content of CNS is completely synthesized by its own cells (7). Interestingly, there is a continuous cholesterol transition from the brain to the general circulation. This is accomplished as a result of the conversion of the cholesterol to the 24S-hydroxycholesterol, which can pass blood-brain barrier, via hydroxylation with the 24-hydroxylase (Cyp46a1), a member of the neuron-specific cytochrome P450, in the CNS (8,9).

The brain cholesterol dysregulation may occur in several neurodegenerative disorders, including Alzheimer's disease, Huntington's disease, Parkinson's disease, and stroke (10). Although the brain constitutes only 2% of body weight, it accounts for 20% of total oxygen consumption (11). Therefore, the brain is highly sensitive to oxidative stress due to limited antioxidant capacity, high-energy requirement and high lipid and iron content (12). The ROS formed in the brain is eliminated with the antioxidant molecules and vitamins as well as the enzymatic inactivation. Vitamins A, C and E are essential antioxidant vitamins in the body (13).

In recent years, the roles of oxidative stress, antioxidant vitamins and changes in brain cholesterol metabolism in the pathophysiology of neurodegenerative diseases are discussed (14). Both vitamin A and vitamin E are important antioxidant vitamins for the brain because they are soluble in fat. Effects of the geraniol on brain cholesterol and fat-soluble vitamins are unknown. Therefore, in this study, we aimed to determine the effect of geraniol on brain cholesterol, vitamin A, and E levels in rats treated with H_2O_2, which is a strong oxidizing agent.

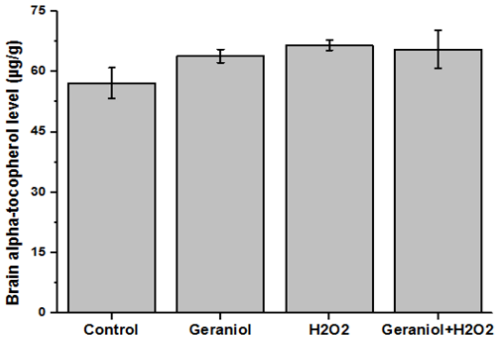

Figure 2. Brain α-tocopherol levels in geraniol and H_2O_2-treated male rats

Results were expressed as mean ± standard error mean (SEM). n=7 for each group. H_2O_2: hydrogen peroxide.

MATERIALS AND METHODS

In this study, Wistar albino adult male rats obtained from the Experimental Research Center of Firat University (FÜDAM) were used. The experimental groups were selected randomly, with seven animals in each group. The groups were designed as; control, geraniol, H_2O_2, and geraniol+H_2O_2. Geraniol (50 mg/kg, dissolved in corn oil) and H_2O_2 (16 mg/kg, dissolved in distilled water) were administered by an intraperitoneal injection for 30 days with one-day interval (5). The control group rats received both vehicle solutions in same ways. During the experiment, the animals were kept at constant temperature (21 ± 1 ºC) and 12 hours night/12 hours daytime (lights turned on 07:00). Food and water are given as ad libitum. This study has been conducted in accordance with the ethical standards and according to the Declaration of Helsinki and according to international and national guidelines and has been approved by the Ethics Committee of Elazig Firat University.

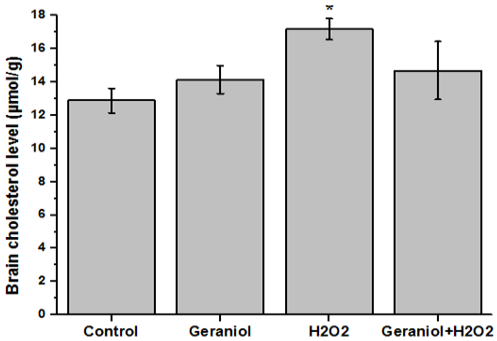

Figure 1. Brain cholesterol levels in geraniol and H_2O_2-treated male rats

Results were expressed as mean ± standard error mean (SEM). *: P < 0.01 compared with control group. (one-way ANOVA followed by a post-hoc Tukey test). n=7 for each group. H_2O_2: hydrogen peroxide.

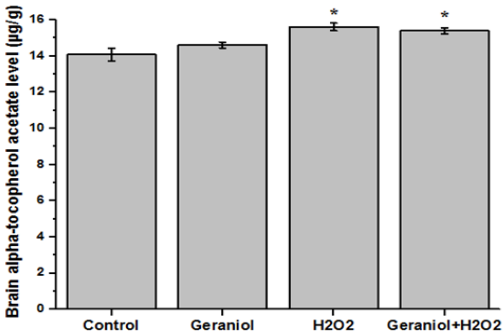

Figure 3. Brain alpha-tocopherol acetate levels in geraniol and H_2O_2-treated male rats

Results were expressed as mean ± standard error mean (SEM). *: P < 0.05 compared with control group. (one-way ANOVA followed by a post-hoc Tukey test). n=7 for each group. H_2O_2: hydrogen peroxide.

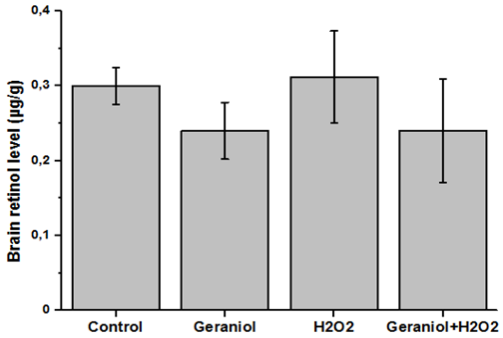

Figure 4. Brain retinol levels in geraniol and H_2O_2-treated male rats

Results were expressed as mean ± standard error mean (SEM). n=7 for each group. H_2O_2: hydrogen peroxide.

Lipid extraction

Brain samples were extracted with isopropanol-hexane- (2/3, v/v) by the method of Hara and Radin (15). For this purpose, frozen brain samples were weighed and homogenized (500 mg tissue) with a 5 ml isopropanol/hexane mixture.

Determination of Cholesterol

Cholesterol was analyzed from lipid extracts according to previous methods with minor modifications (16,17). Briefly, a mixture of isopropyl alcohol / n-hexane (5 ml) was treated with potassium hydroxide solution (5 ml of 0.5M in methanol) that was then vortexed for 30 seconds. Samples tubes were placed in a water bath for 15 minutes (80 ºC). After cooling, 5 ml of hexane and 1 ml of distilled water were added, and then centrifuged for 5 minutes at 5000 rpm. The residue was redissolved with the mobile phase (1 ml of methanol:68/acetonitrile:28/ distilled water:4, v: v: v). Finally, a 20 µl of sample was injected into the HPLC column. Detection was operated using a UV spectrophotometer 208 nm for cholesterol. Quantification was carried out by external standardization using Class-VP chromatography software (Shimadzu, Japan). The results of measurement were expressed as µmol/g.

Determination of α-tocopherol, α-tocopherol acetate, and retinol

For lipophilic vitamins, HPLC conditions were as follows: 1 ml of the mobile phase of acetonitrile:60/ methanol:38/distilled water:2 (v / v / v) and flow rate of 1 mL/min (40 ºC). Chromatographic analysis was performed using a Supelcosil LC 18 HPLC analytical column (250 x 4.6 mm, 5 µm, Sigma-Aldrich, USA). Detection was operated using a UV spectrophotometer 325 nm for retinol and 208 nm for alpha-tocopherol and α-tocopherol acetate (16,17). Quantification was carried out by external standardization using Class-VP chromatography software (Shimadzu, Japan). The results of measurement were expressed as µg/g.

Statistical analysis

All data were presented as mean±standard error mean (SEM). Results were analyzed using one-way analysis of variance (ANOVA) followed by a post hoc Tukey's test (SPSS 17). A p value lees then 0.05 was accepted as statistically significant.

RESULTS

Brain Cholesterol Levels

Brain cholesterol levels are shown in Figure 1. There was a significant increase in brain cholesterol level in the H_2O_2 group (17,17±0,63 µmol/g tissue) compared to control group (12,88±0,73 µmol/g tissue, p <0.01). The differences in mean cholesterol concentrations were not detected between geraniol (15,13±0,50 µmol/g tissue) and geraniol + H_2O_2 (14,68±1,74 µmol/g tissue) groups.

Brain α-tocopherol, α-tocopherol acetate, and retinol levels

The brain α-tocopherol levels of the geraniol (63,91±1,65 µg/g tissue), H_2O_2 (66,57±1,27 µg/g tissue), and geraniol + H_2O_2 (65,52±8,75 µg/g tissue) groups were not different from the control group (57,21±3,79 µg/g tissue, Figure 2). The differences in α-tocopherol acetate levels were not detected between geraniol-treated (14,6±0,16 µg/ g tissue) and control group (14,08±0,35 µg/g tissue), while H_2O_2 (15,62±0,2 µg/g tissue) and geraniol + H_2O_2 (15,4±0,16 µg/g tissue) groups had higher α-tocopherol acetate levels than control (p <0,05, Figure 3). The brain retinol levels of the geraniol (0,24±0,03 µg/ g tissue), H_2O_2 (0,31±0,06 µg/g tissue), and geraniol + H_2O_2 (0,24±0,06 µg/ g tissue) groups were not different from the control group (0,3±0,02 µg/g tissue, Figure 4).

DISCUSSION

More than half of the body cholesterol is obtained by synthesis, and the rest is taken with nutrients. On the other hand, the brain has higher cholesterol content than any other organ, and this is entirely achieved by endogenous cholesterol synthesis (7). Therefore, understanding the cholesterol metabolism and the changes in the brain may help to understand the pathophysiology of neurodegenerative diseases. In our study, the effects of geraniols on brain cholesterol levels, vitamin E and vitamin A levels in rats treated with H_2O_2 were evaluated. The level of

brain cholesterol was significantly increased in the H_2O_2-treated group. In the geraniol+H_2O_2 group, it can be said that cholesterol level is same as the control group. Although H_2O_2 is not a free radical, it can form hydroxyl radical, a very strong ROS, as well as superoxide radical due to reaction with transition metal ions (18). Several researchers reported that the oxidative stress can impair cholesterol metabolism in the brain, and this effect may result in a cholesterol deposition in the brain tissue (19,20). Thus, our results indicate that the increase in brain cholesterol level of the H_2O_2 group is a reflection of the oxidative stress.

Recently, Kreilaus et al. (21) reported that 24-hydroxycholesterol decreased by 60%, cholesterol increased by 30%, and cholesterol oxidation products due to oxidative stress increased by 50-70% in postmortem brain tissue of suffering Huntington disease. Thus, it can be said that the increase in cholesterol level of the H_2O_2 group is probably related to the dysregulation of 24-hydroxycholesterol, a cholesterol carrier, and brain cholesterol synthesis. H_2O_2 is an oxidant agent, and its negative effect on lipid peroxidation and cholesterol regulation should be taken into consideration because the in vivo administration of this molecule induces oxidative stress in the body (5,22). Moreover, geraniol has antioxidant activity, and it exerts an ameliorative role in the H_2O_2-induced oxidative stress (5). In the geraniol + H_2O_2 group, brain cholesterol level was same as the control group. This result may be related to an antioxidant effect of the geraniol.

Geraniol has the ability to cross the blood-brain barrier (23). Although the effect of geraniol on brain cholesterol regulation is unknown, it has been suggested that this monoterpene has an inhibitory effect on mevalonate pathway and lipid metabolism (24). Mevalonate is an important step for cholesterol synthesis and cell proliferation in the body. This process is completed by firstly conversion of acetyl-CoA to 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA), and then by conversion to cholesterol from mevalonate with a series of biochemical reactions (25). In the recently reported that geraniol has a cholesterol-lowering effect in the rat serum (26) and mice (27). Regarding brain cholesterol level, in accordance with the above reports, we observed that the level of cholesterol increased in the H_2O_2 group but not in the geraniol + H_2O_2 group.

In the present study, there were no significant changes in the brain α-tocopherol level. However, α-tocopherol acetate concentrations increased in the H_2O_2 and geraniol + H_2O_2 groups. The α-tocopherol is the most biologically active member of the vitamin E family (28). The members of vitamin E family are metabolized in the body via cytochrome P450 enzymes (29). ROS production occurs in the cell membrane and microsomal areas except for mitochondria due to changes in cytochrome p450 activity in the physiological or especially pathophysiological conditions (30). The H_2O_2 is a microsomal ROS product that occurs in reactions involving cytochrome P450 (31). An activity of the cytochrome p450 enzymes may be affected by oxidative stress in the brain and other organs because H_2O_2 can inhibit cytochrome p450 enzymes (32,33). In the present study, changes in the α-tocopherol acetate level of the H_2O_2 group may be a result of this interaction. However, high levels of α-tocopherol acetate in the H_2O_2 group as well as geraniol + H_2O_2 group also indicate that, apart from its antioxidants role, geraniol can interact with cytochrome p450 enzymes. It is known that there is a relationship between cytochrome p450 activity and geraniol metabolism in the cells (34,35). In a recent study reported that geraniol treatment in rats with non-alcoholic steatohepatitis models reduce oxidative stress and regulate cytochrome p450 activity (36).

In conclusion, H_2O_2 administration caused an alteration in the brain cholesterol and α-tocopherol acetate levels. We suggest that geraniol may exert a modulating role on the effects of H_2O_2–induced oxidative stress in the brain of male rats.

Conflict of interest: *Authors declare that there is no conflict of interest between the authors of the article.*

Financial conflict of interest: *Authors declare that they did not receive any financial support in this study.*

Address correspondence to: *Zafer Şahin, Karadeniz Teknik Üniversitesi, Tıp Fakültesi, Fizyoloji Anabilim Dalı, 61080, Trabzon*
e-mail: *zafersahin55@yahoo.com*

REFERENCES

1. Tiwari M, Kakkar P. Plant derived antioxidants - Geraniol and camphene pro-tect rat alveolar macrophages against t-BHP induced oxidative stress. Toxicol in vitro 2009;23(2):295-301.
2. Takechi H, Miyazawa M. Biotransformation of Geraniol by the larvae of com-mon cutworm (Spodoptera litura). J Oleo Sci 2006;55(3):143-9.
3. Chen W, Viljoen AM. Geraniol - A review of a commercially important fra-grance material. South African J Botany 2010;76(4):643-51.
4. Wiseman DA, Werner SR, Crowell PL. Cell cycle arrest by the isoprenoids perillyl alcohol, geraniol, and farnesol is mediated by p21(Cip1) and p27(Kip1) in human

pancreatic adenocarcinoma cells. J Pharmacol Exp Ther 2007;320(3):1163-70.
5. Ozkaya A, Sahin Z, Gorgulu AO, et al. Geraniol attenuates hydrogen perox-ide-induced liver fatty acid alterations in male rats. J Intercult Ethnopharmacol 2016;6(1):29-35.
6. Dietschy JM, Turley SD. Thematic review series: Brain lipids. Cholesterol metabolism in the central nervous system during early development and in the mature animal. Lipid Res 2004;45:1375-97.
7. Björkhem I, Meaney S. Brain cholesterol: Long secret life behind a barrier. Arterioscler Thromb Vasc Biol 2004;24:806-15.
8. Björkhem I, Lütjohann D, Breuer O, et al. Importance of a novel oxidative mechanism for elimination of brain cholesterol. Turnover of cholesterol and 24(S)-hydroxycholesterol in rat brain as measured with 18O2 techniques in vivo and in vitro. J Biol Chem 1997;272(48):30178-84.
9. Lund EG, Guileyardo JM, Russell DW. cDNA cloning of cholesterol 24-hydroxylase, a mediator of cholesterol homeostasis in the brain. Proc Natl Acad Sci USA 1999;96(13):7238-43.
10. Martín MG, Pfrieger F, Dotti CG. Cholesterol in brain disease: sometimes de-terminant and frequently implicated. EMBO Rep 2014;15(10):1036-52.
11. Shulman RG, Rothman DL, Behar KL, et al. Energetic basis of brain activity: implications for neuroimaging, Trends Neurosci 2004;27:489-95.
12. Juurlink BH, Paterson PG. Review of oxidative stress in brain and spinal cord injury: suggestions for pharmacological and nutritional management strate-gies. J Spinal Cord Med 1998;21:309-34.
13. Canter PH, Wider B, Ernst E. The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: a systematic review of randomized clinical trials. Rheumatology (Oxford) 2007;46(8):1223-33.
14. Gamba P, Testa G, Gargiulo S, Set al. Oxidized cholesterol as the driving force behind the development of Alzheimer's disease. Front Aging Neurosci 2015;7:119.
15. Hara A, Radin NS. Lipid extraction of tissues with a low-toxicity solvent. Anal Biochem 1978;90(1):420-6.
16. López-Cervantes J, Sánchez-Machado DI, Ríos-Vázquez NJ. High-performance liquid chromatography method for the simultaneous quantication of retinol, alpha-tocopherol, and cholesterol in shrimp waste hydrolysate. J Chromatogr A 2006;1105(1-2):135-9.
17. Bal R, Türk G, Tuzcu M, et al. Effects of the neonicotinoid insecticide, clothianidin, on the reproductive organ system in adult male rats. Drug Chem Toxicol 2013;36(4):421-9.
18. Gutteridge JM. Lipid peroxidation and antioxidants as biomarkers of tissue damage. Clin Chem 1995;41:1819-28.
19. Ghosh C, Dick RM, Ali SF. Iron/ascorbate-induced lipid peroxidation changes membrane fluidity and muscarinic cholinergic receptor binding in rat frontal cortex. Neurochem Int 1993;23(5):479-84.
20. Cutler RG, Kelly J, Storie K, et al. Involvement of oxidative stress-induced ab-normalities in ceramide and cholesterol metabolism in brain aging and Alz-heimer's disease. Proc Natl Acad Sci USA 2004;101(7):2070-5.
21. Kreilaus F, Spiro AS, Mclean CA, et al. Evidence for altered cholesterol me-tabolism in Huntington's disease postmortem brain tissue. Neuropathol Appl Neurobiol 2016;42(6):535-46.
22. Sahin Z, Ozkaya A, Cuce G, et al. Investigation of the effect of naringenin on oxidative stress-related alterations in testis of hydrogen peroxide-administered rats. J Biochem Mol Toxicol 2017;00:e21928.
23. Rekha KR, Selvakumar GP, Sethupathy S, et al. Geraniol ameliorates the motor behavior and neurotrophic factors inadequacy in MPTP-induced mice model of Parkinson's disease. J Mol Neurosci 2013;51(3):851-62.
24. Yu SG, Hildebrandt LA, Elson CE. Geraniol, an inhibitor of mevalonate biosynthesis, suppresses the growth of hepatomas and mela-nomas transplanted to rats and mice. J Nutr 1995;125(11):2763-7.
25. Hegardt FG. Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase: A control enzyme in ketogenesis. Biochem J 1999;338(Pt3):569-82.
26. Andrade BF, Braga CP, Dos Santos KC, et al. Effect of inhaling cymbopogon martinii essential oil and Geraniol on serum biochemistry parameters and oxidative stress in rats. Biochemistry Research International, vol. 2014, Article ID 493183, 7 pages, 2014. doi:10.1155/2014/493183.
27. Galle M, Kladniew BR, Castro MA, et al. Modulation by geraniol of gene ex-pression involved in lipid metabolism leading to a reduction of serum-cholesterol and triglyceride levels. Phytomedicine 2015;22(7-8):696-704.
28. Goti D, Hrzenjak A, Levak-Frank S, et al. Scavenger receptor class B, type I is expressed in porcine brain capillary endothelial cells and contributes to selective uptake of HDL-associated vitamin E. J Neurochem 2001;76:498-508.
29. Traber MG. Vitamin E regulatory mechanisms. Annu Rev Nutr 2007;27:347-62.
30. Yasui H, Hayashi S, Sakurai H. Possible involvement of singlet oxygen spe-cies as multiple oxidants in p450 catalytic reactions. Drug Metab Pharmacokinet 2005;20(1):1-13.
31. Rashba-Step J, Cederbaum AI. Generation of reactive oxygen intermediates by human liver microsomes in the presence of NADPH or NADH. Mol Pharmacol 1994;45(1):150-7.
32. Karuzina II, Archakov AI. Hydrogen peroxide-mediated inactivation of micro-somal cytochrome P450 during monooxygenase reactions. Free Radic Biol Med 1994;17(6):557-67.
33. Joo H, Lin Z, Arnold FH. Laboratory evolution of peroxide-mediated cyto-chrome P450 hydroxylation. Nature 1999;399(6737):670-3.
34. Hagvall L, Baron JM, Börje A, et al. Cytochrome P450-mediated activation of the fragrance compound geraniol forms potent contact allergens. Toxicol Appl Pharmacol 2008;233(2):308-13.
35. Seo KA, Kim H, Ku HY, et al. The monoterpenoids citral and geraniol are moderate inhibitors of CYP2B6 hydroxylase activity. Chem Biol Interact 2008;174(3):141-6.
36. Chen J, Fan X, Zhou L, et al. Treatment with geraniol ameliorates methionine-choline-decient diet-induced non-alcoholic steatohepatitis in rats. J Gastroenterol Hepatol 2016;31(7):1357-65.