

Olive oil biophenols and women's health

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ABSTRACT

Olea europea, the olive tree, is an ancient tree that originates from the Mediterranean environment of Asia Minor. The edible olive fruit is also used for its oil, gained by the process of pressing, a nutrient with proven beneficial effects. Virgin olive oil is the natural juice of the olive fruit, which plays a major role in the healthy Mediterranean diet. The source of its health effects are the biophenols and squalenes (oleocanthal, tyrosol, hydroxytyrosol, oleuropein) it contains. They provide an exceptional antioxidative activity, removing harmful compounds from the body. Oxidants are essential in the genesis of many diseases and conditions, such as cardiovascular disorders, cancer, osteoporosis, Alzheimer disease, and premenstrual syndrome. Oleic acid, an unsaturated fatty acid, has demonstrated a significant effect in the prevention of malignant diseases such as colon cancer and breast cancer. Biophenols from olive oil successfully suppress the synthesis of LDL, a protein that is crucial in the development of cardiovascular disease, by reducing blood pressure and the development of atherosclerotic plaques. In addition, there is strong evidence of the antimicrobial effect of the biophenols from olive oil that successfully destroy colonies of microorganisms which may cause respiratory tract, intestinal, and genital tract infections.

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INTRODUCTION

Hormonal replacement therapy (HRT) is not the only possibility to manage certain aspects of adult women's health. Huge Women's Health Initiative Study (WHI) (1) assessing the impact of HRT mainly on cardiovascular health, malignant diseases and osteoporotic fractures, have consternated not only lay users, but prescribers too. Namely, increased cancer, stroke and coronary heart disease risk associated with long term use of postmenopausal hormone therapy (HT) have rapidly declined the number of women treated with HT, either estrogen alone or estrogen plus progestogen (2). According to the recent position statements from leading organizations dealing with menopause, individualization of therapy and lower dosage HT becomes the state of the art (3). Not only WHI, but also results of other studies published in the past few years, have induced curiosity for non-estrogen containing treatments in climacteric medicine (4). Those who do not want, or interfere with hormone therapy must be given information about the merits of alternatives that are often inadequately explored. A way of life that implements a healthy Mediterranean diet allows aging with lower risk (5).

OLIVE OIL AND ITS HEALTH BENEFITS

Virgin olive oil is the result of the first and second so-called "cold" pressing of the olive fruit, without the addition of chemical substances and the use of heat. More than thirty of the structurally different olive oil biophenols that have been isolated so far originate from two fractions obtained by pressing, the glycerol (90-99%) and non-glycerol (0.4-5%) fractions (6). The biological and health benefits of olive oil are attributed to its high content of unsaturated fatty acids contained in the biophenols (7). They reduce low-density lipoprotein oxidation immediately after food ingestion (8). Additional low-density lipoprotein oxidation and peroxidation provide one of the most harmful effects on total cardiovascular health and represent a risk factor for the development of a range of chronic non-infectious diseases (9). The beneficial effect of olive oil is increased by its high percentage of mono-unsaturated oleic acid, which is less susceptible to lipid peroxidation than the poly-unsaturated fatty acids; also, its high content of α -tocopherol may enhance the antioxidative effect of olive oil

and other vegetable oils rich in vitamin E, i.e. its fraction in the form of α -tocopherol (10).

Olive oil polyphenols are complex mixtures of various compounds: 3,4-dihydroxyphenyl ethanol, 4-hydroxyphenyl ethanol (tyrosol), 4-hydroxyphenylacetic acid, protocatechinic acid, syringic acid, vanillin acid, caffeic acid, and coumarin acid (11). The concentration of the phenolic fraction in olive oil varies, depending on the cultivator, climate, and ripeness of the fruit; in virgin olive oil it amounts to approximately 500 mg/L (12). Olive oil biophenols are categorized into three groups: simple phenols (tyrosol and hydroxytyrosol), secoiridoids (oleuropein and ligstroside aglycone and their decarboxylated dialdehyde derivatives), and lignans (pinoresinols) (13). They all display a high antioxidative activity; consequently, the daily intake of recommended doses of olive oil results in a considerable protective effect against colon and breast cancer, as well as skin cancer and premature aging of the skin (14, 15). From the range of components contained in olive oil polyphenols, hydroxytyrosol is the most important one. It exists as a free molecule, but is also part of complex compounds (e.g., oleuropein) (16). Laboratory tests showed that oleuropein has a stronger effect than standard antioxidants (e.g. hydroxytoluene) (17). Olive oil contains polyphenols which have a significantly greater antioxidative effect than those contained in other vegetable oils. Although most vegetable oils (sunflower, soy, rape seed) contain similar amounts of unsaturated fatty acids with attributable health benefits, they are nevertheless ineffective in fighting certain basic factors associated with chronic diseases (18). Therefore, most studies aiming to prove the benefits of olive oil use biophenols from the specific non-glycerol, non-saponifiable fraction obtained by pressing of the olive fruit (19, 20).

It is an epidemiological fact that there is a significantly lower incidence of degenerative diseases and conditions in the Mediterranean population. High-reliability studies conducted with a great number of subjects have proven that olive oil plays a key role in the beneficial effects of the so-called Mediterranean diet (21), typically characterized by a lower intake of red meat, which is substituted by white meat and plenty of fish, as well as by a daily intake of fruit, vegetables, stone fruit, and olive oil (22). Epidemiological stu-

dies recording the morbidity and mortality from potentially fatal diseases have shown that the incidence of myocardial infarction and cerebral insult, breast and colon cancer, cerebral dementia, and osteoporosis is significantly lower in the Mediterranean countries (15). This diet, part of the Mediterranean lifestyle, is undoubtedly one of the basic contributing factors of such a favorable health pattern. In addition to the diet itself, there are other typical features contributing to the mentioned health benefits: lifelong family commitments, the afternoon siesta, the controlled enjoyment of red wine, and undisturbed sleep (23).

Impact of olive oil on blood pressure

The daily intake of 50 milliliters, i.e., three table spoonfuls of olive oil has been proven to result in significant health benefits (24). A considerable number of well-designed studies showed that olive oil has a moderate, but significant lowering effect on blood pressure, due to tiny compounds contained in the olive fruit, but not found in other oils (alpha-tocopherol and specific polyphenols) (25). An experimental model showed that the pressure-lowering effect is additionally enhanced by oleic acid found in high amounts (70-80%) in olive oil (26). This acid affects the lipid component of the cell membrane (H₂ passage phase) by controlling the G protein signal mediators through adenylate cyclase and C phospholipase, thus reducing blood pressure (27). By stratification, which included olive oil as a separate entity of the Mediterranean diet, a 5-year prospective EPIC study from Greece conducted with 20,343 subjects (11,658 women) without a previous history of arterial hypertension showed a considerable reduction of both systolic and diastolic pressure (-0,8 SD; (95% CI -1.1, -0.6; < 0.001) (28). A random controlled study involving hypertensive subjects on various diet regimens over the course of one year showed that extra virgin olive oil reduced the need for conventional medication, probably due to the mechanism of nitric oxide increase (29).

Olive oil reduces the risk of coronary disease by lowering cholesterol levels and an accompanying antiinflammatory effect

Almost all epidemiological and metabolic studies have found that unsaturated fatty acids reduce the risk of coronary disease. A study involving 148

women and 700 men proved that the daily use of olive oil in food preparation significantly reduces the risk of ischemic heart disease, and that as much as 47% fewer coronary incidents were recorded in the subject group which used olive oil on a daily basis, regardless of their different health profiles and lifestyles (30).

Olive oil reduces oxidation and levels of the LDL cholesterol fraction whose oxidation is partly responsible for the development of atherosclerosis (31). Simultaneously, it raises the levels of protective HDL cholesterol. Olive oil polyphenols decrease oxidative stress by removing free radicals, the malignant toxic products of oxidation (32). Biophenols contained in virgin olive oil inhibit the cell oxidation of LDL by increasing the mRNA transcription of glutathione enzymes (33).

Inflammation plays a key role in the pathogenesis of atherosclerosis. Carluccio MA et al. have discovered that olive oil reduces the concentration of cytokines (interleukin 6, TNF α , IFN γ), molecules which stimulate the inflammatory response in the vessel walls by activating monocytes and producing macrophages in the early stages of atherogenesis (34). The effect is the same as that produced by conventional antiinflammatory drugs such as ibuprofen (35).

Olive oil reduces the deposits of free fatty acids in the liver

Uncontrolled intake of fats and carbonated sweet drinks as well as increased levels of blood sugar accompanied by a rise in oxidative stress result in increased triglyceride deposits in the liver (36). An olive oil-rich diet will prevent the formation of such deposits of dangerous fats, regulate the levels of sugar and glucagon-like peptide-1 in insulin-resistant diabetics, and simultaneously enhance the action of sugar transporters (transporters 2) within the liver metabolism (37).

Olive oil biophenols reduce body weight

Studying obesity as a consequence of the urge for an excessive food intake, researchers have found that eating stimulates the cells in the intestinal epithelial mucosa to produce oleoylethanolamide (OEA), a transport medium for fats. OEA, influenced by oleic acid from olive oil, acts as a sensor for additional food intake (38). In other words, olive oil provides the feeling of satiety.

A diet rich in unsaturated fatty acids from olive oil reduces waist girth, one of the significant indicators of metabolic disease, along with a reduction in the body mass index (39).

Malignant tumors and olive oil

Olive oil contains a number of compounds which by their antioxidative action reduce the risk of cell damage and their consequential uncontrolled growth and division (40). In addition to oleic acid, such effects are provided by squalenes, tocopherol (vitamin E), and other biophenols (41).

According to experimental models, olive oil may affect all the phases of carcinogenesis. According to Adler et al., an experimental study on mice showed that resveratrol, one of olive oil biophenols, inhibits the action of NF κ B transcription factor, which in turn inhibits caspases, key enzymes for cell apoptosis, and thus stops the autonomous growth of tumor cells (42, 43). Olive oil compounds such as resveratrol, hydroxytyrosol, tyrosol, oleic acid, and oleuropein induce apoptosis mediated by the Fas/Fas ligand, stimulate tumor suppressor protein p53 activity, and remove cyclin-dependent kinases 1 and 2 during the cell cycle (44).

In addition, resveratrol also inhibits angiogenesis, which is yet another way of inhibiting carcinogenesis (44).

The incidence of colon cancer has been shown to be significantly lower in those who use olive oil as part of their daily diet (45). *Helicobacter pylori* is a microorganism involved in the pathogenesis of gastric ulcer and certain types of stomach cancer. Experimental models have shown that biophenols from olive oil demonstrate a high antimicrobial activity against eight biotypes of the *H. pylori* bacterium, three of which are even resistant to antibiotic treatment (46). These results raised speculations about olive oil acting as a chemopreventive agent in the pathogenesis of gastric ulcer. However, this biological action is yet to be proven in clinical trials.

A group from the Institute of Oncology from Granada, Spain, has obtained remarkable results using an experimental *in vitro* model of MCF-7 and SKBR3 breast cancer cells. They managed to prove that that extra virgin olive oil biophenols drastically reduce the process of division and dissemination of the most malignant breast cancer

types by down-regulation of the human epidermal growth factor receptor 2 (HER-2) expression and activity in cultivated breast cancer cells (47). Hydroxytyrosol, tyrosol, oleic acid, the lignans pinoresinol and 1-/acetoxypinoresinol as well as the secoiridoids oleuropein and oleuropein aglycone, demonstrated strong tumoricidal effects through the induction of cell apoptosis in HER-2 positive cells (48). Moreover, olive oil biophenols enhance the growth inhibitory effects of *trastuzumab* (monoclonal HER-2 antibody) in breast cancer cells with Her-2/neu oncogene amplification (49). However, *in vitro* concentrations used in the study were significantly higher than those used in daily life (47).

Breast tissue density is one of the biggest risks for overlooking suspicious shadows during mammogram analysis (50). A study carried out by a group of Italian researchers showed that olive oil biophenols in the Mediterranean diet significantly decreased the density of breast tissue in mammography imaging (51).

A case-control study from Greece estimated that increasing intake of monounsaturated fat, mostly olive oil, by about one standard deviation was associated with a 26% risk reduction of endometrial cancer (OR 0.74; 95% CI 0.54-1.3) (52).

Multiple sclerosis and Alzheimer disease

A one-year double-blind random study investigated how various dietary regimens affected subjects with multiple sclerosis. In the study group on the olive oil-based diet recommended by the North American Society of Cardiology (AHA Step I diet), as compared to the conventional "Fish Oil" diet with an increased intake of omega-3 fatty acids, a significantly reduced symptomatology regarding exhaustion and tiredness was recorded already within the first 6 months (53).

Epidemiological studies showed that the Mediterranean population is notably less affected by Alzheimer disease, a fact that was attributed to the above-average intake of olive oil (54, 55). A revolutionary experimental study on laboratory animals has shown that oleocanthal, the olive oil biophenol, not only enhances the signal transmission between nerve cells by blocking toxic beta-amyloid proteins in the synapses, but also aids new cell growth in the subgranular zone of the hippocampus and the subventricular zone of the lateral

ventricles (56). Those brain centers are responsible for memory and cognitive processes, mental abilities significantly impaired in patients whose cognition degenerates either by aging or due to the neurodegenerative Alzheimer disease (57).

The skin and olive oil

Olive oil contains polyphenols such as squalene, tocopherol, and resveratrol, important antioxidative agents in the prevention of a number of dermatoses (58). Resveratrol in particular has been studied recently for its influence on the slowing of skin aging.

Resveratrol stimulates the activity of sirtuin, a life-prolonging factor for fibroblasts, cells responsible for the production of collagen (59). Since collagen is the basic component of the extracellular dermal matrix whose amounts diminish during aging (60), the importance of olive oil in slowing the aging process of the skin is indisputable.

According to various studies, nicotinamide-adenine-dinucleotide (NAD), an oxidoreductase co-enzyme, inhibits the effect of sirtuin (SIRT1) (61). However, resveratrol inhibits the interaction between the NAD co-enzyme and sirtuin, thus enabling its beneficial effect on the fibroblasts (62). The amount of resveratrol necessary to stop the skin aging process has not been determined yet; besides, the marked chemical instability of this compound presents a considerable difficulty in the technological production process (63). Almost one third of the composition of olive oil is made up by a polyunsaturated fatty acid called linolenic acid, which inhibits cyclooxygenase as well as E_2 prostaglandin synthesis (64). Prostaglandin E_2 is an important inflammatory mediator present in common dermatoses such as psoriasis and atopic dermatitis (65), and the topical application of olive oil in the chronic phase of the disease decreases prostaglandin levels in the dermis, thus reducing the inflammatory response (66).

In addition to linolenic acid, the biophenol oleocanthal, isolated from virgin olive oil, has been proven to have an antiinflammatory effect due to its action as a non-selective cyclooxygenase inhibitor and cortisol receptor blocker (35).

Olive oil reduces the concentration of antiinflammatory cytokines interleukin 6, $TNF\alpha$, and $IFN\gamma$, which play a key role in the immunopathogenesis of psoriasis (35).

In everyday dermatological clinical practice, olive oil is used for the prevention of irritative and allergic contact dermatitis because it is neither an irritant nor an allergen, according to the chemical compound register of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) (67). An epidemiological study carried out by the ECETOC proved that olive oil is not a sensitizer because it does not chemically react with peptides in the epidermis, which contain nucleophilic amino acids such as cysteine and lysine. Topical application of olive oil creates a protective lipid film over the *stratum corneum* which prevents the absorption of irritants and allergens. The period of action of the topically applied olive oil amounts to approximately four hours (68).

Experimental models on mice have shown that topical application of olive oil inhibits the early phase of herpes simplex virus type 1 and 2 as well as varicella-zoster virus replication (69, 70).

OLIVE OIL BIOPHENOLS TARGETING SPECIFIC ISSUES

Premenstrual syndrome (PMS) is typically characterized by irritability, difficulty concentrating, insomnia, bloating and edema, painful periods and breast tenderness, nausea, and diarrhea. By reducing oxidative processes in the brain, vitamin E, triterpenes, and phenols contained in olive oil significantly decrease PMS-related mood swings. Linoleic acid reduces the transformation of arachidonic acid into prostaglandin (PgE_2) (71), a powerful hormone which affects the uterus and is thus responsible for its painful contractions during periods (72). Oleocanthal, by binding to cortisol receptors, reduces the inflammatory reaction and consequential edema, i.e., indirectly controls body weight in the second phase of the menstrual cycle (73).

Sexual lubrication of the vagina by olive oil application may have a detrimental effect on sperm motility and fertilization potential, and is thus not recommended for couples undergoing treatment for infertility (74).

An experimental model showed that bone remodeling was more pronounced in laboratory animals which had been treated with a polyphenol-rich diet (75). Only one study so far suggests a possible influence of olive oil on bone mass ma-

intenance and osteoporosis prevention; its results showed that women on a Mediterranean diet rich in olive oil had better bone density levels than those on a standard diet (76).

Research has shown that high-quality olive oil reduces low-density lipoprotein (LDL) peroxidation to a significantly higher extent than sunflower oil in hypercholesterolemic postmenopausal women (77).

Extra virgin olive oil is the best nutritional supplement for pregnant women, due to its ideally balanced nutritionally valuable fats important for intrauterine fetal development as well as the optimal fatty tissue development during early infancy (78).

In conclusion, the nutritional value of olive oil exceeds its gastronomic effect. One of the most

important components of the Mediterranean diet, olive oil is not just a dietary supplement, but also an important preventive factor in the pathogenesis of numerous degenerative diseases and conditions.

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REFERENCES

1. Writing Group for the Women's Health Initiative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized control trial. *JAMA* 2002; 288:321-33.
2. Faber A, Bouvy ML, Loskamp L, van de Berg PB, Egberts TCG, de Jong-van den Berg LTW. Dramatic change in prescribing of hormone replacement therapy in the Netherlands after publication of the Million Women Study: a follow-up study. *Br J Clin Pharmacol* 2005; 60:641-7.
3. Pines A. Guidelines and recommendations on hormone therapy in the menopause. *J Midlife Health*. 2010; 1:41-2.
4. Albertazzi P. Non-estrogenic approaches for the treatment of climacteric symptoms. *Climacteric* 2007; 10:115-20.
5. Fističić I, Čanić T, Duić Z, Fističić M, Čiglar S. Alternative hormone therapy in postmenopause. *Lijec Vjesn* 2006; 128:99-104.
6. Marrugat J, Covas MI, Fitó M, Schröder H, Miró-Casas E, Gimeno E, López-Sabater MC, de la Torre R, Farré M; SOLOS Investigators. Effects of differing phenolic content in dietary olive oils on lipids and LDL oxidation--a randomized controlled trial. *Eur J Nutr* 2004; 43:140-7.
7. Fitó M, de la Torre R, Farré-Albaladejo M, Kymenets O, Marrugat J, Covas MI. Bioavailability and antioxidant effects of olive oil phenolic compounds in humans: a review. *Ann Ist Super Sanita* 2007; 43:375-81.
8. Vissers MN, P L Zock PL, Katan MB. Bioavailability and antioxidant effects of olive oil phenols in humans: a review. *European Journal of Clinical Nutrition* 2004; 58:955-65.
9. Perrella J, Berco M, Cecutti A, Gerulath A, Bhavnani BR. Potential role of the interaction between equine estrogens, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) in the prevention of coronary heart and neurodegenerative diseases in postmenopausal women. *Lipids Health Dis* 2003; 2:4.
10. Gillingham LG, Harris-Janz S, Jones PJ. Dietary monounsaturated fatty acids are protective against metabolic syndrome and cardiovascular disease risk factors. *Lipids* 2011; 46:209-28.
11. Konstantinidou V, Covas MI, Muñoz-Aguayo D, Kymenets O, de la Torre R, Saez G, Tormos Mdel C, Toledo E, Martí A, Ruiz-Gutiérrez V, Ruiz Mendez MV, Fitó M. In vivo nutrigenomic effects of virgin olive oil polyphenols within the frame of the Mediterranean diet: a randomized controlled trial. *FASEB J* 2010; 24:2546-57.
12. Cicerale S, Lucas L, Keast R. Biological activities of phenolic compounds present in virgin olive oil. *Int J Mol Sci* 2010; 11:458-79.
13. El Riachy M, Priego-Capote F, León L, Rallo L, Luque de Castro MD. Hydrophilic antioxidants of virgin olive oil. Part 1: Hydrophilic phenols: A key factor for virgin olive oil quality. *European Journal of Lipid Science and Technology* 2011; 113:678-91.
14. Gibson TM, Ferrucci LM, Tangrea JA, Schatzkin A. Epidemiological and clinical studies of nutrition. *Semin Oncol* 2010; 37:282-96.
15. Psaltopoulou T, Kosti RI, Haidopoulos D, Dimopoulos M, Panagiotakos DB. Olive oil intake is inversely related to cancer prevalence: a systematic review and a meta-analysis of 13800 patients and 23340 controls in 19 observational studies. *Lipids in Health and Disease* 2011; 10:127.
16. Miro-Casas E, Covas MI, Farré M, Fitó M, Ortuño J, Weinbrenner T, Roset P, de la Torre R. Hydroxytyrosol disposition in humans. *Clin Chem* 2003; 49:945-52.

17. Andreadou I, Iliodromitis EK, Mikros E, Constantinou M, Agalias A, Magiatis P, Skaltsounis AL, Kamber E, Tsantili-Kakoulidou A, Kremastinos DT. The olive constituent oleuropein exhibits anti-ischemic, antioxidative, and hypolipidemic effects in anesthetized rabbits. *J Nutr* 2006; 136:2213-9.
18. Parnham MJ, Verbanac D. Mild plant and dietary immunomodulators. In: Nijkamp FP, Parnham MJ (eds.). *Principles of Immunopharmacology*. 3rd revised and extended edition. Basel: Springer AG 2011: 451-72.
19. Cicerale S, Lucas L, Keast R. Biological activities of phenolic compounds present in virgin olive oil. *Int J Mol Sci* 2010; 11:458-79.
20. Tripoli E, Giammanco M, Tabacchi G, Di Majo D, Ciammanco S, La Guardia M. The phenolic compounds of olive oil: structure, biological activity and beneficial effects on human health. *Nutr Res Rev* 2005; 18: 98-112.
21. Pérez-Martínez P, García-Ríos A, Delgado-Lista J, Pérez-Jiménez F, López-Miranda J. Mediterranean diet rich in olive oil and obesity, metabolic syndrome and diabetes mellitus. *Curr Pharm Des* 2011; 17: 769-77.
22. Cicerale S, Lucas L, Keast R. Antimicrobial, antioxidant and anti-inflammatory phenolic activities in extra virgin olive oil. *Curr Opin Biotechnol* 2011 [Epub ahead of print]
23. Waterman E, Lockwood B. Active components and clinical applications of olive oil. *Altern Med Rev* 2007; 12:331-42.
24. Panagiotakos D, Pitsavos C, Chrysoshoou C, Palliou K, Lentzas I, Skoumas I, Stefanadis C. Dietary patterns and 5-year incidence of cardiovascular disease: a multivariate analysis of the ATTICA study. *Nutr Metab Cardiovasc Dis* 2009; 19:253-63.
25. López-Miranda J, Pérez-Jiménez F, Ros E, De Caterina R, Badimón L, Covas MI, Escribá E, Ordovás JM, Soriguer F, Abiá R, de la Lastra CA, Battino M, Corella D, Chamorro-Quirós J, Delgado-Lista J, Giugliano D, Esposito K, Estruch R, Fernandez-Real JM, Gaforio JJ, La Vecchia C, Lairon D, López-Segura F, Mata P, Menéndez JA, Muriana FJ, Osada J, Panagiotakos DB, Paniagua JA, Pérez-Martínez P, Perona J, Peinado MA, Pineda-Priego M, Poulsen HE, Quiles JL, Ramírez-Tortosa MC, Ruano J, Serra-Majem L, Solá R, Solanas M, Solfrizzi V, de la Torre-Fornell R, Trichopoulou A, Uceda M, Villalba-Montoro JM, Villar-Ortiz JR, Visioli F, Yiannakouris N. Olive oil and health: summary of the II international conference on olive oil and health consensus report, Jaén and Córdoba (Spain) 2008. *Nutr Metab Cardiovasc Dis* 2010; 20:284-94.
26. Bermudez B, Lopez S, Ortega A, Varela LM, Pacheco YM, Abia R, Muriana FJ. Oleic acid in olive oil: from a metabolic framework toward a clinical perspective. *Curr Pharm Des* 2011; 17:831-43.
27. Terés S, Barceló-Coblijn G, Benet M, Alvarez R, Bressani R, Halver JE, Escribá PV. Oleic acid content is responsible for the reduction in blood pressure induced by olive oil. *Proc Natl Acad Sci U S A* 2008; 105:13811-6.
28. Psaltopoulou T, Naska A, Orfanos P, Trichopoulos D, Mountokalakis T, Trichopoulou A. Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. *American Journal of Clinical Nutrition* 2004; 80:1012-18.
29. Ferrara LA, Raimondi AS, d'Episcopo L, Guida L, Dello RA, Marotta T. Olive oil and reduced need for antihypertensive medications. *Arch Intern Med* 2000; 160:837-42.
30. Kontogianni MD, Panagiotakos DB, Chrysoshoou C, Pitsavos C, Zampelas A, Stefanadis C. The impact of olive oil consumption pattern on the risk of acute coronary syndromes: The CARDIO2000 case-control study. *Clin Cardiol* 2007; 30:125-9.
31. Masella R, Vari R, D'Archivio M, Di Benedetto R, Matarrese P, Malorni W, Scazzocchio B, Giovannini C. Extra virgin olive oil biophenols inhibit cell-mediated oxidation of LDL by increasing the mRNA transcription of glutathione-related enzymes. *J Nutr* 2004; 134:785-91.
32. Fitó M, Cladellas M, de la Torre R, Martí J, Alcántara M, Pujadas-Bastardes M, Marrugat J, Bruguera J, López-Sabater MC, Vila J, Covas MI, members of the SOLOS Investigators. Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: a randomized, crossover, controlled, clinical trial. *Atherosclerosis* 2005; 181:149-58.
33. Cicerale, S., Conlan, X. A., Sinclair, A. J., & Keast, R. S. J. Chemistry and health of olive oil phenolics. *Critical Reviews in Food Science and Nutrition* 2009; 49:218-36.
34. Carluccio MA, Massaro M, Scoditti E, De Caterina R. Vasculoprotective potential of olive oil components. *Mol Nutr Food Res* 2007; 51:1225-34.
35. Beauchamp GK, Keast RS, Morel D, Lin J, Pika J, Han Q, Lee CH, Smith AB, Breslin PA. Phytochemistry: ibuprofen-like activity in extra-virgin olive oil. *Nature* 2005; 437:45-6.
36. Assy N, Nassar F, Nasser G, Grosowski M. Olive oil consumption and non-alcoholic fatty liver disease. *World J Gastroenterol* 2009; 15:1809-15.
37. Hansen KB, Rosenkilde MM, Knop FK, Wellner N, Diep TA, Rehfeld JF, Andersen UB, Holst JJ, Hansen HS. 2-Oleoyl glycerol is a GPR119 agonist and signals GLP-1 release in humans. *J Clin Endocrinol Metab* 2011; 96:E1409-17.
38. Schwartz GJ, Fu J, Astarita G, Li X, Gaetani S, Campolongo P, Cuomo V, Piomelli D. The lipid messenger OEA links dietary fat intake to satiety. *Cell Metab* 2008; 8:281-8.
39. Paniagua JA, Gallego de la Sacristana A, Romero I, Vidal-Puig A, Latre JM, Sanchez E, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Monounsaturated Fat-Rich Diet Prevents Central Body Fat Distribution and Decreases Postprandial Adiponectin Expression Induced by a Carbohydrate-Rich Diet in Insulin-Resistant Subjects. *Diabetes Care* 2007; 30:1717-23.
40. Ilavarasi K, Kiruthiga PV, Pandian SK, Devi KP. Hydroxytyrosol, the phenolic compound of olive oil protects human PBMC against oxidative stress and DNA damage mediated by 2,3,7,8-TCDD. *Chemosphere* 2011; 84:888-93.
41. Obied HK, Prenzler PD, Konczak I, Rehman AU, Robards K. Chemistry and bioactivity of olive biophenols in some antioxidant and antiproliferative in vitro bioassays. *Chem Res Toxicol* 2009; 22:227-34.
42. Adler AS, Kawahara TL, Segal E, Chang HY. Reversal of ageing by NFκB blockade. *Cell Cycle* 2008; 7:556-9.

43. Adler AS, Sinha S, Kawahara TL, Zhang JY, Segal E, Chang HY. Motif module map reveals enforcement of ageing by continual NfκB activity. *Genes Dev* 2007; 21:3244-57.
44. Bråkenhielm E, Cao R, Cao Y. Suppression of angiogenesis, tumor growth, and wound healing by resveratrol. *The FASEB Journal* 2001; 15:1798-800.
45. Hashim YZ, Eng M, Gill CI, McGlynn H, Rowland IR. Components of olive oil and chemoprevention of colorectal cancer. *Nutr Rev* 2005; 63:374-86.
46. Romero C, Medina E, Vargas J, Brenes M, De Castro A. In vitro activity of olive oil polyphenols against *Helicobacter pylori*. *J Agric Food Chem* 2007; 55:680-6.
47. Menendez JA, Vazquez-Martin A, Garcia-Villalba R, Carrasco-Pancorbo A, Oliveras-Ferraro C, Fernandez-Gutierrez A, Segura-Carretero A. Anti-HER2 (erbB-2) oncogene effects of phenolic compounds directly isolated from commercial Extra-Virgin Olive Oil (EVOO). *BMC Cancer* 2008; 8:377.
48. Menendez JA, Papadimitropoulou A, Vellon L, Lupu R. A genomic explanation connecting "Mediterranean diet", olive oil and cancer: oleic acid, the main monounsaturated fatty acid of olive oil, induces formation of inhibitory "PEA3 transcription factor-PEA3 DNA binding site" complexes at the Her-2/neu (erbB-2) oncogene promoter in breast, ovarian and stomach cancer cells. *Eur J Cancer* 2006; 42:2425-32.
49. Menendez JA, Vellon L, Colomer R, Lupu R. Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses Her-2/neu (erbB-2) expression and synergistically enhances the growth inhibitory effects of trastuzumab (Herceptin) in breast cancer cells with Her-2/neu oncogene amplification. *Ann Oncol* 2005; 16:359-71.
50. Conner P. Breast response to menopausal hormone therapy-aspects on proliferation, apoptosis and mammographic density. *Ann Med* 2007; 39:28-41.
51. Masala G, Ambrogetti D, Assedi M, Giorgi D, Del Turco MR, Palli D. Dietary and lifestyle determinants of mammographic breast density. A longitudinal study in a Mediterranean population. *International Journal of Cancer* 2006; 118:1782-9.
52. Tzonou A, Lipworth L, Kalandidi A, Trichopoulou A, Gamatsi I, Hsieh CC, Notara V, Trichopoulos D. Dietary factors and the risk of endometrial cancer: a case-control study in Greece. *Br J Cancer* 1996; 73:1284-90.
53. Weinstock-Guttman B, Baier M, Park Y, Feichter J, Lee-Kwen P, Gallagher E, Venkatraman J, Mek-sawan K, Deinehart S, Pendergast D, Awad AB, Ramanathan M, Munschauer F, Rudick R. Low fat dietary intervention with omega-3 fatty acid supplementation in multiple sclerosis patients. *Prostaglandins Leukot Essent Fatty Acids* 2005; 73:397-404.
54. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. *Annals of Neurology* 2006; 59:912-21.
55. Materljan E, Materljan M, Materljan B, Vlačić H, Baričević-Novaković Z, Sepčić J. Multiple sclerosis and cancers in Croatia - a possible protective role of the "Mediterranean diet". *Coll Antropol* 2009; 33:539-45.
56. Valente T, Hidalgo J, Bolea I, Ramirez B, Anglés N, Reguant J, Morelló JR, Gutiérrez C, Boada M, Unze-ta M. A diet enriched in polyphenols and polyunsaturated fatty acids, LMN diet, induces neurogenesis in the subventricular zone and hippocampus of adult mouse brain. *J Alzheimers Dis* 2009; 18:849-65.
57. Niedermeyer E, Ghigo JO. Alzheimer dementia: an overview and a promising new concept. *Am J Electroneurodiagnostic Technol* 2011; 51:82-91.
58. Viola P, Viola M. Virgin olive oil as a fundamental nutritional component and skin protector. *Clin Dermatol* 2009; 27:159-65.
59. Alcaín FJ, Villalba JM. Sirtuin activators. *Expert Opinion on Therapeutic Patents* 2009; 19:403-14.
60. Calleja-Aguis J, Muscat-Baron Y, Brincat MP. Skin ageing. *Menopause Int* 2007; 13:60-4.
61. Schlicker C, Boanca G, Lakshminarasimhan M, Steegborn C. Structure-based development of novel sirtuin inhibitors. *Aging (Albany NY)* 2011; 3:852-72.
62. Lagouge M, Argmann C, Gerhart-Hines Z. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1α. *Cell* 2006; 127:1109-22.
63. Reddy MA, Jain N, Yada D, Kishore C, Vangala JR, P Surendra R, Addlagatta A, Kalivendi SV, Sreedhar B. Design and synthesis of resveratrol-based nitro-vinylstilbenes as antimitotic agents. *J Med Chem* 2011; 54:6751-60.
64. Saha SS, Ghosh M. Antioxidant effect of vegetable oils containing conjugated linolenic acid isomers against induced tissue lipid peroxidation and inflammation in rat model. *Chem Biol Interact* 2011; 190:109-20.
65. Kanda N, Mitsui H, Watanabe S. Prostaglandin E(2) suppresses CCL27 production through EP2 and EP3 receptors in human keratinocytes. *J Allergy Clin Immunol* 2004; 114:1403-9.
66. Verallo-Rowell VM, Dillague KM, Syah-Tjundawan BS. Novel antibacterial and emollient effects of coconut and virgin olive oils in adult atopic dermatitis. *Dermatitis* 2008; 19:308-15.
67. Gerberick F, Vassallo J, Bailey R, Morrall S, Lepoittevin JP. Development of peptide reactivity assay for screening allergens. *Toxicol Sci* 2004; 81:332-43.
68. Lodén M, Andersson AC. Effect of topically applied lipids on surfactant-irritated skin. *Br J Dermatol* 1996; 134:215-20.
69. Docherty JJ, Smith JS, Fu MM, Stoner T, Booth T. Effect of topically applied resveratrol on cutaneous herpes simplex virus infections in hairless mice. *Antiviral Research* 2004; 61:19-26.
70. Docherty JJ, Sweet TJ, Bailey E, Faith SA, Booth T. Resveratrol inhibition of varicella-zoster virus replication in vitro. *Antiviral Research* 2006; 72:171-7.
71. Yoon JH, Baek SJ. Molecular targets of dietary polyphenols with anti-inflammatory properties. *Yonsei Med J* 2005; 46:585-96.
72. Durham PL, Vause CV, Derosier F, McDonald S, Cady R, Martin V. Changes in salivary prostaglandin levels during menstrual migraine with associated dysmenorrhea. *Headache* 2010; 50:844-51.
73. Ciceralo S, Conlan X, Sinclair A, & Keast R. S. J. Chemistry and health of olive oil phenolics. *Critical Reviews in Food Science and Nutrition* 2009; 49:218-36.
74. Kutteh WH, Chao CH, Ritter JO, et al. Vaginal lubricants for the infertile couple: effect on sperm activity. *Int J Fertil Menopausal Stud* 1996; 41:400-4.

75. Santiago-Mora R, Casado-Díaz A, De Castro MD, et al. Oleuropein enhances osteoblastogenesis and inhibits adipogenesis: the effect on differentiation in stem cells derived from bone marrow. *Osteoporos Int* 2011; 22:675-84.
76. Kontogianni MD, Melistas L, Yanakoulia M et al. Association between dietary patterns and indices of bone mass in a sample of Mediterranean women. *Nutrition* 2009; 25:165-71.
77. Rowe S, Alexander N, Almeida NG, et al. Translating the Dietary Guidelines for Americans 2010 to bring about real behaviour change. *J Am Diet Assoc* 2011; 111:28-39.
78. Verbanac D. Nutrition habits in pregnant women and early childhood as a tool for obesity prevention. *Pediatrics Croatica* 2004; 48:41-5.

Biofenoli maslinovog ulja i zdravlje žene

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SAŽETAK

Olea europea, odnosno maslina, je drevno stablo koje je poteklo iz mediteranskog okruženja Male Azije. Plod masline nije samo kulinarSKI dodatak; maslinovo ulje, produkt njena tlačenja, sadrži cijeli niz dobrobiti po zdravlje. Djevičansko maslinovo ulje je prirodni sok masline, tekući je i najvažniji dio zdravstveno potvrđene mediteranske dijeta. Njena pomoć zdravlju izvire iz biofenola i skvalena (oleokantal, tirozol, hidroksitirozol, oleuropein). Oni pružaju izuzetnu protuoksidativnu aktivnost uklanjajući iz organizma štetne spojeve koji narušavaju zdravlje. Oksidansi leže u temeljima mnogih bolesti i stanja - srčanožilnih, malignih, osteoporoze, Alzheimerove bolesti, predmenstrualnog sindroma. Nezasićena oleinska masna kiselina pokazala je značajan učinak u prevenciji zloćudnih bolesti, primjerice raka debelog crijeva i raka dojke, a biofenoli maslinovog ulja uspješno suzbijaju sintezu LDL-a, bjelančevine koja je ključna u nastanku krvnožilnih bolesti, smanjujući krvni tlak i nastanak aterosklerotskog plaka.

Ključne riječi: maslinovo ulje, biofenoli, zdravlje