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File: ■ Olive (*Olea europaea*, Oleaceae) Leaf
■ Oxidative Stress
■ Cardiovascular Disease

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RE: Olive Leaf Constituents Reduce Myocardial Oxidative Damage

Efentakis P, Iliodromitis EK, Mikros E, et al. Effects of the olive tree leaf constituents on myocardial oxidative damage and atherosclerosis. *Planta Med*. June 2015;81(8):648-654.

Olive (*Olea europaea*, Oleaceae) leaf extract has antioxidant, anti-inflammatory, antihypertensive, vasodilator, antithrombotic, and hypoglycemic properties. The most abundant constituents of the dried leaf extract are oleuropein, oleuropein aglycone, oleacein, hydroxytyrosol, tyrosol, and elenolic acid. Research suggests that olive leaf extracts can mitigate the oxidative stress and inflammation associated with the development of cardiovascular disease (CVD). This article reviews the effects of olive leaf extract and its major constituents on myocardial oxidative damage and atherosclerosis.

The production of reactive oxygen species (ROS) results in oxidative stress. Key factors in the progression of CVD associated with oxidative stress are endothelial damage, reduced production of endothelial nitric oxide synthase (eNOS) and thus, decreased nitric oxide (NO) concentrations, depressed levels of endogenous enzymes that neutralize ROS, and increased levels of oxidized low-density lipoproteins (ox-LDLs).

Oleuropein is a potent antioxidant with the ability to scavenge superoxides and hydroxyl radicals. In vitro and in vivo studies have found that oleuropein decreases LDL oxidation and lowers concentrations of ROS and biomarkers of oxidative stress, as well as total cholesterol and triglycerides. Among the olive leaf constituents, oleuropein has the greatest anti-atherosclerotic activity. In animal models, oleuropein protected against the effects of ischemia and reduced infarct size. In addition, oleuropein supplementation increased superoxide dismutase concentrations and reduced the risk of thrombosis.

Oleuropein aglycone, a metabolite of oleuropein also referred to as 3,4-DHPEA-EA, has antioxidant activity comparable to caffeic acid, oleuropein, and hydroxytyrosol, and has also been found to reduce the oxidation of LDL.

The oleuropein metabolite oleacein has even more potent antioxidant and anti-inflammatory properties than oleuropein. It inhibits the production of ROS and decreases the pro-inflammatory response. Oleacein can permeate the cell membrane of red blood cells and protect against oxidative damage. It directly inhibits 5-lipoxygenase and protects against

endothelial damage in a dose-dependent manner. The anti-ischemic properties of oleacein have not been investigated.

In vitro studies show that hydroxytyrosol prevents ROS damage, upregulates the expression of endogenous antioxidants, and reduces LDL oxidation. However, there is conflicting experimental evidence regarding the anti-atherosclerotic properties of hydroxytyrosol, and studies evaluating its cytoprotective effects against ischemia-reperfusion injury are lacking.

Experimental studies have shown that tyrosol reduces lipid peroxidation and oxidative stress but at a significantly lower extent than hydroxytyrosol. Tyrosol upregulates eNOS expression, reduces infarct size, and ameliorates ischemia-reperfusion injury.

There is no evidence that elenolic acid has cardioprotective effects; however, very few studies have been conducted. Elenolic acid is used as a marker of olive maturity.

Amongst the olive leaf constituents, oleuropein and hydroxytyrosol are the most effective anti-atherosclerotic agents. Compared to oleuropein, hydroxytyrosol is a better free radical scavenger and provides superior protection against LDL oxidation. However, the ethanolic extract of olive leaves showed better protection against oxidative stress and toxicity than the individual phenolic compounds. In the protection against oxidative hemolysis, the order of activity was oleacein > oleuropein aglycone > hydroxytyrosol = oleuropein. Only hydroxytyrosol protected against NO-mediated oxidative stress and it had the highest antioxidant activity compared to oleuropein and tyrosol. Olive phenols have been shown to significantly reduce lipoprotein oxidation and aging-induced oxidative stress, and protect against DNA and endothelial damage.

In vitro, olive leaf extract protected against LDL oxidation. In animal models, olive leaf extract attenuated the symptoms of metabolic syndrome, improved lipid profiles, and reduced levels of oxidative stress markers and inflammatory cytokines. A clinical study evaluating the effects of an olive leaf extract containing 5.4 mg/ml oleuropein found that it decreased inflammatory markers, H_2O_2, and platelet activation.

In summary, olive leaf extracts and their phenolic constituents have been shown to reduce oxidative stress in animal models. Protection against LDL oxidation with concomitant improvements in endogenous antioxidant levels and lipid profiles has also been observed in vivo. These effects have primarily been attributed to hydroxytyrosol and oleuropein. The anti-atherosclerotic, hypocholesterolemic, and anti-ischemic activities of olive leaf extract and its constituents need to be studied in further detail to elucidate the underlying mechanisms of action. The authors conclude that olive leaf constituents have beneficial effects on myocardial oxidative stress; however, the human trials should be systematically reviewed to determine whether these effects are clinically relevant.

—Cheryl McCutchan, PhD

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