World Journal of
Chemical and Pharmaceutical Sciences

Journal homepage: https://zealjournals.com/wjcps/

ISSN: 2945-3186 (Online)

(REVIEW ARTICLE)

Check for updates

Medicinal benefits of lemon balm (*Melissa officinalis*) for human health

Muhammad Arshad Ullah [1,*] and Ali Hassan [2]

[1] *Natural Resources Division, Pakistan Agricultural Research Council, Islamabad, Pakistan.*
[2] *Faculty Agricultural and Food Sciences, Agronomy Department, Pir Mehr Ali Shah - University of Arid Agriculture, Rawalpindi, Pakistan.*

World Journal of Chemical and Pharmaceutical Sciences, 2022, 01(01), 028–033

Publication history: Received on 11 January 2022; revised on 10 March 2022; accepted on 12 March 2022

Article DOI: https://doi.org/10.53346/wjcps.2022.1.1.0025

Abstract

Melissa officinalis L, also known as lemon balm, bee balm, honey balm, is a perennial herb. Lemon balm occurs naturally in sandy and scrubby areas but also grown on damp wasteland, at elevations ranging from sea level to the mountains. *Melissa officinalis* is cost-effective, and compared with the economic indicators of traditional crops grown on fertilized land; this herb provides much higher profits. The leaf of Melissa officinalis contains flavonoids (quercitrin, rhamnocitrin, luteolin), polyphenolic compounds (rosmarinic acid, caffeic acid, and protocatechuic acid), monoterpenoid aldehyde, monoterpene glycosides, triterpenes (ursolic and oleanolic acids), sesquiterpenes, tannins, and essential oils (citral). Antimicrobial activities of the extracts and of rosmarinic acid of this plant were evaluated and were confirmed. The essential oil of *Melissa officinalis* L was shown to have anti-inflammatory activities, in treating various diseases associated with inflammation and pain. *Melissa officinalis* L relieves stress-related effects. Extract have the potential to prevent oxidative damage by preventing free radical– mediated oxidative stress. *Melissa officinalis* showed strong reducing power and exhibited a significant inhibition of deoxyribose degradation. The high phenolic content and radical scavenging activities of extracts of Melissa officinalis L was confirmed.

Four known compounds isolated from dried stems and leaves of Melissa officinalis are as quadranoside III, salvianic acid A, rosmarinic acid, and luteolin. Commercial bag lemon balm gave the highest antioxidant. Lemon balm (*Melissa officinalis* L.) and its preparations have a mildly soothing, antiviral effect, improve the digestive tract, and relax intestinal spasms. Lemon balm is a natural source of rosmarinic acid (RA). RA is one of the main phenolic acids in the chemical composition of *Melissa officinalis* L., and it determines the pharmacological effect and the medical use of the plant. Lemon balm has bacteriostatic, antimicrobial, and antiviral effects. It has antiviral effects; some authors state that they can be used against HIV-1 infection. RA in lemon balm has demonstrated more active antioxidant activity compared to α-tocopherol.

The advantage that gel has over ointments or cream is that it is a more stable, non slimy, and semisolid form of medication. Due to its characteristic sensory properties (easily applicable on the skin, easily cleaned with water, and leaving no greasy membrane on skin, unlike other ointments), gel is suitable for the modeling of natural preparations that are usually applied several times a day for longer periods of time. Rosmarinic acid is more easily released from emulsion bases than from ointments.

The skin is the interface between the body and its environment and acts as a barrier protecting from adverse external factors. Keratinocytes are the principal cell type comprising the epidermis and constituting 90% of the total amount of epidermal cells. For this reason, the human keratinocyte cell line HaCaT that was used in this research was an excellent model to evaluate the biological effect of the active substanceof the modeled preparations .Chemically, rosmarinic acid is a derivative of two connected phenolic acids (coffee and 3,4-dihydroxyphenyl lactic acid) and has 4OH groups. It is

*Corresponding author: Muhammad Arshad Ullah
Pakistan Agricultural Research Council, Islamabad, Pakistan.

the most potent antioxidant among the hydroxycinnamic acids .Studies have shown that rosmarinic acid is an effective 6 Evidence-Based Complementary and Alternative Medicine scavenger of the DPPH radical, and it also scavenges the reactive nitrogen species, peroxynitrite, and various ROS.

Keywords: Rosmarinic acid; Hydroxycinnamic acids; Favonoids (quercitrin, rhamnocitrin, luteolin); Caffeic acids

1. Introduction

Economically, cultivating *Melissa officinalis* is cost-effective, and compared with the economic indicators of traditional crops grown on fertilized land; this herb provides much higher profits [1]. *Melissa officinalis* L, also known as lemon balm, bee balm, honey balm, [2] is a perennial herb. Lemon balm occurs naturally in sandy and scrubby areas but has also been reported to grow on damp wasteland, at elevations ranging from sea level to the mountains. In Iran, this plant is known locally by the names Badranjbooye, Var-angboo, and Faranjmoshk [2].

Historically lemon balm has been said to possess sedative/ tranquilizing, anti-gas, fever-reducing, antibacterial, spasmolytic, hypotensive, memory-enhancing, menstrual-inducing, and thyroid-related effects; antiviral and antioxidant activities; antifungal, antiparasitic, and antispasmolytic activities; flatulence; asthma; bronchitis; amenorrhea; cardiac failure; arrhythmias; ulcers; and wounds [3; 4]. The leaf of *Melissa officinalis* contains flavonoids (quercitrin, rhamnocitrin, luteolin), polyphenolic compounds (rosmarinic acid, caffeic acid, and protocatechuic acid), monoterpenoid aldehyde, monoterpene glycosides, triterpenes (ursolic and oleanolic acids), sesquiterpenes, tannins, and essential oils (citral) [5].

Antimicrobial activities of the extracts and of rosmarinic acid of this plant were evaluated and were confirmed [6]. The essential oil of *Melissa officinalis* L was shown to have anti-inflammatory activities, supporting the traditional application of this plant in treating various diseases associated with inflammation and pain [7]. Euvegal forte was effective in the treatment of younger children with restlessness and dyssomnia and it was very well tolerated [8]. For the first time, it has been shown that chronic administration of Melissa officinalis L relieves stress-related effects. It is critical that further studies incorporate a placebo and investigate physiological stress markers [9].

It was revealed that essential oils of *Melissa officinalis* L have good potential for antioxidant activity and can be used in lipid-containing foods. It is a rich source of antioxidants, in particular from the group of phenolic compounds [10]. Its activity is comparable with synthetic antioxidants (BHA and BHT), and antioxidant activity is related to phenolic compounds like citronellal and neral [11]. It showed that the extract of Melissa was rich in bound forms of phenolic compounds such as hydroxycinnamic acids and flavonoids, rosmarinic and caffeic acids [12].

Melissa officinalis and *Mentha suaveolens* showed acetyl cholinesterase inhibitory capacity is higher than 50%in the essential oil fraction. Melissa officinalis showed both high acetyl cholinesterase inhibitory capacity and antioxidant activity. Besides, *Melissa officinalis* showed appreciable antioxidant activity only in the polar fractions [13]. Ethyl acetate fraction presented the highest flavonoids content as well as the antioxidant activities when compared with other tested fractions [14].

This is of significant importance as it indicates that the extract may have the potential to prevent oxidative damage *in vivo* by preventing free radical– mediated oxidative stress [15].*Melissa officinalis* showed strong reducing power and exhibited a significant inhibition of deoxyribose degradation [16]. The high phenolic content and radical scavenging activities of extracts of Melissa officinalis L was confirmed [17]. In a study, *Melissa officinalis* had very high levels of phenolics (13.2 mg GAE/100 g dw) in 32 plant spices [18]. In another study, it had the highest levels of phenolics and flavonoids [19].

Four known compounds have been isolated from dried stems and leaves of *Melissa officinalis*. The known compounds were identified as quadranoside III, salvianic acid A, rosmarinic acid, and luteolin. Free radical scavenging and antimicrobial activities of the extracts and of rosmarinic acid, the major component, were evaluated [20].

The highest value of phenol compounds was obtained for the extracts of solid residues of supercritical extraction at 10 MPa, 323 K, and 30 minutes [21].Overall, cultivated and *in vitro* cultured samples presented the lowest amounts of phenolic compounds; otherwise, commercial samples showed the highest contents [22].The highest a-linolenic acid, tocopherols (including a-, c-, and d-isoforms), and ascorbic acid contents were also observed in this sample. However, it was the commercial bag lemon balm that gave the highest antioxidant [23].

In an animal study, *Melissa officinalis* aqueous extract possessed potent antioxidative and neuroprotective properties, validating its efficacy in attenuating Mn-induced oxidative stress in the mouse brain [24]. Among the purified compounds, quercetin had the highest antioxidant activity followed by gallic acid, quercitrin, and rutin [25]. In a clinical trial the capability of Melissa officinalis L infusion on improvement of oxidative stress status was studied in radiology staff. It was 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 [26].

In another animal study on boars, the protective ability of extracts of mate tea and lemon balm was investigated. It was indicated that the highest concentration of lemon balm produced significant improvement in curvilinear trajectory, straightness, and amplitude of lateral head displacement after thawing [27]. Antioxidants act in one or more of the following ways: reducing agents, free radical scavengers, potential complexes of pro-oxidant metals, and quenchers of singlet oxygen [28]. Phenolic compounds are the most important compounds that have antioxidant activities [29; 30; 31; 32; 33; 34; 35; 36]. It was found that the antioxidant activity of phenolic compounds in the plant extract is mostly because of rutin, quercitrin, galic acid, and quercetin, with the highest antioxidant activity belonging to quercetin and then to galic acid, quercitrin, and rutin, respectively. The extract of this plant is able to prevent the production of chemically active species and it may block lipid peroxidation through various processes [37].

Lemon balm (*Melissa officinalis* L.) and its preparations have a mildly soothing, antiviral effect, improve the digestive tract, and relax intestinal spasms [38; 39]. Lemon balm is a natural source of rosmarinic acid (RA). RA is one of the main phenolic acids in the chemical composition of *Melissa officinalis* L., and it determines the pharmacological effect and the medical use of the plant [24; 39; 40;]. Current studies have shown that lemon balm preparations have bacteriostatic, antimicrobial, and antiviral effects [24]. Currently, there are very comprehensive surveys that attempt to show the effect of lemon balm against herpes simplex virus [41; 42; 43; 44; 45]. Since lemon balm has antiviral effects, some authors state that they can be used against HIV-1 infection. There is evidence in scientific literature that lemon balm has antihistamine effects; thus it can be used externally by placing the cut grass on insect bites or other irritated areas [7]. RA in lemon balm has demonstrated more active antioxidant activity compared to α-tocopherol [21].

When modeling a semisolid preparation, it is highly important to choose appropriate base substances because they determine the physicochemical properties and therapeutic effects of the final product [46]. The advantage that gel has over ointments or cream is that it is a more stable, nonslimy, and semisolid form of medication [47]. Due to its characteristic sensory properties (easily applicable on the skin, easily cleaned with water, and leaving no greasy membrane on skin, unlike other ointments), gel is suitable for the modeling of natural preparations that are usually applied several times a day for longer periods of time. Gel ensures easy and safe administration of such preparations at home by nonmedical persons [48]. The results of scientific research revealed that rosmarinic acid is more easily released from emulsion bases than from ointments [49].

In order to reach the maximum effect of these preparations, their pH should be close to that of the skin (5.4 to5.9) [50]. In patients with atopic dermatitis, the pH of the skin may increase (6.0 to 6.5) [51]. Substance penetration into or through the skin occurs in a coherent sequence when dissolved molecules released from the dosage form each the surface of the stratumcorneum and penetrate through it [52]. Materials can penetrate through the skin by intracellular, extracellular, and additional “shunt” (through hair follicles and gland ducts) routes [53; 54]. Substance penetration using the intracellular polar route occurs when molecules diffuse through the cytoplasm of dead keratinocytes and the surrounding lipid matrix [55]. This state of oxidative stress can affect all important cellular components like proteins, DNA, and membrane lipids, which is considered to be the main mechanism of cell damage [56]. There is research confirming that exogenous molecules from dietary sources such as polyphenols are very efficient in preventing the alteration caused by oxidative stress [57] because they scavenge and suppress the formation of free radicals. Thus the use of preparations with antioxidant activity is critical for cells that are in oxidative stress conditions.

The skin is the interface between the body and its environment and acts as a barrier protecting from adverse external factors. Keratinocytes are the principal cell type comprising the epidermis and constituting 90% of the total amount of epidermal cells [58]. For this reason, the human keratinocyte cell line HaCaT that was used in this research was an excellent model to evaluate the biological effect of the active substance of the modeled preparations .Chemically, rosmarinic acid is a derivative of two connected phenolic acids (coffee and 3,4-dihydroxyphenyl lactic acid) and has 4 OH groups. There are studies showing that it is the most potent antioxidant among the hydroxycinnamic acids [59]. Studies have shown that rosmarinic acid is an effective 6 Evidence-Based Complementary and Alternative Medicine scavenger of the DPPH radical, and it also scavenges the reactive nitrogen species, peroxynitrite, and various ROS [60].

The results of experiments done with cell cultures show that, through its antioxidant activity, RA could be able to attenuate H_2O_2 -induced cell injury [61]. On the other hand, 150μM of H_2O_2 and 300μMo f H_2O_2 are relatively high doses

to induce apoptosis in Jurkat T cells and in HaCaT cells, respectively [62]. It was shown that very severe oxidative stress activates a large number of signaling pathways since ll s and causes cell death via either apoptotic or necrotic mechanisms [63].

2. Conclusion

Melissa officinalis is cost-effective, and compared with the economic indicators of traditional crops grown on fertilized land; this provides much higher economic profits *Melissa officinalis* L, also known as lemon balm, bee balm, honey balm, is a perennial herb. It and its preparations have a mildly soothing, antiviral effect, improve the digestive tract, and relax intestinal spasms. Lemon balm is a natural source of rosmarinic acid (RA). RA is one of the main phenolic acids in the chemical composition of *Melissa officinalis* L., and it determines the pharmacological effect and the medical use of the plant. Lemon balm preparations have bacteriostatic, antimicrobial, and antiviral effects. There is evidence in scientific literature that lemon balm has antihistamine effects; thus it can be used externally by placing the cut grass on insect bites or other irritated areas. RA in lemon balm has demonstrated more active antioxidant activity compared to-tocopherol.

References

[1] Gurcık L, Dubravska R, Miklovicova J. Economics of the cultivation of *Salvia officinalis* and *Melissa officinalis*. Agric Econ Czech. 2005; 51:348-356.

[2] Rasmussen P. Lemon balm—*Melissa officinalis*, also known as lemon balm, bee balm, garden balm, Melissa, melissengeist. J Prim Health Care. 2011; 3:165-166.

[3] Setorki M, Rafieian-Kopaei M, Merikhi A, et al. Suppressive impact of Anethum graveolens consumption on biochemical risk factors of atherosclerosis in hypercholesterolemic rabbits. Int J Prev Med. 2013; 4:889-895.

[4] Akhlaghi M, Shabanian G, Rafieian-Kopaei M, Parvin N, Saadat M, Akhlaghi M.Citrus aurantium blossom and preoperative anxiety. Rev Bras Anestesiol. 2011; 61: 702-712.

[5] Sofowora A, Ogunbodede E, Onayade A. The role and place of medicinal plants in the strategies for disease prevention. Afr J Tradit Complement Altern Med. 2013; 10:210-229.

[6] Abdellatif F, Boudjella H, Zitouni A, Hassani A. Chemical com-position and antimicrobial activity of the essential oil from leaves of Algerian *Melissa officinalis* L.EXCLI J. 2014; 13: 772-781.

[7] Bounihi A, Hajjaj G, Alnamer R, Cherrah Y, Zellou A. *In vivo* potential anti-inflammatory activity of *Melissa officinalis* L. essential oil. Adv Pharmacol Sci. 2013; 101759.

[8] Muller S.F, Klement S. A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssomnia in children. Phytomedicine. 2006; 13:383-387.

[9] Cases J, Ibarra A, Feuillere N, Roller M, Sukkar SG. Pilot trial of *Melissa officinalis* L. leaf extract in the treatment of volunteers suffering from mild-to-moderate anxiety disor-ders and sleep disturbances. Med J Nutr Metab. 2011; 4: 211-218.

[10] Capecka E, Mareczek A, Leja M. Antioxidant activity of fresh and dry herbs of some Lamiaceae species. Food Chem. 2005; 93: 223-226.

[11] Meftahizade H, Sargsyan E, Moradkhani H. Investigation of anti-oxidant capacity of *Melissa officinalis* L. essential oils J Med Plant Res. 2010;4:1391-1395.

[12] Triantaphyllou K, Blekas G, Boskou D. Antioxidative properties of water extracts obtained from herbs of the species Lamiaceae. Int J Food Sci Nutr. 2001;52:313-317.

[13] Ferreira A, Proenca C, Serralheiro M, Araujo M. The *in vitro* screening for acetylcholinesterase inhibition and antioxidant activity of medicinal plants from Portugal. J Ethnopharmacol. 2006; 108:31-37.

[14] Pereira RP, Boligon AA, Appel AS, et al. Chemical composition, antioxidant and anticholinesterase activity of Melissa officinalis. Industrial Crops Products. 2014;53:34-45.

[15] Dastmalchi K, Dorman HD, Oinonen PP, Darwis Y, Laakso I, Hitunen R. Chemical composition and *in vitro* antioxidative activity of a lemon balm (*Melissa officinalis* L.) extract.LWT Food Sci Technol. 2008; 41: 391-400.

[16] Kamdem JP, Adeniran A, Boligon AA, Athyade ML. Antiox-idant activity, genotoxicity and cytotoxicity evaluation of lemon balm (*Melissa officinalis* L.) ethanolic extract: its potential role in neuroprotection. Industrial Crops Products. 2013; 51:26-34.

[17] Canadanovic-Brunet J, Cetkovic G, Djilas S, et al. Radical scavenging, antibacterial, and antiproliferative activities of *Melissa officinalis* L. extracts. J Med Food. 2008; 11: 133-143.

[18] Wojdyło A, Oszmian´ski J, Czemerys R. Antioxidant activity and phenolic compounds in 32 selected herbs. Food Chem. 2007; 105: 940-949.

[19] Dias MI, Barros L, Sousa MJ, Ferreira IC. Systematic comparison of nutraceuticals and antioxidant potential of cultivated, *in vitro* cultured and commercial Melissa officinalissamples. Food Chem Toxicol. 2012; 50:1866-1873.

[20] Mencherini T, Picerno P, Scesa C, Aquino R. Triterpene, antioxidant, and antimicrobial compounds from *Melissa officinalis*. J Nat Prod. 2007; 70:1889-1894.

[21] Ribeiro M, Bernardo-Gil M, Esquıvel M. Melissa officinalis L.: study of antioxidant activity in supercritical residues. J Super critical Fluids. 2001; 21:51-60.

[22] Barros L, Duen˜as M, Dias MI, Sousa MJ, Santos-Buelga C, Ferreira IC. Phenolic profiles of cultivated, *in vitro* cultured and commercial samples of Melissa officinalis L. infusions. Food Chem. 2013; 136: 1-8.

[23] Herodez S.S, Hadolin M, Skerget M, Knez Z. Solvent extraction study of antioxidants from Balm (*Melissa officinalis* L.) leaves. Food Chem. 2003; 80:275-282.

[24] Martins EN, NTC Pessano,L Lealetal. Protective effect of *Melissa officinalis* aqueous extract against Mn-induced oxidative stress in chronically exposed mice, Brain Research Bulletin. 2012; 87(1): 74–79.

[25] Pereira RP, Fachinetto R, de Souza Prestes A, et al. Antioxidant effects of different extracts from *Melissa officinalis*, *Matricaria recutita* and *Cymbopogon citratus*. Neurochem Res. 2009;34: 973-983.

[26] Zeraatpishe A, Oryan S, Bagheri MH, et al. Effects of *Melissa officinalis* L. on oxidative status and DNA damage in subjects exposed to long-term low-dose ionizing radiation. Toxicol Ind Health. 2011; 27:205-212.

[27] Luno V, Gil L, Olaciregui M, Jerez RA, de Blas I, Hozbor F. Antioxidant effect of lemon balm (*Melissa officinalis*) and mate tea (Ilex paraguensys) on quality, lipid peroxidation and DNA oxidation of cryopreserved boar epididymal spermatozoa. Andrologia. 2015; 47:1004-1011.

[28] Khayyal MT, El-Ghazaly MA, Kenawy SA, et al. Antiulcero-genic effect of some gastrointestinally acting plant extracts and their combination. Arzneimittelforschung. 2000; 51:545-553.

[29] Madihi Y, Merrikhi A, Baradaran A, et al. Impact of Sumac on postprandial high-fat oxidative stress. Pak J Med Sci. 2013; 29: 340-345.

[30] Rafieian-Kopaie M, Baradaran A. Plant's antioxidants: from laboratory to clinic. J Nephropathol. 2013; 2:152-153.

[31] Nasri H, Rafieian-Kopaei M. Medicinal plants and antioxidants: why they are not always beneficial? Iran J Public Health. 2014; 43:255-257.

[32] Rafieian-Kopaei M, Nasri H. Re: Erythropoietin ameliorates oxidative stress and tissue injury following renal ischemia/ reperfusion in rat kidney and lung. Med Princ Pract. 2014; 23:95.

[33] Nasri H, Tavakoli M, Ahmadi A, Baradaran A, Nematbakhsh M, Rafieian-Kopaei M. Ameliorative effect of melatonin against contrast media induced renal tubular cell injury. Pak J Med Sci. 2014; 30:261-265.

[34] Baradaran A, Nasri H, Rafieian-Kopaei M. Comment on: Anti-oxidative stress activity of Stachys lavanduli folia aqueous extract in humans.Cell J. 2013; 15: 272-273.

[35] Sedighi M, Nasri H, Rafieian-kopaei M, Mortazaei S. Reversal effect of *Achillea millefolium* extract on ileum contractions. J Herb Med Pharmacol. 2013; 2(1):5-8.

[36] Shirzad H, Taji F, Rafieian-Kopaei M. Correlation between antioxidant activity of garlic extracts and WEHI-164 fibro-sarcoma tumor growth in BALB/c mice. J Med Food. 2011; 14:969-974.

[37] Zarei A, S Changizi-Ashtiyani, S Taheri, N Hosseini. A brief overview of the effects of *Melissa officinalis* L. extract on the function of various body organs, Zahedan Journal of Research in Medical Sciences. 2015; 15: 29–34.

[38] Vejdani R, HRM Shalmani, M Mir-Fattahi et al. The efficacy of an herbal medicine, Carmint, on the relief of abdominal pain and bloating in patients with irritable bowel syndrome: a pilot study, Digestive Diseases and Sciences. 2006; 51(8):1501–1507.

[39] Lee J,E Jung, J Koh, YS Kim, D Park. Effect of rosmarinic acid on atopic dermatitis, Journal of Dermatology. 2008; 35(12): 768–771.

[40] Moradkhani H, E Sargsyan, H Bibak et al. *Melissa officinalis* L., a valuable medicine plant: a review, Journal of Medicinal Plants Research. 2010; 4(25): 2753–2759.

[41] Arceusz A, M Wesolowski. Quality consistency evaluation of *Melissa officinalis* L. commercial herbs by HPLC fingerprint and quantitation of selected phenolic acids, Journal of Pharmaceutical and Biomedical Analysis. 2013;83: 215–220.

[42] Astani A, J Reichling, P Schnitzler. Melissa officinalis extract inhibits attachment of herpes simplex virus *in vitro*, Chemotherapy. 2012; 58(1): 70–77.

[43] Awad R, A.Muhammad T, Durst VL, Trudeau, JT Arnason. Bioassay-guided fractionation of lemon balm (L.) using an *in vitro* measure of GABA transaminase activity, Phytotherapy Research. 2009; 23(8): 1075–1081.

[44] Ince A.E, Sahin S, Sumnu G.S. Extraction of phenolic compounds from melissa using microwave and ultrasound," Turkish Journal of Agriculture and Forestry. 2013; 37(1): 69– 75.

[45] Mazzanti G, L Battinelli, C Pompeo, et al. Inhibitory activity of Melissa officinalis L. extract on Herpes simplex virus type 2 replication, Natural Product Research. 2008; 22(16): 1433– 1440.

[46] Foldvari M. Non-invasive administration of drugs through the skin: challenges in delivery system design, Pharmaceutical Science & Technology Today. 2000; 3(12): 417–425.

[47] Verma A, S Singh, R Kaur, A Kumar, UK Jain. Formulation, optimization and evaluation of clobetasolpropionate gel, International Journal of Pharmacy and Pharmaceutical Sciences. 2013; 5(4): 666–674.

[48] Dodov MG, K Goracinova, M Simonoska, S Trajkovic-Jolevska JT, Ribarska, MD Mitevska. Formulation and evaluation of diazepamhydrogel for rectal administration, Acta Pharmaceutica. 2005; 55(3): 251–261.

[49] Stelmakien e A, K Ramanauskien e, V Briedis. Release of rosmarinic acid from semisolid formulations and its penetration through human skin ex vivo, Acta Pharmaceutica. 2015; 65(2): 199–205.

[50] Schmid-Wendtner MH, HC Korting. The pH of the skin surface and its impact on the barrier function," Skin Pharmacology and Physiology. 2006; 19(6): 296–302.

[51] Rizi K, RJ Green, MX Donaldson, AC Williams. Usingp Habnormalities in diseased skin to trigger and target topical therapy," Pharmaceutical Research. 2011; 28(10):2589–2598.

[52] Cal K. Across skin barrier: known methods, new performances, Frontiers in Drug Design & Discovery. 2009; 4(1):162–188.

[53] Drake DR, KA Brogden DV Dawson, PW Wertz. Thematic review series: skin lipids. Antimicrobial lipids at the skin surface, The Journal of Lipid Research. 2008; 49(1): 4–11.

[54] Moss GP, JC Dearden, H Patel, MTD Cronin. Quantitative structure-permeability relationships (QSPRs) for percutaneous absorption, Toxicology *in vitro*. 2002; 16(3): 299–317.

[55] Touboul D, F Halgand, A Brunelle, et al. Tissue molecular ion imaging by gold cluster ion bombardment, Analytical Chemistry. 2004; 76(6): 1550–1559.

[56] Fadel O, K El Kirat, S Morandat. The natural antioxidant rosmarinic acid spontaneously penetrates membranes to inhibit lipid peroxidation in situ, Biochimica et Biophysica Acta— Biomembranes. 2011; 1808(12):2973–2980.

[57] Sivaranjani N, SV Rao, G Rajeev. Role of reactive oxygen species and antioxidants inatopic dermatitis, Journal of Clinical and Diagnostic Research. 2013; 7(12): 2683–2685.

[58] Lee ER, YJ Kang, JH Kim, HT Lee, SG Cho. Modulation of apoptosis in HaCaT keratinocytes via differential regulation of ERK signaling pathway by flavonoids, The Journal of Biological Chemistry. 2005; 280(36): 31498–31507

[59] Soobrattee MA, VS Neergheen, A Luximon-Ramma, OI Aruoma, T Bahorun. Phenolics as potential antiox-idant therapeutic agents: Mechanism and actions, Mutation Research—Fundamental andMolecular Mechanisms of Mutage-nesis. 2005; 579(1-2): 200–213.

[60] Kelsey NA, HM Wilkins, DA Linseman. Nutraceutical antioxidants as novel neuroprotective agents, Molecules. 2010; 15(11): 7792–7814.

[61] Gao LP, HL Wei, HS Zhao, SY Xiao, RL Zheng,. Antiapoptotic and antioxidant effects ofrosmarinic acid in astrocytes, Pharmazie. 2005; 60(1): 62–65.

[62] ChkhikvishviliI, T Sanikidze, N Gogia et al. Rosmarinic acid-rich extracts of summer savory (Satureja hortensisL.) pro-tect jurkat T cells against oxidative stress, Oxidative Medicine and Cellular Longevity. 2013; ArticleID456253: 9.

[63] Martindale JL,NJ Holbrook. Cellular response to oxidative stress: signaling for suicide and survival, Journal of Cellular Physiology. 2002; 192(1): 1–15.