Journal of Natural Sciences Research www.iiste.org
ISSN 2224-3186 (Paper) ISSN 2225-0921 (Online)
Vol.4, No.19, 2014

Review: Beneficial Health Effects of Olive Leaves Extracts

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Abstract
The olive leaves are well known for many useful pharmacological effects. Olive leaves extracts have anti-microbial, anti-inflammatory, anti-oxidant anti-hypertensive, anti-hypercholestermic, anti-hyperglycemic, anti-thrombotic, diuretic and anti-tumor properties. In this review article, we have showed huge collective medical activities of olive leaves extracts that can be applied for treating variety of health problems.
Keywords: Olive leaves extracts, Polyphenols, Oleuropein, Oleuropeosides, Health benefits.

1. Introduction

The olive leaves have a rich history of medicinal uses (Soni et al., 2006). There are many references citing the medicinal use of the plant (*Olea europaea*) in ancient times. The plant is cultivated widely in the Mediterranean region, Arabian Peninsula, the Indian subcontinent and Asia (Somova et al., 2003).
Effects of olive leaves like the antioxidant, hypoglycemic, antihypertensive, antimicrobial, and anti-atherosclerotic have been reported in various studies (Wang et al., 2008). In this paper, some of these studies on the beneficial health effects of olive leaves are reviewed.

2. Chemical characteristics of olive leaves

The chemical composition of olive leaves vary depending on origin, proportion of branches on the tree, storage conditions, climatic conditions, moisture content, and degree of contamination with soil and oils. In addition, the structural carbohydrates and nitrogen content in olive leaves depends on factors such as the variety of the olive tree, climatic conditions, year of harvest, proportion of wood, etc (Molina-Alcaide et al., 2008; Delgado-Pertinez et al., 2000; Martin-Garcia et al., 2003; Martin-Garcia et al., 2008).

Polyphenols in olive leaves

Olive leaves are important for their secondary metabolites such as the secoiridoid compounds oleacein and oleuropein (Pereira et al., 2007; Sato et al., 2007; Ferreira et al., 2007; Pereira et al., 2006). They are well known for their beneficial effects on metabolism when used as a traditional herbal drug. These properties are attributed to the phenolic compounds of olive leaves.
Olive leaves have the highest antioxidant and scavenging ability among the different parts of the olive tree (e.g. oleuropein content in olive oil ranges between 0.005% and 0.12% while that in olive leaves ranges between 1% and 14%) (Japon-Lujan et al., 2006).
There are five groups of phenolic compounds principally present in olive leaves:
1- Oleuropeosides (oleuropein and verbascoside).
2- Flavones (luteolin-7-glucoside, apigenin-7-glucoside, diosmetin-7-glucoside luteolin, and diosmetin).
3- Flavonols (rutin).
4- Flavan-3-ols (catechin).
5- Substituted phenols (tyrosol, hydroxytyrosol, vanillin, vanillic acid, and caffeic acid).

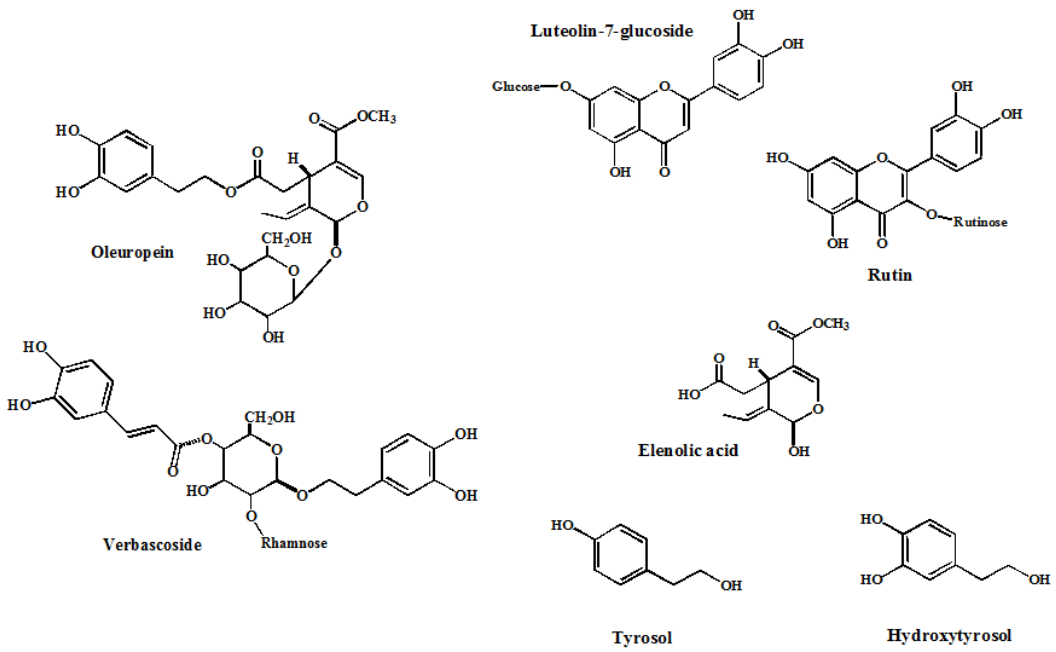

Figure1. Structure of phenolic compounds principally present in olive leaves

The most abundant compound in olive leaves is oleuropein, followed by hydroxytyrosol, the flavone-7-glucosides of luteolin and apigenin, and verbascoside. Hydroxytyrosol is a precursor of oleuropein, and verbascoside is a conjugated glucoside of hydroxytyrosol and caffeic acid.

The total polyphenol content and the total flavonoid content of olive tree leaves were determined to be 2.058 mg GAE (gallic acid equivalent) per 100 g and 858 mg CTE (catechin equivalent) per 100 g, respectively, reflecting values similar to that of red-grape peel (Makris et al., 2007). The bitter compound oleuropein, the predominant secoiridoid in the olive tree, is a potent antioxidant with anti-inflammatory properties.

Oleuropein, is a heterosidic ester of elenolic acid and dihydroxyphenylethanol (Benavente-Garcia et al., 2000). Hydroxytyrosol is the principal degradation product of oleuropein. Oleuropein is present in high amounts in unprocessed olive fruit and leaves, while hydroxytyrosol is more abundant in the processed olive fruit and olive oil. The decrease in the concentration of oleuropein and the increase in the concentration of hydroxytyrosol occur due to chemical and enzymatic reactions that take place during maturation of the fruit or as a result of olive processing (e.g. oil production) (Tan et al., 2003). Several studies have investigated the phenolic composition of olive leaves (Ferreira et al., 2007; Liakopoulos et al., 2006; Hollman et al., 1995; Singh et al., 2008; Dimitrios et al., 2006; Andrikopoulos et al., 2002; Visioli et al., 2008). Analysis of olive-leaf aqueous extracts identified seven phenolic compounds: caffeic acid, verbascoside, oleuropein, luteolin 7-O-glucoside, rutin, apigenin 7-Oglucoside, and luteolin 4′-O-glucoside. Higher amounts of phenolic compounds were found in the aqueous extract of olive leaves than in the hydromethanolic extracts of the same and other olive-leaf cultivars (Makris et al., 2007).

Furthermore, the major compounds in the hydro-methanolic extracts were flavonoids, while the major compound in the aqueous extract was oleuropein, representing ~73% of the total identified compounds. Caffeic acid was found to be a minor compound, corresponding to ~1% of the total phenolic compounds. Phenolic compounds of olive leaves such as rutin, luteolin 7-O-glucoside, luteolin 7-O-rutinoside, luteolin 4-O-glucoside, apigenin 7-Oglucoside, and apigenin 7-O-rutinoside are reported in the literature, but data about their constancy, amounts, or distribution among cultivars are scarce (Liakopoulos et al., 2007).

3. Traditional uses of olive leaves

- Olive leaves used orally for stomach and intestinal diseases.
- Olive leaves chewed as a mouth cleanser.
- Decoctions of the dried fruit and leaves taken orally for diarrhea and to treat urinary tract infections.
- Hot water extract of the fresh leaves taken orally to treat high blood pressure (hypertension) and to induce urination (diuresis).
- Hot water extract of the dried plant taken orally for bronchial asthma.

4. Effects of olive-leaves extracts

Oleuropein, the main constituent of olive leaves extract, protects membrane from lipid oxidation (Somova et al.,

2003; Ferreira et al., 2007), causes dilatation of coronary blood vessels (Singh et al., 2008), shows anti-arrhythmic action (Somova et al., 2003), improves lipid metabolism (Molina-Alcaide et al., 2008), protects enzymes from oxidative damage (Somova et al., 2003; Pereira et al., 2007; Sato et al., 2007; Ferreira et al., 2007), prevents hypertensive cell death in cancer patients (Somova et al., 2003), and demonstrates antiviral properties (Soni et al., 2006; Pereira et al., 2007). Hydroxytyrosol, an oleuropein derivative, improves cardiac diseases and tumor diseases with effects similar to those of oleuropein (Somova et al., 2003). In addition, hydroxytyrosol protects against atherosclerosis and prevents diabetic neuropathy (Sato et al., 2007).

4.1 Antioxidant activity of olive leaves Phenolic compounds

Reactive oxygen and nitrogen species are essential in normal physiological mechanisms of energy supply, detoxification, chemical signaling, and immune function. They are continuously produced in the human body and are controlled by endogenous enzymes such as superoxide dismutase, glutathione peroxidase, and catalase. When there is an overproduction of these reactive species, due to exposure to external oxidant substances, or a failure in the defense mechanisms, damage to valuable bio-molecules (DNA, lipids and proteins) may occur. This damage has been associated with an increased risk of cardiovascular disease, cancer, and other chronic diseases.

Intake of antioxidants from the diet will reduce the risks of chronic diseases (Dimitrios et al., 2006). The protective effects of diets rich in fruit and vegetables against cardiovascular diseases and certain cancers have been attributed partly to antioxidants (Benavente-Garcia et al., 2000). The potential importance of antioxidant plant phenols has prompted the efforts in the efforts of researchers to:

1) Increase the content of phenolic compounds in plants.

2) Produce less hydrophilic derivatives by enzyme modification of their structure with improved Phytotheraputic characteristics.

Oleuropein has been shown to be a potent antioxidant with anti-inflammatory properties. Prevention of free radical formation by oleuropein may be due to its ability to chelate metal ions, such as Cu and Fe, which catalyze free radical generation reactions (Andrikopoulos et al., 2002), as well as its ability to inhibit several inflammatory enzymes, such as lipoxygenases, without affecting the cyclo-oxygenase pathway (Visioli et al., 2002).

Both oleuropein and hydroxytyrosol have been shown to be scavengers of superoxide anion as well as inhibitors of the respiratory burst of neutrophils and hypochlorous acid-derived radicals (Chimi et al., 1991). Both compounds also scavenged hydroxyl radicals, with oleuropein showing greater activity (De la Puerta et al., 1999). Hydroxytyrosol and oleuropein were also reported to be effective scavengers of the 1,1- diphenyl-2-picrylhydrazyl (DPPH) radical (Gordon et al., 2001).

The antioxidant activity of oleuropein was studied using in vivo methods. One of the studies investigated the effect of oleuropein obtained from olive leaves on oxidative stress and enzymatic and nonenzymatic antioxidants in alloxan-induced diabetic rabbits (Al-Azzawie et al., 2006). Enrichment of refined olive with olive leaves resulted in an appreciable resistance to oxidative deterioration due to the phenolic antioxidant content of the leaves and extract (Bouaziz et al., 2008).

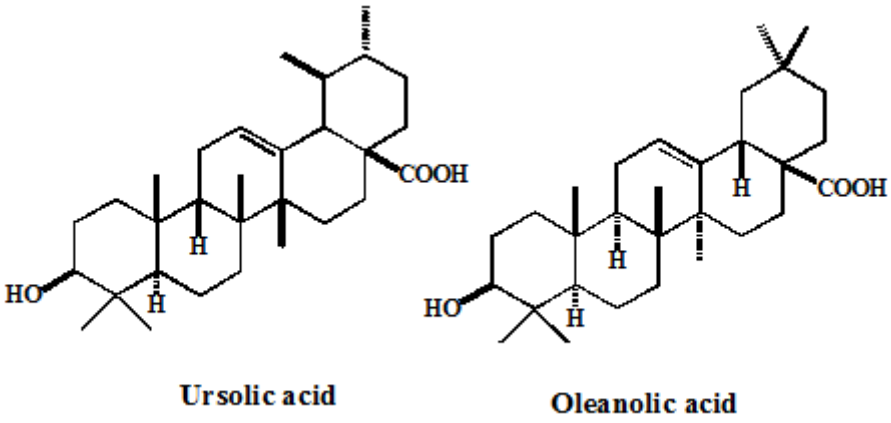

Figure 2. Structure of pentacyclic triterpenoid acids in olive leaves

4.2 Anti-atherosclerotic effect of olive leaves

The phenolic compounds of olive leaves and olive oils in the Mediterranean diet have been associated with a reduced incidence of heart disease. Accordingly, these antioxidant-rich diets might prevent the deleterious effects of oxidative metabolism by scavenging free radicals, thus inhibiting oxidation and delaying atherosclerosis. The process may involve phospholipase C activation and arachidonic acid metabolism, and is thought to reduce hydrogen peroxide (Dimitrios et al., 2006). The cardiovascular effects of olive-leaf extracts

have been well studied and attributed to the main components of the European cultivar leaves, oleuropein and oleacein (Lasserre et al., 1983).

The secoiridoid derivatives (oleuropeoside) in olive leaves are responsible for the vaso-dilating and relaxing properties of their extracts (Kimura et al., 2012).

The antihypertensive, diuretic, anti-atherosclerotic, antioxidant, and hypoglycemic effects of oleanolic acid, ursolic acid, and samples of extracts of olive leaves obtained from African olive leaves (AO), Greek olive leaves (GO), and Cape Town (CT) species were investigated by using a Dahl salt-sensitive (DSS), insulin-resistant rat genetic model of hypertension (Somova et al., 2003). DSS untreated rats developed hypertension spontaneously with significantly increased heart rate. The insulin resistant rats displayed significantly increased blood glucose by 26% and were prone to develop early atherosclerosis with significantly increased total cholesterol by 108%, along with a more than fourfold increase in low density lipoprotein (LDL) cholesterol and triglycerides. All of the samples showed a potent hypoglycemic, anti-hyperlipidemic (anti-atherosclerotic), and antioxidant activity. It was emphasized that GO and CT with a high level of pure oleanolic acid (2.47%) displayed the best antihypertensive, diuretic/natriuretic, anti-hyperlipidemic, hypoglycemic, and antioxidant activities. Polyphenols were found in olive leaves were capable of in vitro platelet activation in healthy, nonsmoking males (Singh et al., 2008).

4.3 Cardioprotective effects of olive-leaves polyphenols

Oleuropein, which was found to be completely nontoxic in several animal species, has antitumor activity (Hamdi et al., 2008). Doxorubicin (DXR), an anthracycline antibiotic clinically known as adriamycin, is an anti-neoplastic drug that is highly effective against many malignant diseases. It was reported that the clinical use of DXR is often limited because of its undesirable serious cardiotoxic side effects, which frequently lead to congestive heart failure (Hamdi et al., 2008).

The effect of oleuropein on cardiotoxicity induced by acute DXR treatment in rats has been investigated. It was found that all groups treated with oleuropein had very low cytoplasmic vacuolization in cardiomyocytes compared to the DXR group, indicating that oleuropein protects against DXR-induced cardiotoxicity. Oleuropein successfully attenuated DXR-induced cardiotoxicity by inhibiting lipid peroxidation products, by decreasing oxidative stress, and by reducing nitric oxide species in cardiomyocytes. For this reason, acute DXR cardiotoxicity might be successfully treated with oleuropein (Andreadou et al., 2008).

4.4 Anti-inflammatory activity

Oleuropein and hydroxytyrosol, inhibit leukotriene B4 generation involved in a wide range of pro-inflammatory pathways as well as eicosanoid production (Visioli et al., 2008). Luteolin is also a key component, which showed anti-inflammatory activity in animal models and anti allergic effects in test-tube studies. Apigenin, also in the leaf, inhibits the inflammatory mediator's nitric oxide and prostaglandin E2 (De la Puerta et al., 1999).

4.5 Antimicrobial activity

Both Oleuropein and hydroxytyrosol showed antimicrobial (*Bacillus subtilis, B. cereus, Staphylococcus aureus, Salmonella typhi, Vibrio cholerae, V. parahemolyticus and Micrococcus sp.),* anti-protozoal and antiviral activity. Oleuropein acts through elenolic acid, a hydrolysis products (Sudjana et al., 1999).

The olive leaf extract is proved to have anti-fungal properties. It is especially useful in cases of candida overgrowth, also known as a yeast infection. This fungal excess may cause a variety of symptoms, including digestive upset, fatigue, and respiratory concerns.

4.6 Hypoglycemic effect of olive leaves

Olive-tree leaves are well known as a traditional anti-diabetic and antihypertensive herbal drug (Pereira et al., 2006). Olive leaves have also been used as a medical herb to treat diabetic hyperglycemia, hypertension, and infectious diseases. They are especially widely recognized as a traditional remedy for diabetes and hypertension in Europe (Komaki et al., 2008).

Mechanisms suggested for explaining the hypoglycemic effect of oleuropein in diabetes (Al-Azzawie et al., 2006):

1) Glucose-induced insulin release.
2) Increase peripheral uptake of glucose.

In addition, part of the effect of oleuropein on diabetes and its complications derives from its antioxidant activity.

Blood glucose levels were significantly decreased in oleuropein-treated diabetic rabbits compared with diabetic control rabbits, who continued to exhibit elevated glucose levels throughout the study period (Al-Azzawie et al., 2006).

The results demonstrated that oleuropein may be beneficial in inhibiting hyperglycemia and oxidative stress induced by diabetes, and they suggest that administration of oleuropein may be helpful in the prevention of diabetic complications associated with oxidative stress.

It is also reported that oleuropein in olive leaves accelerated the uptake of glucose by the cell (Gonzalez et al., 1992). Oleuropein is an agonist for TGR5, a G-protein coupled receptor that is activated by bile

acids and that mediates some of their various cellular and physiological effects. The anti-hyperglycemic activity of a TGR5 agonist isolated from olive-tree leaves was proved (Pereira et al., 2006). TGR5 was identified as the first cell-surface receptor activated by bile acids, and this receptor is reported to mediate some of the endocrine functions of bile acids.

Bile acids are emerging as important metabolic signaling molecules (Sato et al., 2007). They have been shown to increase energy expenditure in part through activation of mitochondrial function, hence preventing the development of obesity and insulin resistance in mice fed a high-fat diet (Sato et al., 2007). TGR5 slows the weight increase induced by high levels of fat and has potent anti-hyperglycemic activity, which may contribute to the anti-diabetic effect of olive leaves.

Oleanolic acid was reported to lower serum glucose and insulin levels in mice fed a high-fat diet, and it enhanced glucose tolerance (Sato et al., 2007). The findings of their study suggest that both oleuropein and oleanolic acid are involved in the anti-diabetic effect of olive leaves and further emphasize the potential role of TGR5 agonists in improving metabolic disorders.

4.7 Rheumatoid Arthritis

Oleuropein has been found to help prevent and treat symptoms of rheumatoid arthritis. When administered at the earliest sign of arthritis in animal models, oleuropein prevented symptoms from developing and also produced marked improvement in the microscopic appearance of joint tissue from affected animals. When administered after arthritis was fully developed, there was significant improvement in inflammatory changes to joints, compared with untreated animals (Gonzalez et al., 1992).

Oleuropein had similar benefits on osteoarthritis. In animal models of this degenerative joint disease, olive leaf extract improved joint swelling, improved the microscopic appearance of joint tissue, and prevented the production of inflammatory cytokines (Impellizzeri et al., 2011).

4.8 Osteoporosis

The plant is useful in both stimulation of osteoblasts,the cells involved in bone growth as well as in inhibition of osteoclasts, the cells involved in bone removal. These studies are grund-breaking and may lead to additional studies in the near future (Gong et al., 2012).

Oleuropein and hydroxytyrosol at 10 to 100μM had no effect on the production of type I collagen and the activity of alkaline phosphatase in MC3T3-E1 cells, but stimulated the deposition of calcium in a dose-dependent manner. In contrast, oleuropein at 10 to 100μM and hydroxytyrosol at 50 to 100μM inhibited the formation of multinucleated osteoclasts in a dose-dependent manner. Furthermore, both compounds suppressed the bone loss of trabecular bone in femurs of ovary-ectomized mice (6-week-old BALB/c female mice), while hydroxytyrosol attenuated H_2O_2 levels in MC3T3-E1 cells. olive polyphenols oleuropein and hydroxytyrosol may have critical effects on the formation and maintenance of bone, and can be used as effective remedies in the treatment of osteoporosis symptoms (Hagiwara et al., 2011).

4.9 Immune system effect

Most of the flavonoids in olive leaf extract have anti-microbial activity (Ilias et al., 2011).

4.10 Chronic Fatigue

Chronic fatigue syndrome **(CFS**) is associated with immune dysfunction, which allows infections with a variety of opportunistic microbes from herpes-viruses, retro viruses, fungi and parasites. In the U.S.A the use of olive leaf extract has become very popular with doctors, naturopaths and the general public where it is being prescribed for the symptoms of **(CFS)** (Michele et al., 2002).

4.11 Skin & Topical uses

Olive leaf extracts are rich in antioxidants and skin softening properties. Olive leaf helps skin with the presence of flavonoids and oleanolic acid, which stimulate the components of the connective tissue and regularize the tissue - thereby boosting the health of the skin protecting it from aging.

4.12 Warts

Most common warts show up on knees, hands, feet, and elbows. However, there are also some types that establish a colony on mouth, nail beds and even the genital area. Since warts are caused by viruses, particularly the human papiloma virus, olive leaf is an effective agent in this type of skin diseases (Fredrickson et al., 2000).

4.13 Cancer

Olive leaves extract and oleuropein significantly inhibited increases in skin thickness and reductions in skin elasticity, and skin carcinogenesis and tumor growth (Kimura et al., 2012).

Dried olive leaf extract (DOLE) significantly inhibited proliferation and subsequently restricted clonogenicity of the B16 mouse melanoma cell line in vitro. Moreover, late phase tumor treatment with dried olive leaf extract significantly reduced tumor volume in a syngeneic strain of mice. dried olive leaf extract-treated B16 cells were blocked in the G(0) /G(1) phase of the cell cycle, underwent early apoptosis and died by late necrosis. At the molecular level, the dying process started as caspase dependent, but finalized as caspase independent. In concordance, over expression of anti-apoptotic members of the Bcl-2 family, Bcl-2 and Bcl-XL, and diminished

expression of their natural antagonists, Bim and p53, were observed. Despite molecular suppression of the proapoptotic process, dried olive leaf extract successfully promoted cell death mainly through disruption of cell membrane integrity and late caspase-independent fragmentation of genetic material. Taken together, the results of this study indicate that dried olive leaf extract possesses strong anti-melanoma potential. When dried olive leaf extract was applied in combination with different chemotherapeutics, various outcomes, including synergy and antagonism, were observed. This requires caution in the use of the extract as a supplementary antitumor therapeutic (Mijatovic et al., 2011).

Olive leaves extract is effective in reducing IL-1β and TNF-α levels after chemotherapy and exert a therapeutic effect and prevent development of severe oral mucositis (Khadija Muhamed, 2011).

4.14 Antithrombotic effect

Oral pre-treatment of rabbits with 100 mg or 200 mg/kg OLE for 8 weeks had no effect on Activated Partial Thromboplastin Time (APTT). However, the same doses produced a significant prolongation of PT (extrinsic coagulation pathway). The prolongation of PT was more prominent with the higher dose of 200 mg/kg than the smaller dose ($p<0.01$). This antithrombic activity of OLE might be due to modification of the extrinsic but not the intrinsic coagulation system (Abdallah et al., 2011).

4.15 Neurodegenerative diseases

Olive extracts protect central nervous system from the destruction brought on by age-related degenerative conditions such as Alzheimer's and Parkinson's diseases. They suppress inflammation and reduce the damage done by oxidative stress (Mohagheghi et al., 2011).

5. Dosage and Administration

Olive leaf tea may be made by soaking about 2 teaspoons of dried olive leaf in 5 or 6 ounces of boiling water for 30 minutes. After the solid parts are strained out, olive leaf tea may be taken up to four times a day.

6. Potential side effects and drug interactions

6.1 Jarisch-Herxheimer or Herxheimers reaction

It is an immune response to the release of toxins from pathogens which have been destroyed, in this case by the olive leaf extract. The reaction proceeds as follows: Olive leaf compounds attack and damage the cells cause release of toxins, break down and are absorbed by surrounding tissues, which were already displaying symptoms caused by the infection of the pathogens. This increase in the concentration of toxins worsens the original symptoms and elicits a further immune response from the body causing histamine release, swelling and pain the body ramps up its detoxification and cleansing processes which may result in other undesirable symptoms. As the overload of dead organisms is reduced and removed from the body, healing and a surge of energy and feeling of Health improvement follows drinking 4-6 glasses of purified water daily helps the body eliminate these toxins more quickly. The tissue surfaces where most discomfort may be felt are the mucous membranes of the mouth, esophagus, stomach, intestines, sexual and urinary organs, ears, lungs and membranes surrounding the brain and synovial linings of the joints. These can give rise to the following olive leaf side effects: dull headaches, muscle and joint pain, feverishness and sweating, nausea, sore throat and nasal passages, vaginal irritation especially in the case of yeast/fungal infections. Olive leaf side effects may also include dizziness in people who have low blood-pressure, by lowering it further.

6.2 Stomach irritation

This can be caused in some people by very strong olive leaves extracts or tinctures. Olive leaves extracts can be taken with food to minimize irritation

6.3 Diarrhea

This may be caused by stomach irritation described above but the cases involved people with candida overgrowth in the gut. When it turns parasitic, candida albicans forms filaments which embed themselves in the gut lining in place of the beneficial probiotic bacteria. When olive leaf extract damages these filaments, a Herxheimer reaction may occur as described above causing a loose stool.

6.4 Acid reflux/Heartburn

This is experienced after taking olive leaf tinctures (Jacob et. al. 2010). It appears to happen mostly to acid reflux sufferers after taking peppermint-flavored glycerine tinctures, although it has occasionally been reported. As peppermint relaxes smooth muscle, it can relax the lower esophageal or cardiac sphincter (valve) entering the stomach, already loose in an acid reflux sufferer, causing reflux and heartburn. It can sometimes be overcomed by taking an unflavored tincture, or by diluting it in tea or water.

7. Safety and Toxicity of olive leaves extracts

Olive leaves are safe, non-toxic and well-tolerated by the majority of the population. No adverse reactions or toxicity reports have been documented, and no drug interactions are yet known. Olive leaf may stimulate the

thyroid, so if you suffer from hyperthyroid conditions or goiter you should use olive leaf with care. Olive leaf decreases blood sugar and may interact with diabetic medications.

8. Interactions

a. Due to its ability to lower blood pressure, olive leaf increases the effects of drugs that lower blood pressure. Some of the blood pressure-lowering drugs:
- ACE inhibitors (Captopril, Enalapril, Lisinopril, and Monopril)
- Beta blockers (Atenolol, Metoprolol, and Propranolol)
- Calcium channel blockers (Nifedipine, Norvasc, and Verapamil)
- Diuretics (Dyazide, Furosemide, and Hydrochlorothiazide)

b. Due to a possible decrease in blood sugar levels, taking olive leaf may increase the effects of insulin and oral drugs for diabetes, such as: Actos, Amaryl, Avandia, glipizide, glyburide, Glynase, Glyset, metformin (Glucophage), Prandin and Precose**.** Because olive leaf may decrease blood sugar levels, taking it with other blood sugar-lowering herbal products may result in hypoglycemia. Eleuthero, Fenugreek, Ginger (in high amounts) & Kudzu.

c. Olive leaf extract may increase the effect of blood thinners such as Warfarin as it tends to prevent blood platelets from sticking together.

9. Conclusion

olive leaves extracts can be applied safely for treating variety of health problems like microbial infections, inflammatory diseases, oxidative stress, hypertension, hypercholestermeae, type II diabetes, thrombosis, enuresis and cancer.

Conflict of interest

No declarations of interests.

References

Abdallah M. Dub and Aisha M. Dugani (2013). Antithrombotic effect of repeated doses of the ethanolic extract of local olive (*Olea europaea* L.) leaves in rabbits. *Libyan J Med* 8:10

Al-Azzawie HF, Alhamdani MS. (2006). Hypoglycemic and antioxidant effect of oleuropein in alloxan-diabetic rabbits. *Life Sci* 78:1371–1377.

Andreadou I, Sigala F, Iliodromitis EK, et al. (2007). Acute doxorubicin cardiotoxicity is successfully treated with the phytochemical oleuropein through suppression of oxidative and nitrosative stress. *J Mol Cell Cardiol* 42:549–558.

Andrikopoulos NK, Kaliora AC, Assimopoulou AN, Papageorgiou VP. (2002). Inhibitory activity of minor polyphenolic and nonpolyphenolic constituents of olive oil against in vitro low-density lipoprotein oxidation. *J Med Food* 5:1–7.

Benavente-Garcia J, Castillo J, Lorente A, Ortuno A, Del Rio JA. (2000). Antioxidant activity of phenolics extracted from *Olea europaea* L. leaves. *Food Chem* 68:457–462.

Jacob Teitelbaum, Chrystle Fiedle. (2010). Natural remedies to treat yeast overgrowth. Beat Sugar Addiction Now P. 98

Bouaziz M, Fki I, Jemai H, Ayadi M, Sayadi S. (2008) Effect of storage on refined and husk olive oils composition: Stabilization by addition of natural antioxidants from Chemlali olive leaves. *Food Chem* 108:253–262.

Chimi H, Cillard J, Cillard P, Rahmani M. (1991). Peroxyl and hydroxyl radical scavenging activity of some natural phenolic antioxidants. *J Am Oil Chem Soc* 68:307–312.

De la Puerta R, Ruiz Gutierrez V, Hoult JR. (1999). Inhibition of leukocyte 5-lipoxygenase by phenolics from virgin olive oil. *Biochem Pharmacol* 57:445–449.

Delgado-Pertinez M, Gomez-Cabrera A, Garrido A. (2000). Predicting the nutritive value of the olive leaf (*Olea europaea*): digestibility and chemical composition and in vitro studies. *Anim Feed Sci Technol*. 87:187–201.

Dimitrios B. Sources of natural phenolic antioxidants. (2006). Trends Food Sci Technol 17:505–512.

Ferreira ICFR, Barros L, Soares ME, Bastos ML, Pereira JA. (2007). Antioxidant activity and phenolic contents of *Olea europaea* L. leaves sprayed with different copper formulations. *Food Chem.* 103:188–195.

Fredrickson, WR, F and S Group, Inc. (2000). Method and Composition for Antiviral Therapy with Olive Leaves. U.S. Patent 6: 117:884.

Gordon MH, Paiva-Martins F, Almeida M. (2001). Antioxidant activity of hydroxytyrosol acetate compared with that of other olive oil polyphenols. *J Agric Food Chem* 49:2480–2485.

Gong D, Geng C, Jiang L, Wang L, Yoshimura H, Zhong L. (2012). Mechanisms of olive leaf extract-

ameliorated rat arthritis caused by kaolin and carrageenan. *Phytother Res* 26(3):397-402.

Gonzalez M, Zarzuelo A, Ganez M, Utrilla MP, Jimenez J, Osuna I. (1992). Hypoglycemic activity of olive leaf. *Planta Med* 58:513–515.

Hagiwara K, Goto T, Araki M, Miyazaki H, Hagiwara H. (2011). Olive polyphenol hydroxytyrosol prevents bone loss. *Eur J Pharmacol* 662(1-3):78-84.

Hamdi HK, Castellon R. (2005). Oleuropein, a non-toxic olive iridoid, is an antitumor agent and cytoskeleton disruptor. *Biochem Biophys Res Commun* 334:769–778.

Hollman PC, de Vries JH, van Leeuwen SD, Mengelers MJ, Katan MB. (1995). Absorption of dietary guercetin glycosides and quercetin in healthy ileostomy volunteers. *Am J Clin Nutr* 62:1276–1282.

http://www.about-olive-leaf-extract.com/olive-leaf-side-effects.html

http://www.perfectpotion.com.au/news/glossary/olea-europaea-olive-leaf-extract

Impellizzeri D, Esposito E, Mazzon E, et al. (2011). Oleuropein aglycone, an olive oil compound, ameliorates development of arthritis caused by injection of collagen type II in mice. *J Pharmacol Exp Ther* 339(3):859-69.

Ilias Faiza, Kholkhal Wahiba, Gaouar Nassira, Bekhechi Chahrazed, Bekkara Fawzia Atik. (2011) Antibacterial and antifungal Activities of olive (*Olea europaea L.*) from Algeria. *J. Microbiol. Biotech Res* 1 (2): 69-73

Japon-Lujan R, Luque-Rodriguez JM, Luque de Castro MD. (2006). Dynamic ultrasound assisted extraction of oleuropein and related polyphenols from olive leaves. J Chromatogr A.1108:76–82.

Khadija Muhamed Ahmed. (2013). The effect of olive leaf extract in decreasing the expression of two pro-inflammatory cytokines in patients receiving chemotherapy for cancer. A randomized clinical trial. *The Saudi Dental Journal* 25(4): 141–147

Kimura Y, Sumiyoshi M. (2009). Olive leaf extract and its main component oleuropein prevent chronic ultraviolet B radiation-induced skin damage and carcinogenesis in hairless mice. J Nutr 139(11):2079-86.

Komaki E, Yamaguchi S, Maru I, et al. (2003). Identification of anti-aamylase components from olive leaf extracts. *Food Sci Technol Res* 9:35–39.

Lasserre B, Kaiser R, Chanh. (1983). PH. Effects on rats of aqueous extracts of plants used in folk medicine as antihypertensive agents. *Naturwissenschaften* 70:95–96.

Liakopoulos G, Stavrianakou S, Karabourniotis G. (2006). Trichome layers versus dehaired lamina of *Olea europaea* leaves: differ-ences in flavonoid distribution, UV-absorbing capacity, and wax yield. *Environ Exp Bot* 55:294–304.

Makris D, Boskoub G, Andrikopoulos NK. (2007). Polyphenolic content and in vitro antioxidant characteristics of wine industry and other agri-food solid waste extracts. *J Food Compost Anal* 20:125–132.

Martin-Garcia AI, Moumen A, Yez Ruiz DR, Molina-Alcaide E. (2003). Chemical composition and nutrients availability for goats and sheep of two-stage olive cake and olive leaves. *Anim Feed Sci Technol.* 107:61–74.

Martin-Garcia AI, Molina-Alcaide E (2008). Effect of different drying procedures on the nutritive value of olive (*Olea europaea* var. *europaea*) leaves for ruminants. *Anim Feed Sci Technol.* 142:317–329.

Mohagheghi F, Bigdeli MR, Rasoulian B, Hashemi P, Pour MR. (2011) The neuroprotective effect of olive leaf extract is related to improved blood-brain barrier permeability and brain edema in rat with experimental focal cerebral ischemia. *Phytomedicine* 15;18(2-3):170-5.

Molina-Alcaide E, Yáñez-Ruiz D. R. (2008). Potential use of olive by-products in ruminant feeding: A review. *Animal Feed Science and Technology* 147:247-264

Michele Hansen, Andrew Verity. (2002). *Olive Leaf Extract Potent Antibacterial, Antiviral and Antifungal Agent.* P.13 Australia: Goldgolf Pty. Ltd.

Mijatovic SA, Timotijevic GS, Miljkovic DM, Radovic JM, Maksimovic-Ivanic DD, Dekanski DP, Stosic-Grujicic SD. (2011). Multiple antimelanoma potential of dry olive leaf extract. Int J Cancer 128(8):1955-65.

Pereira JA, Pereira APG, Ferreira ICFR. (2006). Table olives from Portugal: phenolic compounds, antioxidant potential and antimicrobial activity. *J Agric Food Chem* 54:8425– 8431.

Pereira AP, Ferreira ICFR, Marcelino F et al. (2007). Phenolic compounds and antimicrobial activity of olive (*Olea europaea* L. Cv. Cobrançosa) leaves. *Molecules* 12:1153–1162.

Sato H, Genet C, Strehle A, et al. (2007). Anti-hyperglycemic activity of a TGR5 agonist isolated from *Olea europaea*. *Biochem Biophys Res Commun* 362:793 – 798.

Singh I, Mok M, Christensen AM, Turner AH, Hawley JA. (2008). The effects of polyphenols in olive leaves on platelet function. *Nutr Metab Cardiovasc Dis* 18:127–132.

Soni MG., Burdock GA., Christian MS, Bitler CM, Crea R. (2006). Safety assessment of aqueous olive pulp extract as an antioxidant or antimicrobial agent in foods. *Food Chem Toxicol* 44:903–915.

Somova LI, Shode FO, Ramnanan P, Nadar A. (2003). Antihypertensive, antiatherosclerotic and antioxidant activity of triterpenoids isolated from *Olea europaea*, subspecies *Africana* leaves. *J Ethnopharmacol* 84:299–305.

Sudjana AN, D'Orazio C, Ryan V, Rasool N, Ng J, Islam N, Riley TV, Hammer KA. (2009). Antimicrobial activity of commercial *Olea europaea* (olive) leaf extract. *Int J Antimicrob Agents* 33: 461–463.

Tan HW, Tuck KL, Stupans I, Hayball PJ. (2003). Simultaneous determination of oleuropein and hydroxytyrosol in rat plasma using liquid chromatography with fluorescence detection. *J Chromatogr* 785:187–191.

Visioli F, Poli A, Galli C. (2002). Antioxidant and other biological activities of phenols from olives and olive oil. *Med Res Rev* 22:65–75.

Wang L, Geng C, Jiang L, Gong D, Liu D, Yoshimura H, Zhong L. (2008). The anti-atherosclerotic effect of olive leaf extract is related to suppressed inflammatory response in rabbits with experimental atherosclerosis. Eur J Nutr. 47(5):235-43.