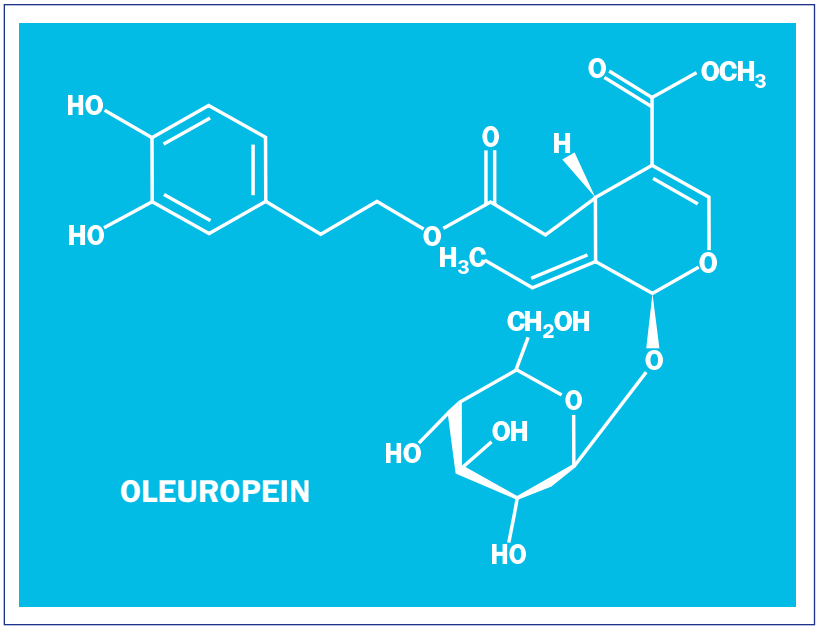
Monograph

Olive Leaf



Introduction

Olive leaf from *Olea europaea*, the olive tree, is native to the Mediterranean and has been known for its medicinal properties since ancient times. It is the first botanical noted in the Bible, where it is described in Ezekiel 47:12, "The fruit thereof shall be for meat, and the leaf thereof for medicine." Ancient Egyptians used it in the process of mummifying royalty, and other cultures including the Greeks employed it as a folk remedy for fever. The leaves of *Olea europaea* are narrow and elongated, dusty-green on top and silvery-white underneath.[1]

The first mention of olive leaf's medicinal use in modern times was in 1843 when Daniel Hanbury of England reported a bitter substance from olive leaf tea was the agent responsible for healing malaria and associated fevers. These findings were reported in 1854 in the *Pharmaceutical Journal*, along with dosing instructions and a recipe for making the curative tea.[2] In 1898, a strong decoction of olive leaves was cited in *King's American Dispensatory* as helpful in regulating body temperature.[3] In the last century, extracts of olive leaf have been studied in both animals and humans and have been found to exhibit strong antimicrobial properties against viruses, bacteria, yeast, and parasites. Olive leaf extract also has numerous cardiovascular benefits, some hypoglycemic activity, and possesses antioxidant activity.

Active Constituents

The primary olive leaf constituents are secoiridoids (oleuropein and its derivatives), hydroxytyrosol,[4] polyphenols (verbascoside, apigenin-7-glucoside, and luteolin-7-glucoside),[5] triterpenes including oleanolic acid,[6] and flavonoids (rutin and diosmin).[7] These constituents afford the tree and its fruits and leaves resistance to damage from pathogens and insects.[8] The primary constituent, oleuropein, first isolated in 1908, is believed to be responsible for many of the therapeutic properties of olive leaf extracts.[9] Although oleuropein is present in the olive fruit and oil, content in the leaf is significantly higher than in other parts of the tree.

Mechanisms of Action

Hypotensive/Vasodilatory

The hypotensive property of olive leaf extract (OLE) was first reported in 1951[10] and confirmed by Italian researchers a decade later.[11] These results spurred numerous *in vitro* and animal studies on its hypotensive properties. In 1991 researchers at the University of Grenada's School of Pharmacy demonstrated that oleuropein exhibited the vasodilatory properties likely responsible for OLE's reported hypotensive action.[12] More recently, two studies demonstrate olive leaf extract suppresses the L-type calcium channel both directly and indirectly, resulting in vasodilation.[13,14]

Antimicrobial

In 1969 researchers demonstrated olive leaf constituents are powerful *in vitro* inhibitors of numerous viruses, including parainfluenza, herpes, pseudorabies, and some forms of polio. Nearly every virus studied, including several cold and influenza viruses, was inactivated when exposed to a constituent of OLE, calcium elenolate.[15] More recently, olive leaf extract was shown to be effective against human immunodeficiency virus (HIV), inhibiting its replication via neutralization of reverse transcriptase and protease.[15,16] Olive leaf also prevents viral infectivity by inhibiting assembly at the cell membrane, interfering with critical amino acid production, and stopping viral shedding.[15,17]

Olive leaf extract also inhibits many gram-negative and -positive bacteria, yeast, and parasites, including the malaria-causing *Plasmodium falciparum*.[18,19] Its antibacterial activity is thought to be via either inactivation of cellular enzymes crucial for bacterial replication or direct attack on the cell membrane resulting in leakage of intracellular components, such as glutamate, potassium, and phosphorus.[20]

Antioxidant/Anti-inflammatory

In 2007, researchers in Australia studying the antioxidant capacity of 55 medicinal herbs found olive leaf extract had the highest radical-scavenging activity of all herbs studied – more than twice that of *Camellia sinensis* (green tea) and *Silybum marianum* (milk thistle).[21] Oleuropein has been shown to decrease the oxidation of low-density lipoprotein (LDL), both *in vitro* and in rabbits.[22,23] Olive leaf extract also possesses anti-inflammatory properties (likely attributable to anti-complement activity) and inhibition of platelet aggregation and thromboxane A_2 production.[24,25]

Hypoglycemic

The University of Grenada researchers who demonstrated olive leaf's vasodilatory properties also report it has a beneficial effect on blood sugar levels in animals. In rats with alloxan-induced diabetes, doses of 16 and 32 mg/kg decreased blood glucose values significantly and increased peripheral glucose uptake in a dose-dependent manner.[26] Its luteolin and oleanolic acid constituents have also been shown to have an inhibitory effect on postprandial glucose increase in diabetic rats.[27]

Clinical Indications

Cardiovascular Disease

Olive leaf extract has a beneficial effect on several aspects of cardiovascular disease via its vasodilatory, anti-platelet aggregation, anti-inflammatory, and antioxidant properties.

Animal studies demonstrate OLE given to hypertensive rats at dosages ranging from 100-1,000 mg/kg for 2-6 weeks significantly lowered mean arterial pressure and heart rate.[28,29] Another animal study showed OLE given to salt-sensitive, genetically hypertensive rats at 60 mg/kg body weight for six weeks prevented the development of severe hypertension and atherosclerosis and improved insulin resistance.[30]

The anti-atherosclerotic effect of olive leaf extract was also demonstrated in rabbits on a high-lipid diet. Twenty-four rabbits were assigned to control, high-lipid diet, or high-lipid diet supplemented with hydroxytyrosol-enriched OLE for six weeks. Animals in the high-lipid diet group had higher levels of cholesterol, triglycerides, and LDL cholesterol, as well as a thick layer of lipid disposition in the aortic intima compared to those in the OLE group. These results support olive leaf's anti-atherosclerotic effect, most likely related to suppression of inflammation.[31]

In a human clinical trial OLE reduced blood pressure in 40 borderline hypertensive pairs of monozygotic twins. Twins from each pair were assigned to control or two treatment groups receiving either 500 or 1,000 mg OLE daily for eight weeks. Body weight, heart rate, blood pressure, glucose, and lipids were measured at two-week intervals. Blood pressure values decreased within pairs, with an average difference in systolic pressure up to 6 mmHg between the 500-mg OLE group and control group and up to 13 mmHg difference between 500-mg and 1,000-mg groups after six weeks; maximum differences in diastolic blood pressure in the same two groups were 5 mmHg in each. At the end of the study, mean blood pressure remained unchanged for those in the control and 500-mg groups, while those in the 1,000-mg group reported a significant decrease in mean systolic blood pressure (137 ± 10 to 126 ± 6; $p<0.01$). All subjects reported decreases in cholesterol, with no significant changes in other parameters.[32]

Another clinical trial (n=30) reported significant decreases in blood pressure in hypertensive patients given 400 mg aqueous OLE four times daily for three months. Full text of the study was unavailable and published in French and actual percentage decrease was not reported in the abstract.[33]

Olive leaf polyphenols have been shown to inhibit *in vitro* platelet function in blood obtained from 11 healthy, nonsmoking males. Olive leaf polyphenols (at increasing concentrations of oleuropein) effected a significant dose-dependent suppression of platelet-ATP release and platelet aggregation.[34]

Viral Infections

Researchers have demonstrated olive leaf constituents, particularly elenolic acid and its salt, calcium elenolate, are effective *in vitro* against many viruses studied, including parainfluenza, *Herpes simplex*, pseudorabies, polio viruses -1, -2, and -3, rhinoviruses, myxoviruses, coxsackie virus, *Varicella zoster*, encephalomyocarditis, and two strains of leukemia virus.[15] No clinical trials have been conducted on OLE as a therapy for viral infections; given their potent *in vitro* broad-spectrum antiviral activity and numerous anecdotal reports attesting to OLE's therapeutic effect, clinical trials are warranted.

HIV

Based on the antiviral activity of olive leaf extract[15,16] and numerous anecdotal reports from AIDS patients,[35] OLE is being widely used to strengthen the immune system, decrease viral load, relieve chronic fatigue, treat Kaposi's sarcoma and *Herpes simplex* virus infections, and reduce the side effects of antiretroviral treatment regimens.[36] An *in vitro* study of an olive leaf extract standardized to oleuropein content incubated with HIV-1 infected H9 cells showed a reversal of many HIV-1 associated changes in cellular signaling. Treating HIV-1 infected cells with OLE upregulates expression of apoptosis inhibitor proteins, calcium and protein kinase C pathway signaling, and ornithine decarboxylase ODC1, suppressing cell-to-cell transmission of HIV-1 and acute infection.[16]

Anecdotal reports of OLE's therapeutic effect in AIDS patients date back to 1996. Some reports involve its use as a monotherapy, while others report its use in conjunction with naltrexone, an immune modulator. All report significant decreases in viral load, some after taking olive leaf extract for only 2-3 weeks. Some patients report increases in CD4, CD8, and white blood cell counts; others report a change in HIV status from positive to negative on ELISA and Western Blot tests for AIDS.[35] These anecdotal reports would require randomized, controlled trials for substantiation.

Colds/Influenza

Anecdotal reports indicate when taken at the onset of cold or flu symptoms, olive leaf extract prevents or shortens the duration of the infection. For viral sore throats, gargling with olive leaf tea may alleviate symptoms, possibly by decreasing inflammation and viral infectivity. In 1977 the effect of olive leaf constituents against influenza A in hamsters was demonstrated. Calcium elenolate administered to infected hamsters as nose drops shortly after influenza A inoculation reduced viral titers of nasal washes and cured infection.[37]

Bacterial, Protozoan, and Fungal Infections

In vitro research demonstrates the effectiveness of OLE against a wide range of pathogens, including *Escherichia coli*, *Pseudomonas fluorescens*, Corynebacterium sp., *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Salmonella typhimurium*, *Erwinia carotovora*, *Candida albicans*, and *Plasmodium falciparum*.[18] Although clinical trials have not evaluated the therapeutic effect of olive leaf extract against these pathogens, anecdotal reports demonstrate clinical efficacy against some organisms.

In 1906 an unreferenced report stated that olive leaves were superior to quinine for treatment of malaria. Later, a case report from a clinic in Mexico revealed a complete cure of a full-blown case of malaria in a 34-year-old woman after taking two olive leaf supplements every six hours for six months.[38]

Olive leaf extract also inhibits the food-borne pathogen, *Bacillus cereus*, both *in vitro* and when administered to humans, by structurally altering germinating spores and delaying growth of the organism.[20] Oleuropein administered to rabbits with experimental multi-drug-resistant *Pseudomonas aeruginosa* sepsis decreased oxidative stress and prolonged survival time.[39]

Diabetes

In vitro and animal studies demonstrate a hypoglycemic effect for olive leaf extracts. In alloxan-induced diabetic rats, OLE was shown to increase peripheral glucose uptake, raise insulin levels, and decrease blood glucose levels at doses of 16 and 32 mg/kg body weight.[26] In diabetic rabbits, oleuropein given at 20 mg/kg body weight for 16 weeks restored blood glucose values to normal and decreased diabetes-associated oxidative stress compared to nondiabetic rabbits.[40]

Hypothyroidism

Olive leaf extract given to mature male rats in 100-, 250-, and 500-mcg doses increased T3 levels in a dose-dependent manner and significantly reduced circulating thyroid stimulating hormone levels at all doses after 14 days of treatment.[41] This animal study suggests a possible use of OLE for hypothyroidism.

Botanical-Drug Interactions

Due to the hypotensive and antiplatelet aggregating properties of olive leaf extract, concomitant use with blood-pressure lowering medications and blood thinners may have a potentiating effect; so caution is advised. Theoretically, olive leaf extract could also have an additive effect when taken in conjunction with antidiabetic medications, although this has not been reported in humans.

Side Effects and Toxicity

Olive leaf extracts appear to be quite safe. In animal experiments, researchers observed no toxicity in rats, even at high doses (1g/kg body weight) for seven days.[42] *In vitro* studies on human cell lines found no toxicity at 1 mg/mL of extract.[16] Studies have not been conducted on the safety of olive leaf extract in pregnant and lactating women. Olive leaf extracts are best taken with food to avoid gastrointestinal irritation.

Dosage

Oral dosages range from 500-2,000 mg powdered OLE daily. Extracts are usually standardized to 17-20 percent oleuropein.

References

1. Olive leaf. Wikepedia, the free encyclopedia. http://en.wikipedia.org/wiki/Olive_leaf [Accessed December 18, 2008]
2. The olive leaf in medicine and history. http://www.oliveleafextract.com/history.html [Accessed December 18, 2008]
3. Felter HW, Lloyd JL. *King's American Dispensatory*. Cincinnati, OH: Ohio Valley Co.; 1898.
4. Briante R, Patumi M, Terenziani S, et al. *Olea europaea* L. leaf extract and derivatives: antioxidant properties. *J Agric Food Chem* 2002;50:4934-4940.
5. Japon-Lujan R. Luque de Castro MD. Superheated liquid extraction of oleuropein and related biophenols from olive leaves. *J Chromatogr A* 2006;1136:185-191.
6. Sato H, Genet C, Strehle A, et al. Anti-hyperglycemic activity of a TGR5 agonist isolated from *Olea europaea*. *Biochem Biophys Res Commun* 2007;362:793-798.
7. Benavente-Garcia O, Castillo J, Lorente J, Alcaraz M. Radioprotective effects *in vivo* of phenolics extracted from *Olea europaea* L. leaves against X-ray-induced chromosomal damage: comparative study versus several flavonoids and sulfur-containing compounds. *J Med Food* 2002;5:125-135.
8. Baidez AG, Gomez P, Del Rio JA, Ortuno A. Dysfunctionality of the xylem of *Olea europaea* L. plants associated with the infection process by *Verticillium dahliae* Kleb. Role of phenolic compounds in plant defense mechanism. *J Agric Food Chem* 2007;55:3373-3377.
9. Walter WM Jr, Fleming HP, Etchells JL. Preparation of antimicrobial compounds by hydrolysis of oleuropein from green olives. *Appl Microbiol* 1973;26:773-776.
10. Samuelsson G. The blood pressure lowering factor in leaves of *Olea europaea*. *Farmacevtisk Revy* 1951;15:229-239.
11. Panizzi L, Scarpati ML, Orient G. The constitution of oleuropein, a bitter glucoside of the olive with hypotensive action. *Gazz Chim Ital* 1960;90:1449-1485.
12. Zarzuelo A, Duarte J, Jimenez J, et al. Vasodilator effect of olive leaf. *Planta Med* 1991;57:417-419.
13. Gilani AH, Khan AU, Shah AJ, et al. Blood pressure lowering effect of olive is mediated through calcium channel blockade. *Int J Food Sci Nutr* 2005;56:613-620.
14. Scheffler A, Rauwald HW, Kampa B, et al. *Olea europaea* leaf extract exerts L-Type Ca(2+) channel antagonistic effects. *J Ethnopharmacol* 2008;120:233-240.

15. Renis HE. *In vitro* antiviral activity of calcium elenolate. *Antimicrob Agents Chemother (Bethesda)* 1969:9;167-172.
16. Lee-Huang S, Zhang L, Huang PL, et al. Anti-HIV activity of olive leaf extract (OLE) and modulation of host cell gene expression by HIV-1 infection and OLE treatment. *Biochem Biophys Res Commun* 2003;307:1029-1037.
17. Micol V, Caturla N, Pérez-Fons L, et al. The olive leaf extract exhibits antiviral activity against viral haemorrhagic septicaemia rhabdovirus (VHSV). *Antiviral Res* 2005;66:129-136.
18. Elliott GA, Buthala DA, DeYoung EN. Preliminary safety studies with calcium elenolate, an antiviral agent. *Antimicrob Agents Chemother (Bethesda)* 1969;9:173-176.
19. Markin D, Duek L, Berdicevsky I. *In vitro* antimicrobial activity of olive leaves. *Mycoses* 2003;46:132-136.
20. Tassou CC, Nychas GJ, Board RG. Effect of phenolic compounds and oleuropein on the germination of *Bacillus cereus* T spores. *Biotechnol Appl Biochem* 1991;13:231-237.
21. Wojcikowski K, Stevenson L, Leach D, et al. Antioxidant capacity of 55 medicinal herbs traditionally used to treat the urinary system: a comparison using a sequential three-solvent extraction process. *J Altern Complement Med* 2007;13:103-109.
22. Visioli F, Galli C. Oleuropein protects low density lipoprotein from oxidation. *Life Sci* 1994;55:1965-1971.
23. Coni E, Di Benedetto R, Di Pasquale M, et al. Protective effect of oleuropein, an olive oil biophenol, on low density lipoprotein oxidizability in rabbits. *Lipids* 2000;35:45-54.
24. Pieroni A, Heimler D, Pieters L, et al. *In vitro* anti-complementary activity of flavonoids from olive (*Olea europaea* L.) leaves. *Pharmazie* 1996;51:765-768.
25. Petroni A, Blasevich M, Salami M, et al. Inhibition of platelet aggregation and eicosanoid production by phenolic components of olive oil. *Thromb Res* 1995;78:151-160.
26. Gonzalez M, Zarzuelo A, Gamez MJ, et al. Hypoglycemic activity of olive leaf. *Planta Med* 1992;58:513-515.
27. Komaki E, Yamaguchi S, Maru I, et al. Identification of anti-alpha-amylase components from olive leaf extracts. *Food Sci Technol Res* 2003;9:35-39.
28. Osim EE, Mbajiorgu EF, Mukarati G, et al. Hypotensive effect of crude extract *Olea africana* (Oleaceae) in normo and hypertensive rats. *Cent Afr J Med* 1999;45:269-274.
29. Khayyal MT, el-Ghazaly MA, Abdallah DM, et al. Blood pressure lowering effect of an olive leaf extract (*Olea europaea*) in L-NAME induced hypertension in rats. *Arzneitmittelforschung* 2002;52:797-802.
30. Somova LI, Shode FO, Ramnanan P, Nadar A. Antihypertensive, antiatherosclerotic, and antioxidant activity of triterpenoids isolated from *Olea europaea*, subspecies africana leaves. *J Ethnopharmacol* 2003;84:299-305.
31. Wang L, Geng C, Jiang L, et al. The anti-atherosclerotic effect of olive leaf extract is related to suppressed inflammatory response in rabbits with experimental atherosclerosis. *Eur J Nutr* 2008;47:235-243.
32. Perrinjaquet-Moccetti T, Busjahn A, Schmidlin C, et al. Food supplementation with an olive (*Olea europaea* L.) leaf extract reduces blood pressure in borderline hypertensive monozygotic twins. *Phytother Res* 2008;22:1239-1242.
33. Cherif S, Rahal N, Haouala M, et al. A clinical trial of a titrated Olea extract in the treatment of essential arterial hypertension. *J Pharm Belg* 1996;51:69-71. [Article in French]
34. Singh I, Mok M, Christensen AM, et al. The effect of polyphenols in olive leaves on platelet function. *Nutr Metab Cardiovasc Dis* 2008;18:127-132.
35. Walker M. *Natures Antibiotic: Olive Leaf Extract*. New York, NY: Kensington Books; 1997:120-128.
36. Lee-Huang S, Hang P, Huang P. Anti-HIV activity of olive leaf extract and synergism with HAART. *Int Conf AIDS* 2004;15:abstract no. WePeA5651.
37. Renis HE. Influenza virus infection of hamsters. A model for evaluating antiviral drugs. *Arch Virol* 1977;54:85-93.
38. Malaria and tropical illness. http://oliveleafextract.com/tropical.html [Accessed November 24, 2008]
39. Koussoulas V, Geladopoulos T, Vassiliadis J, et al. Oleuropein: a novel antioxidant agent for treatment of experimental sepsis induced by multidrug-resistant *Pseudomonas aeruginosa*. 15th European Congress of Clinical Microbiology Infectious Diseases. April 2-5, 2005. Abstract no.: 1133_245.
40. Al-Azzawie HF, Alhamdani MS. Hypoglycemic and antioxidant effect of oleuropein in alloxan-diabetic rabbits. *Life Sci* 2006;78:1371-1377.
41. Al-Qarawi AA, Al-Damegh MA, ElMougy SA. Effect of freeze dried extract of *Olea europaea* on the pituitary-thyroid axis in rats. *Phytother Res* 2002;16:286-287.
42. Petkov V, Manolov P. Pharmacological analysis of the iridoid oleuropein. *Arzneimittelforschung* 1972;22:1476-1486.