Effects of Melissa officinalis L. on oxidative status and DNA damage in subjects exposed to long-term low-dose ionizing radiation

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Abstract

The aim of this study was to determine the capability of *Melissa officinalis L.* (Lemon balm) infusion on improvement of oxidative stress status in radiology staff that were exposed to persistent low-dose radiation during work. The study was a before-after clinical trial performed on 55 radiology staff. They were asked to drink Lemon balm infusion which was prepared like a tea bag twice daily (1.5 g/100 mL) for 30 days. In the plasma, lipid peroxidation, DNA damage, catalase, superoxide dismutase, myeloperoxidase, and glutathione peroxidase activity were measured before and after using Lemon balm infusion.Use of Lemon balm infusion in radiology unit workers resulted in a significant improvement in plasma levels of catalase, superoxide dismutase, and glutathione peroxidase and a marked reduction in plasma DNA damage, myeloperoxidase, and lipid peroxidation. It is concluded that infusion of Lemon balm markedly improve oxidative stress condition and DNA damage in radiology staff when used as a dietary supplement for radiation protection.

Keywords

Lemon balm, oxidative stress, radiology staff, low-dose radiation, toxicity

Introduction

Oxidative stress is characterized by imbalance between the production and removal of reactive oxygen species (ROS). High levels of ROS are dangerous and can cause damages to the cells resulting in severe illnesses. Potential of ROS in induction of mutation and DNA damage is a predisposing factor for cancer, diabetes, and age-related disorders (Abdollahi et al. 2004; Rahimi et al. 2005). Productions of free radicals in the cells are increased by various factors, for example in exposure to ionizing radiation that results in an immediate formation of oxidative stress condition (Ermakov et al., 2009; Shuryak and Brenner, 2009). Ionizing radiation as a two-edge sword is either useful in medicine for diagnosis and treatment of human diseases or an important contributor to the occurrence of occupational diseases such as cataract, cardiovascular disturbance (Zielinski et al., 2009a), and cancer (Jacob et al., 2009; Lowe et al., 2009). Medical workers are exposed to chronic and low-dose ionizing radiation from various sources, and ionizing radiation at low dose has the potency to start carcinogenesis and

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other diseases (Fachin et al., 2009). Our previous study confirmed existence of oxidative stress in radiology unit workers who were exposed to long-term low-dose radiation (Malekirad et al., 2005).

However, to keep the level of ROS under control, living organisms have developed antioxidant systems that consisted of non-enzymatic antioxidants, such as glutathione, ascorbic acid, tocopherol, carotene, uric acid, bilirubin as well as enzymatic scavengers such as superoxide dismutase (SOD), glutathione peroxidase, and catalase (CAT). Antioxidants can inhibit lipid peroxidation (LPO) by decreasing localized oxygen concentration, scavenging free radicals, preventing initiating radical generation, decomposing peroxides, and chain breaking to prevent continued hydrogen abstraction by active radicals. Studies in the recent years have confirmed usefulness of natural and synthetic antioxidants in management of many ailments such as osteoporosis (Salari-Sharif et al., 2010), diabetes and islet transplantation (Hasani-Ranjbar et al., 2009, 2010; Mohseni-Salehi-Monfared et al., 2009a; Momtaz and Abdollahi, 2010; Rahimi et al., 2005), inflammatory bowel diseases (Rezaie et al., 2007), preeclampsia (Rahimi et al., 2009), and pancreatitis (Mohseni-Salehi-Monfared et al. 2009b) and even in the radiology workers (Fani et al., 2008).

Melissa officinalis L. (Lemon balm) belongs to the family Lamiaceae that grows in the Central and Southern Europe, Asia, and northern Iran. In Iran, this plant is known locally as Badranjbooye, Varangboo, and Faranjmoshk (Dastmalchi et al., 2008). Lemon balm extract has been widely used in traditional and modern medicine as a mild sedative, anxiolytic, digestive, carminative, spasmolytic, antibacterial, antitumoral (Birdane et al., 2007; López et al., 2009), and antiviral agent (Geuenich et al., 2008; Mazzanti et al., 2008). The infusion of the leaves from this plant is used as nerve tonic to treat migraines, melancholia, neuroses, hysteria (Canadanović-Brunet et al., 2008), hyperthyroidism, fevers, cold, headaches, sores, gout, insect bites (Birdane et al., 2007), treatment of emotional disorders (Abuhamdah and Chazot, 2008), and ameliorating of cognitive deficit associated with Alzheimer disease (Akhondzadeh et al., 2003). Lemon balm is an aromatic herb and a rich source of natural antioxidants (Dastmalchi et al., 2008; Topal et al., 2008) and has antioxidant effects (Cortes-Cabrera and Prieto, 2010; Pereira et al., 2009). Biological modifiers aim at oxidative harm for radioprotection, which has been studied for decades with little success. Hence, there is a need for better and more potent compounds, especially on the herbal origin, for a better antioxidant defense. Lemon balm infusion has shown high potential of antioxidant activity in vitro and thus might improve human enzymatic antioxidant defense. In the present research, a before-after clinical trial study was performed to explore beneficial effects of Lemon balm on the radiology staff by measuring lipid peroxidation (LPO), myeloperoxidase (MPO), superoxide dismutase (SOD), catalase (CAT), glutathion peroxidase (GPx), and the extent of DNA damage as main blood biomarkers of oxidative stress.

Materials and methods

Materials

Tetraethoxypropane (MDA) from (Sigma, UK), 2-thiobarbituric acid (TBA), trichloroacetic acid (TCA), *n*-butanol from (Merck, Germany), and ELISA kits for oxidative stress biomarkers from (Cayman Chemical Co., USA) were used in this study.

Plant material

The aerial parts of *Melissa officinalis L.* were collected in August 2009 from Botanical Garden of Shaheed Beheshti University, and identified as *Melissa officinalis L.* by Dr MA Vakili from Department of Biology, Faculty of Science, Islamic Azad University, Jiroft Branch. The leaves of *Melissa officinalis L.* was dried in shade at room temperature for 12 days.

Study population

A total of 55 radiology staff, working in the radiology center of a referral University Hospital in Shiraz, was included in the study. The subjects were occupationally exposed to low-dose ionizing radiation (x-ray) not less than 2 years. None of these workers were professionally exposed to any hazardous agent other than ionizing radiation and did not have any radiology diagnostic or therapeutic intervention in the last 12 months. All participants were provided with specific written information about the aims of the study before written consents were obtained, in accordance with the Declaration of Helsinki, and the protocol of study was approved by Islamic Azad University Board. Prior to blood collection, each individual was extensively interviewed by a specialized physician who filled in a structured questionnaire specifying gender, date of birth, smoking or dietary habits, alcohol consumption, previous exposure to diagnostic

x-ray as a patient, use of drugs, and consumption of vitamin supplements or antioxidants. Since exercise, smoking, polyunsaturated fat intake, and dietary antioxidant vitamin intake can affect oxidative status, subjects were given specific guidelines to follow throughout the study. They were instructed not to take any multivitamin in supplement or traditional herbs during the study. For several reasons, the responsible organization did not provide us with the annual radiation exposure of the subjects recorded from their chest badges.

The included subjects were administered Lemon balm infusion twice daily for 30 days at 7.5 a.m. and 2 p.m. everyday. A supervisor carefully checked to make sure that the volunteers were taking infusion properly.

Plasma preparation

Blood samples were collected from all subjects before using Lemon balm infusion and 12 hours after the last dose of 30-day treatment with infusion. Five milliliter of heparinized blood were obtained and centrifuged at 3000 *g* for 30 minutes at 4°C to separate plasma. The plasma samples were stored at −80°C until analyzed.

Infusion preparation and protocol

Lemon balm leaves dried and cleaned and then packed in 1.5 *g* tea bags. The subjects were instructed how to prepare the infusion by mixing a total of 1.5 g in 100 mL 98°C water for 30 minutes (Katalinic et al., 2006). A qualified expert supervised the whole procedure.

Assay of oxidative stress biomarkers

The activities of SOD, CAT, 8-hydroxy-2-deoxy guanosine (8-OH-dG; measure of DNA damage), and MPO were assayed using ELISA kits. The basis of determination of these parameters in the kits has been described previously (Malekirad et al., 2010) but the brief is as follows:

SOD kit utilizes a tetrazolium salt for detection of superoxide radicals generated by xanthine oxidase and hypoxanthine. One unit of SOD is defined as the amount of enzyme needed to exhibit 50% dismutation of the superoxide radical. CAT is involved in the detoxification of hydrogen peroxide by breaking down of two molecules of hydrogen peroxide to two molecules of water and molecular oxygen. The assay was based on the reaction of the enzyme with methanol in the presence of an optimal concentration of hydrogen peroxide. 8-Hydroxy-2-deoxy guanosine (8-OH-dG) kit was assayed using an anti-mouse IgG-coated plate and a tracer consisting of an 8-OH-dG-enzyme conjugate and 8-OH-dG antibody recognizing both free 8-OH-dG and DNA-incorporated 8-OH-dG. Extracellular MPO is a macrophage modulator which provokes the release of the pro-inflammatory cytokine tumor necrosis factor α (TNF)-α in addition to ROS made by these cells. Activity of MPO was estimated by a spectrophotometric assay that measures the rate of oxidation of o-dianisidine by MPO. GPx catalyzes the reduction of hydroperoxides, including hydrogen peroxide, by reduced glutathione. The assay measures GPx activity indirectly by a coupled reaction with glutathione reductase (GR) that led to oxidation of NADPH to $NADP^+$. To measure the rate of LPO, TBA method was used (Esterabeur and Cheeseman, 1990).

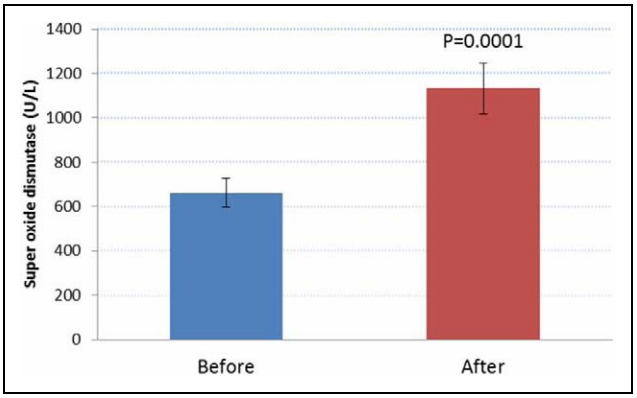

Figure 1. Changes in plasma superoxide dismutase (SOD) before and after treatment with Lemon balm infusion. Data are mean ± SEM. *p* Value of the difference between before and after treatment is shown.

Statistical analysis

All data were analyzed with Stats Direct 2-7-7. A paired *t* test was used for statistical comparisons of biochemical parameters. Pearson correlation coefficient was used to study the association between variables. *p* Values lower than 0.05 were considered statistically significant.

Result

The mean ± SD values for age and history of workers were 30.2 ± 7.08 and 9.9 ± 7.07, respectively. Of

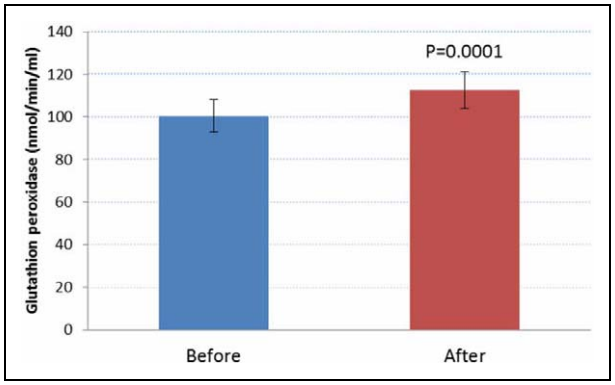

Figure 2. Changes in plasma glutathione peroxiodase (GPx) before and after treatment with Lemon balm infusion. Data are mean ± SEM. *p* Value of the difference between before and after treatment is shown.

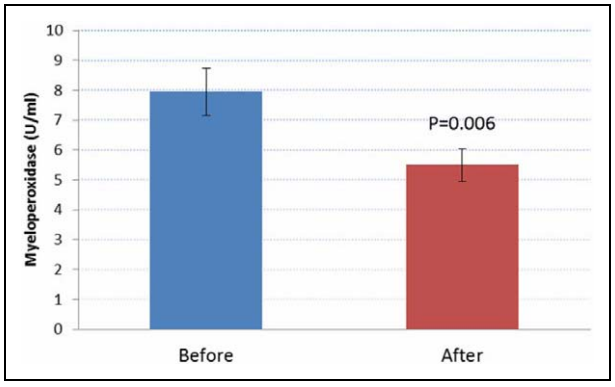

Figure 3. Changes in plasma myeloperoxidase (MPO) before and after treatment with Lemon balm infusion. Data are mean ± SEM. *p* Value of the difference between before and after treatment is shown.

subjects, 20 (36.4%) were male and 35 (63.6%) were female. None of the subjects were alcoholics or smokers.

After using of Lemon balm infusion, the SOD activity increased significantly ($p = 0.0001$). The before and after mean ± SD were 662.05 ± 305.42 and 1132.13 ± 595.56 U/L, respectively (Figure 1). A significant ($p = 0.0001$) increase in GPx activity was observed after administration of Lemon balm infusion (100.53 ± 23.99 nmol/min/mL before versus 112.57 ± 28.43 nmol/min/mL after (Figure 2). A significant ($p = 0.006$) decrease in MPO activity was observed after administration of Lemon balm infusion (7.95 ± 9.33 U/mL before versus 5.50 ± 6.44 U/mL after (Figure 3). A significant decrease ($p = 0.0001$) in 8-OH-dG levels was observed by use of Lemon balm infusion. The mean ± SD before and after using were 434.41 ± 72.63 and

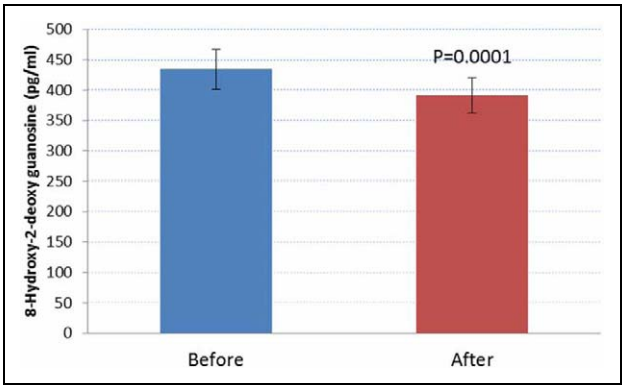

Figure 4. Changes in plasma 8-Hydroxy-2-deoxy guanosine (8-OH-dG) before and after treatment with Lemon balm infusion. Data are mean ± SEM. *p* Value of the difference between before and after treatment is shown.

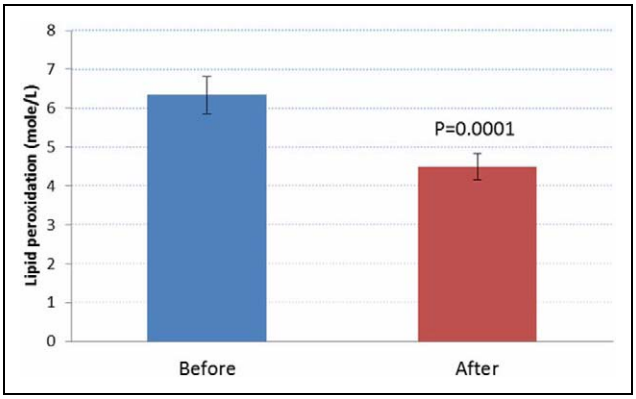

Figure 5. Changes in plasma lipid peroxidation (LPO) before and after treatment with Lemon balm infusion. Data are mean ± SEM. *p* Value of the difference between before and after treatment is shown.

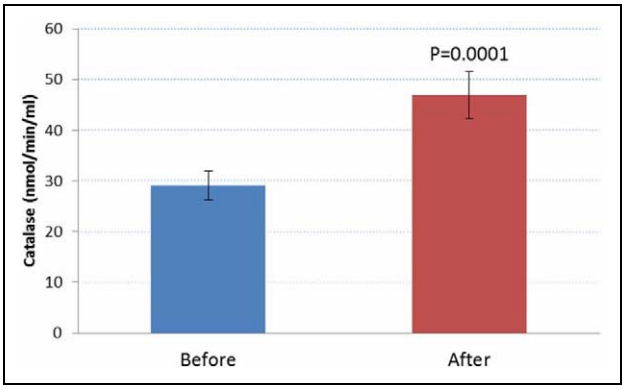

Figure 6. Changes in plasma catalase (CAT) before and after treatment with Lemon balm infusion. Data are mean ± SEM. *p* Value of the difference between before and after treatment is shown.

391.01 ± 25.95 pg/mL (Figure 4). A significant decrease ($p = 0.0001$) in LPO level was observed by use of Lemon balm infusion. The before and after levels were 6.34 ± 1.79 and 4.49 ± 1.75 mole/L, respectively (Figure 5). A significant increase ($p = 0.0001$) in CAT activity was observed by use of before and after. The before and after levels were 29.09 ± 16.72 and 46.89 ± 20.52 nmol/min/mL, respectively (Figure 6).

No linear correlation was found between age and years of employment or oxidative stress markers. The concentration of 8-OH-dG in women (427.52 ± 82.82) was lower than that of men (446.52 ± 49.76) but not significantly ($p = 0.36$).

Discussion

In this study, the effect of *Melissa officinalis L.* infusion on oxidative stress status was investigated in radiology staff. This study showed that the activity of SOD, CAT, and GPx increased significantly but the level of LPO, 8-OHdG, and the activity of MPO significantly decreased. Ionizing radiation generates various free radicals from the ionization of tissues water that are highly reactive and can start a cascade of different ROS. In addition, chronically exposed radiation causes alteration in gene expression patterns (Fachin et al., 2009), cataract (Milacic, 2009), cancer (Jacob et al., 2009; Zielinski et al., 2009b), cardiovascular disease (Zielinski et al 2009a), chromosomal aberrations (Engin et al., 2005), and DNA damage (Zakeri and Hirobe, 2010) in radiology staff. Workers of radiology unit are occupationally exposed to long-term low level dose of ionizing radiation, which may affect their antioxidant status. In hospital workers, especially radiology staff, a high level of LPO and oxidative stress due to chronic exposure to low-dose ionizing radiation has been reported (Malekirad et al., 2005), which may lead to DNA damage and mutagenicity (Engin et al., 2005; Sahin et al., 2009). It seems that free radicals and oxidative stress are the main reason for these effects.

Moreover, after whole-body radiation, the levels of endogenous antioxidants are decreased and the index of oxidative stress such as LPO is increased in the animals and humans (Day, 2008).

Some studies indicate that during occupational exposure, the activity of antioxidant enzymes, such as SOD, CAT, and GPx increase as a protection against the increased free radicals (Durovic et al., 2008) and some other studies show that long-term exposure to low level of ionizing radiation and chronic oxidative stress might reduce antioxidant defense in workers (Kłucinski et al., 2008). However, it seems that there is oxidative stress in radiology workers that are occupationally exposed to low-dose radiation (Puthran et al., 2009), and Lemon balm infusion can improve enzymatic antioxidant system and simultaneously reduce stress oxidative in radiation workers. Many in vitro and ex vivo studies have shown antioxidant activity of *Melissa officinalis* extracts, but in vivo studies especially in human are rare. In vivo studies just showed that *Melissa officinalis L.* extract could decrease LPO in rodents (Birdane et al., 2007) and in liver tissue of hyperlipidemic rats (Bolkent et al., 2005). *Melissa officinalis L.* extract has been useful as rich source of antioxidants (Dastmalchi et al., 2008; Topal et al., 2008) and many studies have shown high phenolic content of polar extracts of this plant and its antioxidant activity and radical scavenging capacity (López et al., 2009). The main phenolic compounds that were identified in tea infusion from Lemon balm, respectively, were rosmarinic acid, luteolin 7-O-glucoside, quercetin 3-rutinoside, gallic acid, quercetin 3-O galactoside, and ferulic acid (Kulišić-Bilušić et al., 2008). These compounds have antioxidant properties and scavenge free radicals (Alamed et al., 2009) and therefore decreasing LPO rate (Pereira et al., 2009; Verma et al., 2009), some of these compounds inhibit or decreasing MPO (Domitrović et al., 2009; Jiang et al., 2009; Shiba et al., 2008) and DNA damage in various cells and tissues (Lima et al., 2006; Min et al., 2009; Silva et al., 2008; Zhang et al., 2008). Antioxidant enzymes level and its activity can be increased by some phenolic compounds that are found in Lemon balm infusion (Haleagrahara et al 2009; Yeh and Yen, 2006; Yeh et al., 2009).

Moreover, after using infusion, it seems that *Melissa officinalis L.*, due to the phenolic compounds, was able to increase the activity of enzymatic antioxidant and to decrease the amount of LPO, MPO, and DNA damage. Hence, it decreases radiation-induced oxidative stress.

Conclusion

The oral administration of Lemon balm infusion may be helpful for the protection of the radiology staff against radiation-induced oxidative stress and improve antioxidant defense system especially enzymatic defense, due to its antioxidant properties.

This potential of Lemon balm infusion seems to be due to its phenolic compounds, especially phenolic acids and flavonoids and their antioxidant activity.

These findings encourage pursuing further studies such as determination of the effect of other antioxidants in ionizing radiation-induced oxidative stress and seeking for natural antioxidants and radioprotective compounds for radiation workers against low-dose radiation exposure. Limitations of this study were lack of information about annual dose of radiation and not being able to control exactly the diet and physical activity during study.

Authors' note

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