Olive leaf extract for cardiovascular disease

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AFTER READING THIS ARTICLE, THE LEARNER SHOULD BE ABLE TO:

- list the components of olive leaf extract suggested to benefit human health;
- describe the suggested health benefits of olive leaf extract components;
- describe the emerging evidence for olive leaf extract for cardiovascular conditions;
- differentiate between the potential effects of low dose versus high dose olive leaf extract.

The 2010 Competency Standards addressed by this activity include (but may not be limited to): 6.2

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Olive leaf extract containing oleuropein and hydroxytyrosol has shown cardiovascular benefits in small human trials.

Introduction

The fruit and oil of the olive plant (*Olea europaea*) are common components of diets across the world and form an integral part of the Mediterranean diet. The benefits of dietary olive oil are now so well supported by evidence that the European Food Safety Authority (EFSA) has approved use of the following health claim 'olive oil polyphenols contribute to the protection of blood lipids from oxidative stress'.[1] This statement has been allowed by EFSA as they acknowledge the substantive body of evidence supporting that olive oil consumption reduces the oxidation of low density lipoprotein (LDL) cholesterol which is implicated in the development of atherosclerosis.

The olive plant is rich in phytochemicals called polyphenols. These naturally occurring compounds are composed of an aromatic ring with one or more hydroxyl groups. There are many thousand different polyphenols. The phenolic content of the olive fruit is complex and depends on the cultivar of the olive plant, maturation of the fruit at picking, the season the fruit was picked and the storage conditions of the fruit after picking.

The most abundant of the polyphenols in the olive plant are:

- a secoiridoid compound called oleuropein (the bitter compound found in unripened olive fruit and olive leaves);
- the simple phenols tyrosol and hydroxytyrosol;
- the flavonoids luteolin and apigenin; and
- the phenolic acid verbascoside.

The oleuropein content of the olive fruit degrades as the fruit matures and is almost undetectable in ripe brown fruit. Conversely the concentration of tyrosol, hydroxytyrosol and verbascoside in the fruit all increase as it matures. Oleuropein is present in large amounts in olive leaf (60–90mg/g dry weight) however due to degradation in ripe fruit is only present in minimal concentration in olive oil.

Polyphenols are important phytochemicals as they assist plants with reproduction, fighting pathogens and pests and protecting against environmental stressors including UV exposure. They also impart the brown colour to the skin of the olive fruit and the characteristic aroma to the oil. The olive plant has developed high concentrations of these protective polyphenols in their thick leaves and dark fruit due to exposure of the plant to the above stressors in the southern European and Mediterranean areas in which they are native. It has been postulated that the polyphenols of the olive plant can be beneficial to humans when taken in the diet.

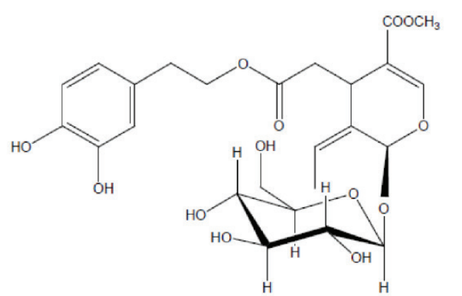

Figure 1: **Oleuropein**

Interest in plant-based antioxidants for human health increased when it was identified that oxidative processes were associated with serious human pathologies including cancer, inflammation and atherosclerosis as well as ageing.

Oxidation and human health

Interest in plant-based antioxidants for human health increased when it was identified that oxidative processes were associated with serious human pathologies including cancer, inflammation and atherosclerosis as well as ageing. Atherosclerosis is caused by hyperlipidaemia and lipid oxidation (particularly oxidation of LDL cholesterol). Lipid oxidation is the first step in the pathophysiological process of atherosclerosis. It leads to activation of immune cells that migrate to the vessel cell wall as well as expression of adhesion molecules that make platelets 'sticky'. These events contribute to plaque formation. Antioxidants have been shown to heal damaged endothelium in human models of atherosclerosis.[2]

Several studies have indicated that the Mediterranean diet, which is high in olives and olive oil (as well as fruit, vegetables, grains, legumes, nuts, seeds and other beneficial oils), is linked to lower incidences of cardiovascular disease and cancers. However there are still some controversies surrounding conflicting outcomes.[3]

The difficulty is that these studies do not specifically identify that polyphenols contribute to the health benefits of the Mediterranean diet. The Mediterranean diet is also high in mono-unsaturated fatty acids (MUFAs, e.g. oleic acid from olive oil) that are known to have health benefits. However, not all MUFA-rich oils (e.g. rapeseed, sunflower and soybean oils) have been shown to have the cardiovascular benefits of olive oil. This indicates that the polyphenols contained in olive oil contribute towards its cardiovascular benefit, however differentiating between the effects of polyphenols and MUFAs in studies is difficult.[4]

It is known that phenolic compounds from olives are absorbed from the diet. Evidence indicates that a diet rich in olives leads to an increase in plasma concentrations of polyphenols.[5] Two of the main phenols in olive oil (tyrosol and hydroxytyrosol) are both absorbed in humans in a dose-dependant manner and then extensively metabolised by the gut and liver.

Olive leaf

As with the fruit and oil of the olive plant, the leaves also contain polyphenols. Olive leaf actually contains markedly higher amounts of polyphenols than both olive fruit and oil (1450mg total phenolics per 100g of fresh leaf compared to 110mg/100g in the olive fruit and 23mg/100mL in the oil).

Oleuropein accounts for 20–40% of the phenolic compounds of olive leaf. Oleuropein is a member of the secoiridoid family of compounds which are known for their antioxidant properties, particularly as scavengers of peroxide (H_2O_2). It has been suggested that olive leaf would also impart the cardiovascular health benefits that are derived from olive fruit and oil due to its higher concentration of polyphenols and antioxidant properties. This follows from the fact that peroxide is involved in platelet aggregation which is an integral part of atherosclerosis and, therefore, cardiovascular disease. However the majority of the evidence supporting the cardiovascular benefits of olive leaf comes from *in vitro* or *in vivo* animal studies. Human trials are few, however human evidence is emerging.

Unlike for olive fruit, the bioavailability of polyphenols from olive leaf is not known. The form of oleuropein found in olive fruit (oleuropein aglycone) and olive leaf (oleuropein glycoside) are different. The olive leaf form of oleuropein is possibly absorbed intact from the gut. Oleuropein-like metabolites have been found in human urine following a single dose of olive leaf.[6] However, further human trials are still needed to determine the bioavailability of phenolic compounds from olive leaf and their associated benefits.

Health benefits of olive leaf

Olive leaf has been used since ancient times to treat a variety of conditions. The medical application of olive leaf was clinically noted in the mid-19th century when it was used to treat fever and malaria. Since then, the suggested benefits for olive leaf cover everything from diabetes to hypertension, compromised immunity, infection and inflammation.

There is some emerging evidence supporting the use of olive leaf for cardiovascular health. The majority of evidence for cardiovascular health is from *in vitro* studies or *in vivo* animal studies. For example, an *in vitro* study in human blood indicated that hydroxytyrosol can decrease platelet aggregation with alkyl ether derivatives of hydroxytyrosol being more effective.[7]

The majority of the human evidence involves the use of olive leaf to reduce blood pressure (BP) and improve lipid profile. It has been postulated that oleuropein reduces BP via blockade of L-type calcium channels and verbascoside via inhibition of angiotensin converting enzyme. This review will focus on the cardiovascular benefits of olive leaf witnessed in humans.

Cardiovascular health benefits

As reported in the European Medicines Agency Assessment Report on *Olea Europaea* (2011), in a small study on 30 people with hypertension (12 treatment naïve and 18 previously treated with antihypertensives), 1.6g of olive leaf extract taken as gel capsules daily for three months resulted in a significant decrease in BP for all participants.[8]

In another small study, 18 young, healthy volunteers were given a single dose of 51mg oleuropein plus 10mg hydroxytyrosol or placebo. The protocol was crossed over after a four week washout period. The participants' vascular function was determined by measuring arterial stiffness. Results indicated that olive leaf significantly improved vascular function as well as decreased inflammatory cytokines.[9]

A small study in adult twins with hypertension found that 500mg of olive leaf extract (equivalent to 100mg oleuropein) daily for eight weeks reduced systolic blood pressure (SBP) by 6mmHg and 1000mg of olive leaf extract (equivalent to 200mg oleuropein) daily reduced SBP by 13mmHg. Diastolic blood pressure (DBP) was reduced by 6mmHg. The drop in SBP for the group receiving 200mg oleuropein was significant compared to that of the 100mg dose (137 +/– 10/80 +/– 10 vs 126 +/– 9/76 +/– 6 respectively). LDL cholesterol levels were also significantly reduced however body weight, heart rate and blood glucose remained unchanged.[10]

In a larger randomised controlled trial, 162 participants with hypertension (defined as SBP 140–159mmHg with DBP above 90mmHg) were randomised to receive daily doses of either 500mg olive leaf extract (100mg oleuropein) or 25mg captopril. The dose of oleuropein was doubled to 200mg and that of captopril to 50mg depending on the response witnessed after therapy initiation. After eight weeks the reduction in SBP and DBP was similar in both the 200mg olive leaf (–11.5 +/– 8.6 and –4.8 +/– 5.5mmHg) and 50mg captopril groups (–13.7 +/– 7.6 and –6.4 +/– 5.2mmHg). The reduction in SBP was similar to that witnessed in the small study in twins discussed above. Patients in the olive leaf group also experienced a reduction in total cholesterol and triglycerides with a small reduction in LDL cholesterol.[11]

A recent study[12] measured the effect of liquid olive leaf extract (standardised to 136.2mg of oleuropein and 6.4mg of hydroxytyrosol) daily on BP in 60 male patients with pre-hypertension (mean BP at baseline of 139/83mmHg). Each study participant took either placebo or olive leaf extract for six weeks followed by a four week washout period and a further six weeks of treatment in a crossover study design. Blood pressure was measured throughout the study period using a 24 hour ambulatory method. Biochemical analyses of blood samples were also performed.

Olive leaf extract containing oleuropein and hydroxytyrosol has shown promise for the treatment of hypertension, hyperlipidaemia and diabetes in small human trials.

Results indicated a modest 3–4mmHg reduction in SBP and 2–3mmHg reduction in DBP after six weeks of olive leaf compared to placebo. The difference was significant on average over the entire 24-hour ambulatory measurement period. Blood pressure during the daytime was significantly lower, however nighttime BP was not. Total cholesterol, LDL cholesterol and triglycerides were also significantly reduced (0.32, 0.19 and 0.18mmol/L respectively). HDL cholesterol, fasting glucose, insulin levels and body composition remained unchanged. There was a significant reduction in the inflammatory marker interleukin-8 however all other markers of inflammation were not significantly different.

While clinical outcomes were not investigated, the authors extrapolated that the modest reduction in BP and lipids caused by olive leaf extract could reduce the risk of heart attack and stroke by 20%. This still remains to be determined.

Insulin sensitivity

There is also emerging evidence supporting the use of olive leaf in pre-diabetes. A small double blind, randomised placebo controlled study (n=46) in obese adult males involved daily doses of 51.1mg oleuropein and 9.7mg hydroxytyrosol for 12 weeks. This was followed by a six week washout and 12-week crossover. A number of physiological parameters were measured. Results indicated that olive leaf significantly improved insulin sensitivity by 15% and pancreatic beta cell function by 28%. At this lower dose, there were no significant changes in blood lipids or ambulatory BP.[13]

Olive leaf dose

It is important to note that the dose of olive leaf extract demonstrating a benefit in the hypertension studies (standardised oleuropein 100–200mg daily) was higher than is often recommended for colds and flu, etc. The lower dose of 51.1mg oleuropein used in the insulin sensitivity study did not benefit BP. Therefore higher strength preparations are preferred for cardiovascular applications. There are a number of different dosage forms of olive leaf available including dried leaf extract and liquid extract, etc. The dose per dosage unit should be standardised. Products that stipulate on the label the dose of oleuropein as opposed to olive leaf extract per dosage unit will enable pharmacists to offer more accurate dosage information to patients.

Adverse reactions to olive leaf

The study comparing olive leaf extract to captopril found that the most frequently reported adverse reactions were cough and vertigo while headache and muscle discomfort were less likely. The researchers concluded that both olive leaf extract and captopril were possible causes for these. All adverse reactions resolved by the end of the study. Patients with a history of biliary tract stones should avoid olive leaf due to a risk of colic. Liver, renal and haematological parameters all remained within target levels.[11]

Summary

Olive leaf extract containing oleuropein and hydroxytyrosol has shown promise for the treatment of hypertension, hyperlipidaemia and pre-diabetes in small human trials. Also studies in human blood have indicated that olive leaf extract can inhibit platelets. The cardiovascular benefits of olive leaf extract are associated with higher doses than are commonly used for other conditions and therefore higher strength products are preferred for cardiovascular applications. More research is required to fully determine the benefits of olive leaf extract for cardiovascular health. ●

1. Agostoni CV, et al. (2011) Scientific Opinion on the substantiation of health claims related to polyphenols in olive and protection of LDL particles from oxidative damage (ID 1333, 1638, 1639, 1696, 2865), maintenance of normal blood HDL-cholesterol concentrations (ID 1639), maintenance of normal blood pressure (ID 3781), anti-inflammatory properties (ID 1882), contributes to the upper respiratory tract health (ID 3468), can help to maintain a normal function of gastrointestinal tract (3779), and contributes to body defences against external agents (ID 3467) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. 2011;9(4):2033. 2031-2033.2025.
2. Rafieian-Kopaei M, et al. Atherosclerosis: Process, Indicators, Risk Factors and New Hopes. Int J Prev Med. 2014 Aug;5(8):927-46.
3. Sleiman D, et al. Effect of Mediterranean diet in diabetes control and cardiovascular risk modification: a systematic review. Front Public Health. 2015;3:69.
4. Ghanbari R, et al. Valuable nutrients and functional bioactives in different parts of olive (Olea europaea L.)—A Review. Int J Mol Sci. 2012;13(3):3291-3340.
5. Kountouri A.M, et al. Bioavailability of the phenolic compounds of the fruits (drupes) of Olea europaea (olives): Impact on plasma antioxidant status in humans. Phytomedicine. 2007;14:659-67.
6. de Bock M, et al. Human absorption and metabolism of oleuropein and hydroxytyrosol ingested as olive (Olea europaea L.) leaf extract. Molecular Nutrition and Food Research. 2013; 57(11): 2079-85.
7. Reyes JJ, et al. Antiplatelet effect of new lipophilic hydroxytyrosol alkyl ether derivatives in human blood. Eur J Nutr. 2013 Mar;52(2):591-9.
8. Cherif S, et al. A clinical trial of a titrated Olea extract in the treatment of essential arterial hypertension. J Pharm Belg. 1996;51(2):69-71.
9. Lockyer S, et al. Secoiridoids delivered as olive leaf extract induce acute improvements in human vascular function and reduction of an inflammatory cytokine: a randomised, double-blind, placebo-controlled, cross-over trial. Br J Nutr. 2015 Jul 14;114(1):75-83.
10. Perrinjaquet-Moccetti T, et al. Food supplementation with an olive (Olea europaea L.) leaf extract reduces blood pressure in borderline hypertensive monozygotic twins. Phytother Res. 2008 Sep;22(9):1239-42.
11. Susalit E, et al. Olive (Olea europaea) leaf extract effective in patients with stage-1 hypertension: comparison with captopril. Phytomedicine. 2011 Feb 15;18(4):251-8.
12. Lockyer S, et al. Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: a randomised controlled trial. European J of Nutrition. 2016 Mar;1-12. Available via http://link.springer.com/article/10.1007/s00394-016-1188-y.
13. de Bock M, et al. Olive (Olea europaea L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomized, placebo-controlled, crossover trial. PLoS One. 2013;8(3):e57622.

1.5 CPD CREDITS GROUP TWO

ADVANCING YOUR PRACTICE

Olive leaf extract for cardiovascular disease

This unit attracts 1.5 Group Two CPD credits. Accreditation number: A1604AJP1. Each question has only one CORRECT answer.

1. Which of the following phenolic constituents of olive leaf is a secoiridoid?
   A Oleuropein
   B Hydroxytyrosol
   C Verbascoside
   D Olea europaea
   E Tyrosol

2. Human trials support the use of olive leaf extract in which of the following cardiovascular conditions?
   A Stroke
   B Hypotension
   C Secondary prevention of myocardial infarct
   D Hypertension
   E Angina

3. Which of the following outcomes was NOT witnessed in the human study comparing olive leaf to captopril?
   A Decreased systolic hypertension
   B Decreased triglycerides
   C Decreased total cholesterol
   D Decreased LDL cholesterol
   E Increased HDL cholesterol

4. True or false? The highest amount of polyphenols in olive is found in the leaf rather than the fruit or the oil.
   A True
   B False

5. True or false? Products containing lower doses of olive leaf used for colds and flu are supported by evidence for cardiovascular conditions.
   A True
   B False