www.nephropathol.com doi: 10.15171/jnp.2019.02 J Nephropathol. 2019;8(1):e02

Journal of Nephropathology

Protective effects of olive in renal failure; a review on current knowledge

Esmaeel Babaeenezhad[1,2], Hassan Ahmadvand[2,3], Reza Mohammadrezaei Kkorramabadi[3*], Shahrokh Bagheri[3], Peyman Khosravi[3], Parisa Jamor[4]

[1]Department of Cardiology, Madani Heart Center, Lorestan University of Medical Sciences, Khorramabad, Iran
[2]Department of Biochemistry, Faculty of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran
[3]Razi Herbal Researches Center, Lorestan University of Medical Sciences, Khorramabad, Iran
[4]Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran

ARTICLE INFO

Article type:
Review

Article history:
Received: 14 February 2018
Accepted: 10 June 2018
Published online: 29 June 2018

Keywords:
Olive
Oxidative stress
Renal failure

ABSTRACT

Context: The pathogenesis of renal damage as a risk factor of renal failure can be due to oxidative stress resulting from an imbalance between the production of free radicals and antioxidants. Therefore, antioxidant therapy can be a good strategy to decrease the effects of such diseases. Hence, the aim of this review was to evaluate the protective effect of olive oil as an herb rich in antioxidant compounds on kidney damage in previous studies.

Evidence Acquisitions: Present review is based on scrutinizing the contents of relevant papers searched in PubMed, Google Scholar, EBSCO, Embase, directory of open access journals (DOAJ), Web of Science and Scopus.

Results: Numerous studies have introduced herbal treatments, being rich sources of antioxidants, as appropriate alternatives for several diseases, including renal damage, when considering the pathogenesis of the diseases. The olive has also been recommended as a plant that has different therapeutic effects, and its therapeutic effects on the kidneys are mentioned in several studies, including the reduction of renal damage parameters and an increase in the antioxidant power of enzymes in the body.

Conclusions: Considering the numerous studies on animal models, particularly rats and renal cell lines, olive oil can be used as a reliable method for the treatment of various kidney damages. However, further studies are also recommended in humans.

Implication for health policy/practice/research/medical education:
Today, the need for plant derived compounds to treat diseases is felt more and more due to the lower side effects. On the other hand, studies have shown that medicinal plants, especially olives, have an effect on kidney disease.

Please cite this paper as: Babaeenezhad E, Ahmadvand H, Mohammadrezaei Kkorramabadi R, Bagheri S, Khosravi P, Jamor P. Protective effects of olive in renal failure; a review on current knowledge. J Nephropathol. 2019;8(1):e02. doi: 10.15171/jnp.2019.02.

1. Context

The pathogenesis of renal damage as a risk factor of renal failure can be due to oxidative stress resulting from an imbalance between the production of free radicals and antioxidants (1). Therefore, antioxidant therapy can be a good strategy to protect the renal damage from free radicals (1). Many studies showed that olive oil, olive leaf and olive fruit and their compounds such as oleuropein, hydroxytyrosol, and oleic acid have antioxidant and anti-inflammatory activities (2).

2. Evidence Acquisitions

For this review, we used a variety of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO, Embase and Directory of Open Access Journals (DOAJ). The search was conducted, using combinations of the following key words and or their equivalents; Olive, Oxidative stress and Renal failure

*Corresponding author: Reza Mohammadrezaei Kkorramabadi;
Email: reza.mr@chmail.ir

Review

3. Protective effects of olive and its various compositions on renal failure

3.1. Protective effects of olive or its various compositions on drug induced nephrotoxicity

3.1.1. Doxorubicin

The antitumor effect of doxorubicin has been introduced for the selection of this compound in order to deal with a range of cancers, such as leukemia, lymphoma, and solid tumors in humans (3). However, the limiting factor in the use of doxorubicin in the treatment of cancer is its toxic effects on vital organs, such as the heart, kidneys, and liver (4, 5). One of the main damaging mechanisms of this drug to various tissues including the heart, liver, and kidneys is related to the oxidative stress and reduction of antioxidants, and also increased oxidants in particular reactive oxygen species (6). Hence, there is a requirement to deal with oxidative stress and antioxidant compounds, in particular administration of herbal medicines. The beneficial effects of the olive plant were evaluated in the study conducted by Kumral and colleagues as an herbal remedy containing multiple antioxidant compounds (7). Kumral et al proved that the use of olive leaf ethanol extract, at the same time as doxorubicin on rats, reduces serum urea compared with a group which was treated only with doxorubicin (8). The results showed that the ethanol extract of olive leaves reduced malondialdehyde (MDA), protein carbonyl, and conjugated diene, while it also increased superoxide dismutase (SOD), glutathione (GSH), and GSH peroxidase in the kidneys (8). Today, antibiotics as antimicrobial agents are administered in the treatment of infections. The side effects of antibiotics, especially gentamicin sulfate, an antibiotic from the aminoglycosides group, have created restrictions on the use of this drug. The most well-known side effect of this anti-gram-negative bacteria antibiotic is nephrotoxicity (8-11).

The improvement of nephrotoxicity associated with the drug has been the subject of numerous research studies. In one study, it was shown that treatment of nephrotoxicity induced by gentamicin using ethanol extract of the olive leaf had a remediation effect in rats (12). Additionally, it was shown that ethanol extract of the olive leaf reduced creatinine, urea, and MDA, and also increased serum GSH, and activities of catalase (CAT) and SOD (12). In addition, the glomerular volume in the group of rats treated with gentamicin and treated olive leaf extract decreased, compared to the group treated only with gentamicin (12). In addition, using a combination of gentamicin and olive oil, this led to a reduction of urea and serum creatinine compared to the group treated only with gentamicin (12).

3.1.2. Cisplatin

Despite limitations in the use of cisplatin due to its side effects, in particular, nephrotoxicity, neurotoxicity, ototoxicity, nausea and vomiting, the drug is still considered as one of the most powerful drugs administered in cancer chemotherapy for testicular, ovarian, neck cervical, head and neck cancers (13). The role of oxidative stress and free radicals has been proven in the nephrotoxicity of cisplatin. In a study, it was shown that olive leaf extract reduced serum creatinine compared with the group treated with cisplatin (13).

3.1.3. Cyclosporine

Renal complications induced by cyclosporine A consumption have been proven in the treatment of transplant rejection and autoimmune diseases that suppress the immune system. Around 30% of patients treated with the drug are influenced by the resultant kidney complications. Acute and chronic nephrotoxicity can be defined as renal complications of this drug (14). The production of free radicals and oxidative stress are the mechanisms of creating renal damages by this drug (14). Another mechanism caused as a result of this drug is kidney damage. Other mechanisms involved in renal complications arising from the consumption of this drug include; activation of the renin-angiotensin system, increased activity of the sympathetic nervous system, increase in endothelium synthesis, induction of cytochrome P450 enzymes in renal microsomes, and vasoconstriction (15). Mostafa-Hedeab et al showed that the treatment given to rats with olive leaf extract improved renal toxicity induced by cyclosporine (14). The use of olive leaf extract increased the amount of GSH and activities of GSH, CAT, and SOD compared to the group treated with cyclosporine (14).

The mechanism of action of 2,4-dichlorophenoxyacetic acid can be justified as an herbicide by disrupting cell division and protein synthesis and overall production of oxygen-free radicals (16).

In the research conducted by Nakbi et al, the treatment of male rats given 2,4-dichlorophenoxyacetic acid was studied using hydrophilic and lipophilic compounds of olive oil (16). It was shown that renal marker levels, including creatinine, urea, albumin, and uric acid, were recovered due to their synergistic effects of these compounds. MDA levels were also improved in the group treated with olive oil. Activities of antioxidant enzymes such as CAT, superoxide (SOD) and GSH peroxidase in the group treated with olive oil increased when compared to the group given 2,4-dichlorophenoxyacetic acid, the same as the control group (16,17). Histologically, the group treated with olive oil compared to the groups

treated with combinations of hydrophilic and lipophilic compounds had a significant recovery rate in relation to glomerulus atrophy, the tubular expansion, vascular and tissue congestion, degeneration tubular, and necrosis caused by 2,4-dichlorophenoxyacetic acid (16,17).

3.1.4. Carbon tetrachloride

Carbon tetrachloride is often known as a poison that affects the liver. Cytochrome P450, as a liver enzyme, converts this toxin into the CCl3 and Cl radicals (18). The obtained CCl3 from this toxin as a free radical eventually targets the lipid membrane of endoplasmic reticulum (19). A study on improving the effects of olive leaf extract on nephrotoxicity induced by carbon tetrachloride in rats revealed that olive leaf extract, especially in a dose of 100 mg per kg (20), leads to reduced urea and creatinine in the treated groups using this extract, and an increase in serum uric acid with the same level as the control group. The activity of enzymes including SOD, CAT and GSH levels also increased, while the activity of MDA, decreased in terms of the antioxidant system. Histological studies also revealed improvements in the group treated with olive leaf extract (20).

3.1.5. Amikacin

Amikacin is widely used as an antibiotic of the aminoglycoside group in the treatment of infections caused by gram-negative bacteria (21). Today, the use of this antibiotic has been limited due to its proven toxic effects on the kidneys and side effects, such as tubular necrosis, in several studies on animal and human models. The production of oxygen-free radicals, similar to other aminoglycosides, is the main mechanism of nephrotoxicity developed by consumption of this aminoglycoside (22). Various studies, including the study of Abdel-Gayoum and colleagues, on improving the effects of olive oil and leaf extract on nephrotoxicity-induced amikacin in rats have shown that the amount of creatinine and urea decreased in those groups treated with olive oil and olive leaf extract, particularly olive oil compared to the control group. Histological studies also showed improvements in the treatment groups (23).

3.1.6. Thioacetamide

Thioacetamide can be viewed as a hepatic toxin and carcinogen (24). The toxic complications of this compound are not only limited to the liver, but involve several organs such as the kidneys, spleen, lungs, intestines, and brain (24,25). Al-Attar et al studied the protective effects of olive leaf extract on nephrotoxicity of this substance in the kidneys of mice and proved that the levels of urea and serum creatinine in the group treated with olive leaf extract reduced, but not significantly. In terms of histological, the normality of the kidney structure was proved in the group treated with the extract (24,25).

3.1.7. Chromium

Extensive use of chrome in the industry is expanding. The complications of dealing with this compound on humans are classified in a variety of types such as nephrotoxicity, hepatic toxicity, and carcinogenicity (26, 27). A study by Saber and colleagues looked at improving the effects of pure olive oil on nephrotoxicity induced by chromium in rats and revealed that olive oil reduced urea, creatinine, and MDA, while it increased SOD, CAT, and GSH in rats poisoned with chromium (27).

3.1.8. Mercuric chloride

Adverse effects of mercury chloride on human health, especially the kidneys, have been proven in various studies (28). Suggested mechanisms for the traumatic effect of this toxic substance are lipid peroxidation and hydrogen peroxide production in the mitochondria of renal cells (28). A study conducted by Necib et al on the protective effects of olive oil in renal dysfunction and oxidative stress induced by mercury chloride in rats demonstrated that treatment using olive oil reduced the IL1, IL6, TNFα, urea, creatinine, and uric acid, while it increased MDA and GSH, GSH-PX, and GST (28, 29). Acute kidney injury can be as a result of some form of renal ischemia-reperfusion. Heart failure, heart attack, kidney transplant, nephrectomy, and hemorrhagic shock are the main causes of renal ischemia-reperfusion (30). Damage to the kidneys through the renal ischemia-reperfusion can be related to oxidative stress and the production of free radicals, particularly reactive oxygen species (30). In a research, improving the effect of olive leaf extract was investigated on renal ischemia-reperfusion, and it was found that olive leaf extract reduced urea, creatinine, and serum MDA and increased GSH levels. Tubular necrosis in the groups treated with olive leaf extract was significantly increased compared to the untreated group. The inner diameter of near tubules and the amount of casts in all groups treated with olive leaf extract were significantly reduced (30).

3.2. Protective effects of olive and its various compositions on kidney stones

A high incidence of kidney stones in all societies has been observed as being a problem for public health. An aggregation of calcium oxalate crystals causes calcium oxalate stones, which are the most common type of kidney

stones. The excretion of most kidney stones is performed without pain. However, sometimes these stones are cause of obstructions. Hence, the administration of herbs in their treatment can be very useful. The effect of olive oil on the treatment of kidney stones has also been analyzed in some studies (31). Herbal preparations affect the kinetic factors of calcium oxalate crystallization in synthetic urine: implications for kidney stone therapy (31).

3.3. Protective effects of olive and its some compositions on lupus erythematosus

Lupus erythematosus is an autosomal disease that is more common in women compared to men. This autoimmune disease is caused by the spontaneous reaction of the immune system, particularly lymphocytes with the body's own tissues (32). One of the tissues involved in these diseases is the kidney, but its exact involvement mechanism is not well understood. Aparicio-Soto et al concluded in their study that female mice poisoned with Peristan, as animal models of systemic lupus erythematosus treated using olive oil, saw improved kidney damage through the activation of the HO-1/Nrf-2 antioxidant pathway, and repression activation of JAK/STAT, NF-Kb, and MAPK-induced by lupus erythematosus (33).

4. Some important chemical compositions of olive and protective effects on renal injury and other diseases

4.1. Oleuropein

The most abundant phenolic compounds in the leaves of tree are oleuropein with its bitter taste (8, 34). The antimicrobial effects of this compound against bacteria, viruses, retrovirues, fungi, yeast, and yeast have been proven (35). In addition, the inhibition effect of oleuropein on platelet aggregation and eicosanoid production affect the following: prevention of heart disease, improvement of lipid metabolism, obesity, cancer, antioxidant, anti-inflammatory, anti-atrophic, liver protective, anti-aging nervous system, and skin protector (8,35-37). A study by Mahmoudi et al showed the protective effect of oleuropein on the kidneys of lactating rats affected by Bisphenol A (38). The results showed that, in mother and baby groups treated with the phenolic compounds, the urea and serum creatinine returned to normal levels, while the MDA level decreased significantly. A significant increase in the amount of CAT and total antioxidant capacity was observed in the groups treated with oleuropein. Histologically, the glomerular necrosis decreased especially in near and far twisted tubules in the groups treated with oleuropein. Ahmadvand et al studied the effects of oleuropein on lipid peroxidation, lipid profile, atherogenic index, and paraoxonase 1 in rats. Nephrotoxicity in rats using gentamicin revealed a significant decrease in level of MDA, triglycerides, cholesterol, LDL-C, VLDL and atherogenic index in the groups treated with oleuropein. In contrast, oleuropein additionally increased level of HDL-C and PON1 (paraoxonase 1) activity in treated group (8,37,39). In another study on the protective effects of oleuropein against cisplatin-induced nephrotoxicity in mice animal models, it was found that oral administration of oleuropein, particularly in a dose of 20 mg/kg, reduced urea and serum creatinine (8). Coping with oxidative stress, inflammation, decreased apoptosis, and inhibition of MAPK/ERK pathway signaling pathways, suppression of other signaling pathways, including MAPK and the inhibition of ERK, are among the additional effects of oleuropein in order to improve the nephrotoxicity damage induced by cisplatin (40).

In another study on the antioxidant effects of oleuropein in the treatment of renal failure caused by bacterial lipopolysaccharide, it was shown that the levels of urea and creatinine decreased in those groups treated with oleuropein. The parameters of antioxidant enzymes such as SOD, CAT and GPX also increased in the group treated with oleuropein. Histological studies showed the healing effects of this substance (8,34,41).

4.2. Oleic acid

Seventy-two percent of olive oil is formed from a monounsaturated fatty acid called oleic acid (42). A double bond in this fatty acid gives some advantages over olive oil, such as its antioxidant properties (42). Various anti-cancer therapeutic effects of this fatty acid on chemical protection have been proven in a range of cancers such as colorectal and breast cancer (42). In one study, the effect of nitro-oleic acid was proven in renal ischemia-reperfusion (43). In this study, plasma urea and creatinine, tissue myeloperoxidase (MPO), the expression of inflammatory factors and cytokines, renal oxidative stress, and tissue damage of the kidneys in mice treated with nitro-oleic acid decreased compared to renal ischemia-reperfusion (43). In another study, the effect of oleic acid was investigated on the growth of monkey kidney cells. In this study, it was proved that 10 to 20 µg/ml of oleic acid can be used as a supplement to cell growth in serum replaced by MK2. However, levels higher than 20µg can cause an inhibition of cell growth (44).

4.3. Hydroxytyrosol

Hydroxytyrosol as a simple phenolic compound comprises a major part of phenolic compounds in olive oil (45). This combination is obtained from hydrolysis of secoiridoids,

such as oleuropein and oligodendrocyte (45). The highest antioxidant activity of phenolic compounds in olive oil can be attributed to hydroxytyrosol. The reason for its antioxidant, anti-oxidation of LDL-C, anti-tumor, anti-inflammatory, inhibiting activation of endothelial cells, anti-atherogenic, anti-thrombotic, cholesterol-lowering, decreased immune response, protection of red blood cells against H2O2, antiplatelet, anti-cancer and cardiovascular protective properties of this compound can be related to its powerful anti-free-radical properties (45,46). Deiana et al, studied the LLC-PK1 cell line from pig epithelial cells and found that glucuronide metabolites obtained from hydroxytyrosol inhibit oxidative damage and cell death (47). The inhibition is performed through a significant inhibition of MDA, fatty acid hydroperoxides, and 7-Ketocholestrol. In another study conducted by Deiana et al (47), the effect of hydroxytyrosol and its metabolite, homovanillic alcohol was investigated on renal epithelial LLC-PK1 cells damaged by H2O2. In this study, the protective effect of homovanillic alcohol and hydroxytyrosol in a dose of 10 µmole was evaluated on lipid peroxidation induced by H2O2. In fact, a 10 µmole dose of homovanillic alcohol and hydroxytyrosol reduced the MDA and increased unsaturated fatty acids and cholesterol (47). In total, the protective effect of hydroxytyrosol was reported more than the metabolites of homovanillic alcohol. Other studies, including a study conducted by Loru and colleagues on LLC-PK1 kidney cells, revealed that doses of 1, 5 and 10 µM of hydroxytyrosol, especially a dose of 10 µM, decreases the MDA level in treated group compared with control group (48). Therefore, hydroxytyrosol, with its antioxidant properties, inhibits the production of fatty acids, hydroperoxides and 7-Ketocholesterol. In another study on the protective effects of hydroxytyrosol in nephrotoxicity induced by cyclosporine, it was proven that this phenolic compound eliminates superoxide produced by cyclosporine (49). Additionally, hydroxytyrosol increases GSH, but has no protective effect on the GFR, the aorta, renal artery systolic and diastolic pressures (49). Other studies, such as the study conducted by Capasso and colleagues on immortal rat kidney cells, showed that hydroxytyrosol inhibits peroxidation of the membrane lipid and generates reactive oxygen species, resulting in a protective effect against renal toxicity (49). Hamden and colleagues demonstrated that hydroxytyrosol increased the activity of antioxidant enzymes such as CAT, SOD, and GSH peroxidase, and reduced lipid peroxidation and urea and serum creatinine levels in the kidneys (50). The study conducted by Mahmoudi et al, on the protective effect of hydroxytyrosol on the kidneys of lactating rats affected by Bisphenol A and their offspring, revealed that, in both mothers and offspring groups treated with this phenolic compound, serum creatinine returned to normal and MDA levels decreased significantly (38). An increase in the amount of CAT and total antioxidant capacity was observed in the groups treated with hydroxytyrosol. Histologically, glomerular necrosis and, in particular, tubular necrosis of the near and far twisted tubules decreased in the groups treated with hydroxytyrosol (48).

4.5. Tyrosol

The olive tree – and, more specifically, pure olive oil – can be considered as one of the main sources of tyrosol (4- (2-hydroxy ethyl phenol)) as a phenol compound (51). Several properties have been introduced for tyrosol, including antioxidants, especially against the oxidant compounds such as peroxynitrite and superoxide anti-neoplastic, anti-osteoporosis, inhibiting the oxidation of LDL-C, anti-stress properties, anti-depressants, anti-inflammatory, protective cardiovascular system and nervous system protection (51,52). In the study conducted by Chandramohan et al, the administration of tyrosol in rats with diabetes increased the activity of hexokinase and glucose-6-phosphate dehydrogenase enzyme in the animals' kidneys (53). On the other hand, the recovery of activity of carboxymethyl pyruvate kinase, fructose 1, 6-bisphosphatase, and glucose 6-phosphatase was observed in the kidneys of diabetic rats using this antioxidant. In addition to the mentioned effects, tyrosol led to the recovery of activities of enzymatic and non-enzymatic antioxidants (vitamins E and C) in all mice treated with this compound (53).

5. Conclusions

According to the previous studies, acute and chronic kidney diseases are among those factors that can lead to renal failure and, hence, impose real costs to the economy. On the one hand, due to the complexity of the pathogenesis of the disease, it is possible that different systems are mostly involved in the pathogenesis of kidney disease, especially oxidative stress and the production of free radicals such as reactive oxygen species. Therefore, according to the mechanism of pathogenicity, appropriate therapeutic strategies for the treatment of these diseases often involves the elimination of the antioxidant compounds through antioxidant treatment and by strengthening the internal antioxidant system, and weighing the scales toward the antioxidant compounds against the oxidant compounds. In order to provide antioxidant sources for the treatment of kidney diseases, many chemical drugs are currently used. However, due to their various side effects, the

use of antioxidant compounds derived from plants have been recommended in various and related studies as rich resources. However, various active ingredients (oleuropein, hydroxytyrosol and oleic acid) are derived from different parts of the olive plant, such as leaves, fruits, and their products. Olive oil that can be used as a protective compound for coping with kidney disease (renal toxicity, renal ischemia-reperfusion, kidney stones, kidney damage caused by lupus erythematosus and urinary tract infections) and reduce kidney damage parameters (urea, creatinine and MDA), as mentioned above. Hence, it is suggested that, due to the numerous health benefits of the olive tree that have been listed and its active components, and the scant studies on the effects of herbal treatments for diseases, especially renal damage, further studies should be conducted in this field in order to discover further pharmaceutical products from this plant.

Authors' contribution

Primary draft; HA and RMK. Editing the final manuscript: HA. All authors read and sign the final paper.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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