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 biphenols from olive oil that successfully destroy colonies of microorganisms which may cause respiratory tract, intestinal, and genital tract infections.

Key words: olive oil, biophenols, health
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 alpha-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 alpha-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-
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 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 sattiy.
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 NFκB 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 oleuropaein 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 E2 prostaglandin synthesis (64). Prostaglandin E2 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, TNFα, and IFNγ, 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 cystein 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-zooster 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 (PgE2) (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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Olea europea, or olive, is an ancient tree that originated in the Mediterranean region of Southwest Asia. The olive fruit is not only a culinary addition; olive oil, a product of its pressing, contains a whole range of health benefits. Virgin olive oil, a natural fluid, is the most well-known Mediterranean diet. Its benefits to health derive from biophenols and squalene (oleokantal, tyrosol, hydroxytyrosol, oleuropein). They provide exceptional antioxidant activity by removing harmful compounds that damage health. Oxidant lies at the heart of many diseases and conditions – cardiovascular, malignant, osteoporosis, Alzheimer’s disease, premenstrual syndrome. Unsaturated oleic acid has shown a significant effect in the prevention of harmful diseases, for example, cancer of the white blood and thyroid, and biofenols olive oil effectively reduce the synthesis of LDL, a protein that is key in the development of blood diseases, reducing blood pressure and the formation of atherosclerotic plaques.

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