



# Oxidative stress, free radicals, kidney disease and plant antioxidants

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## Abstract

Over generation of reactive molecules leads to oxidative stress which is a causative agent of many diseases occurrence including kidney disease. Oxidative stress at kidney tissue induces the cellular signaling pathways which may activate construction of growth and pro-inflammatory mediators, finally, lead to glomerulosclerosis and renal fibrosis. Both enzymatic and low molecular weight antioxidants are able to ameliorate these injurious impacts. Therefore, antioxidants are chemoprotective agents that neutralize cellular macromolecules oxidative damages. Numerous components are recognized to exert antioxidative properties that are originated from medicinal plants and have been administering as resourceful therapeutic approach in various diseases such as kidney failure. Therefore, we summarized the nephron-protective effects of several medicinal plants which are recently investigated at clinical trials.

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## Introduction

Kidney is a susceptible organ to reactive oxygen species (ROS) generated cellular injuries, because of polyunsaturated fatty acids abundance in its cellular compositions. ROS may induce the pathological mechanisms which cause glomerulosclerosis, tubulointerstitial fibrosis, tubular cells apoptosis and senescence, and also deactivated cellular regenerative pathways (1), which finally result to disturb glomerular filtration rate (GFR). Renal failure is usually prevalent and adversely influences human health, life span and raises costs to health-care systems in throughout the world. Renal toxicities, glomerulonephritis, vasculopathies and diabetic nephropathy may promote oxidative conditions, increase susceptibility of acute renal failure (2).

This review will begin with an introduction from basic molecular mechanisms of radicals and pro-oxidants metabolism, with a brief description of oxidative stress phenomenon and with a definition of antioxidant defense systems of living systems. Finally, this review will briefly discuss impacts of several medicinal plants on preventing and improving of oxidative stress induced renal injury.

## Materials and Methods

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## Key point

Antioxidants are chemoprotective substances that neutralize cellular macromolecules oxidative damages. Numerous components are identified to exert antioxidative efficacies that are originated from medicinal plants and have been administering as resourceful therapeutic approach in various diseases such as kidney failure.

journals (DOAJ), Google Scholar, and Web of Science were searched with key words as; oxidative stress, endothelial dysfunction, renal injury, diabetes mellitus, reactive oxygen species, kidney disease and plant antioxidants.

## Reactive species

All cellular processes such as growth, regulation and biosynthesis are chemically intra- and intermolecular reactions that cause some compounds (reductant or reducing agent) donate electrons or hydrogen and some others (oxidant or oxidizing agent) accept electrons or donate oxygen. Those reactions are called redox. Atoms and molecules containing unpaired electrons are at unstable energy conditions, therefore, they tend to accept electrons from other molecules to convert to the molecules with lowest energy state. These unstable



compounds with one or two unpaired electrons are called radical that are able to change chemical structure and reactivity of other molecules following redox reactions. In some papers, radicals are often incorrectly called free-radical which is inaccurate term, because, a radical is always free. Reactivity is another term which describes the tendency of a substance has been undergone chemical reaction. It depends on the nature and concentration of reactant (3). All radicals are not highly reactive and all reactive substances are not radical. Reactive molecules can also be produced during normal cellular metabolism. Reactive species (RSs) originated from oxygen are one of them. Oxygen molecule is an essential component for aerobic metabolism and life. Electron-transport chain (ETC) occurs in internal mitochondrial membrane and oxygen is diminished to water by cytochrome oxidase. Less than 10% of consumed oxygen in aerobic metabolism is changed to ROS (hydroxyl and superoxide radicals, hydrogen peroxide) through one-electron continuous pathways. Peroxides can react with cellular macromolecules such as lipids, nucleic acids and proteins and form peroxides that are oxygen originated. Others RSs are capable to donate oxygen to other substances. There are also other reactive species, such as reactive nitrosative species (nitric oxide, peroxynitrite, and related compounds), carbonyl (glyoxal, methylglyoxal), carbon, sulfur, halogens, and so on (4).

All of reactive species (RSs) have various wide range of reactivity with biological compounds. Therefore, similar responses are not resulted at redox reactions. Lipid peroxides are a form of peroxy radicals which result from peroxidation of polyunsaturated fatty acids with two or more double bonds. However, they have capability to generate malondialdehyde (MDA) as a decomposition product with low reactivity, but it is potentially harmful for other cellular macromolecules such as proteins and nucleic acids. The alternations of DNA structure and gene expression are produced from interaction of MDA and nucleic acids which finally may result in forming cancerous cells (5).

Some normal cellular functions such as responding to stimulus and regulation of intracellular signaling pathways are directed by some RSs interaction. Enzymatic pathways including the activity of membrane-bound NADH and NADPH oxidases, the metabolism of arachidonic acid by lipoxygenase, the activity of xanthine oxidase, cyclooxygenases (COX) and as well as the mitochondrial cytochrome P450 generate ROS which may have harmful consequences at cellular imbalance redox conditions (6,7). NADPH oxidases expanding family, a superoxide-producing system, exists in cytosol of non-phagocytic and phagocytic cells which it is able to induce cellular transformation or senescence.

### Pro-oxidants

Human are in exposure of many environmental chemicals dependent on their life style, such as metals (cadmium, lead and arsenic), pesticides, fungal toxins, ionizing and

nonionizing radiation, ethanol intake, drugs and as well as smoking. They disrupt the biological processes and exert serious adverse effects. In biological environments, every compound is able to accept electrons (oxidant or oxidizing agent) and induce the production of various radicals and a non-radical compound is named pro-oxidant (8).

Lead and cadmium are environmental pollutants which induce generation of RSs and/or reduction of the antioxidant defense system to promote oxidative damage in various tissues. Kidney is one of target organs for these pollutants which can cause acute and chronic nephropathy. Cadmium induces lipid peroxidation through upregulating NO generation that can react with super oxide anions and finally, promotes peroxynitrate production. This toxic metal also generates ROS through increasing free available iron which is capacity to participate at Fenton reaction, as a result of replacing iron ions in various cytoplasmic and membrane proteins. Lead and cadmium also enable to inactivate the enzymatic-antioxidative system such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) through reacting with SH-groups of enzymes and replacing the divalent cations which contribute to enzymes structures (9).

Likewise, arsenic is other dangerous metal that has different range of toxicity depending on its oxidation state, longtime exposure and chemical form. It is responsible to suppress antioxidative defense system, damage to mitochondria structure, change energy metabolism and in addition increase lipid peroxidation in renal cells (10). Chronic ethanol consumption is another cause of oxidative nephropathy. Hyperacetylation of mitochondrial proteins of renal tubular cells and hepatocytes are induced at early stage of ethanol toxicity. Subsequently, numerous metabolic enzymes functions and antioxidative pathways such as lipid and proteins metabolism, oxidative phosphorylation, glutathione and as well as thioredoxin, are interrupted concurrent with deletion of renal total antioxidant capacity (11).

Some elements need a little amount for normal physiological functions such as zinc (Zn), copper (Cu), iron, selenium and so on. These trace elements are necessary to apply enzymes activity that involve at antioxidative defense system, carbohydrate and lipid metabolisms. Cu is one of these elements, participates at structure of numerous enzymes such as Cu, Zn-SOD which enables to convert superoxide anion to  $H_2O_2$ , therefore, Cu deficiency leads cells to be susceptible to oxidative damage. Recent investigations have reported Cu deficiency increases DNA injury at Jurkat T-lymphocytes. Free Cu ions can also participate in redox reaction and induce cellular toxicity through catalyzing hydroxyl radicals formation in the presence of superoxide anions or reducing agents, therefore Cu ions can act as pro-oxidant or/and antioxidant agent at biological systems.

Iron is other critical trace elements for cell growth, oxygen utilization, various enzymes activity and response of immune system. Excess ionic iron (abnormal iron metabolism) intensifies redox reactions as a transition

metal and induces cellular oxidative damage.  $H_2O_2$  molecules are converted into toxic hydroxyl radical by Iron at Fenton reaction. Formation of ferric and ferrous at redox reduction can increase generation of numerous radicals, hence promoting tissue damage (12).

### Oxidative stress

If removal and generation processes of reactive species stay at dynamic steady state, cells can save normal biological processes. Sometimes redox steady state is disrupted as the result of biomolecules damage and disorder of signaling pathways which have been accrued by the imbalance between the oxidizing and reducing agents. The cell is at toxic situation that is called oxidative stress, damage and injury or toxic oxidation. All these terms have the same meaning. There are several reasons for disturbing cellular redox balance and occurrence of oxidative stress including 1) increasing autoxidation of endogenous and exogenous compounds lead to ROS generation; 2) depletion or inactivation of reductants (antioxidative compounds); and 3) decreasing reductants production. Oxidative damage outcomes are different and depend on the amount, and place of reactive species production, ROS type, the performance of antioxidative systems and as well as cellular targets that interact with (4). Cell can be adaptation with oxidative stress through regenerating damaged molecules or activating apoptotic signaling pathways.

The several signaling pathways or central mediators are activated in response to oxidative stress, including p38 mitogen-activated protein kinase (MAPK), the extracellular signal-regulated kinase (ERK) and c-Jun amino-terminal kinase (JNK) signaling cascades, p53 activation, the phosphoinositide 3-kinase (PI 3 K)/Akt pathway, the nuclear factor (NF)- $\kappa$ B signaling system and the heat shock response. They are not activated only in oxidative injury (8). Oxidative stress may be main pathological process of the numerous diseases such as cardiovascular complications (atherosclerosis, hypertension), ischemia-reperfusion, cystic fibrosis, cancer, type-2 diabetes and nephropathies, pregnancy-related disorder, schizophrenia, Parkinson's and Alzheimer's diseases and so on (13).

Inflammation and oxidative stress are inseparably linked and both of them initiate the occurrence of other and can damage to cellular organelles via triggering several signaling pathways such as the nuclear translocation of NF- $\kappa$ B signaling pathways which finally activate phagocytic immune cells and promote the generation of reactive nitrogen and oxygen species. Among inflammation, up-regulating adhesion molecules expression and pro-inflammatory cytokines, intensify the imbalance of arachidonic acid metabolites and chemoattractant molecules increase endothelial dysfunction that eventually lead to the development of hypertension and atherosclerosis (14). Inflammation, as a major cause of organ injury, has critical role in pathological processes of metabolic disorders, such as diabetic ketoacidosis.

Diabetes mellitus is a pro-inflammatory state that induces activation of signaling pathway such as NF- $\kappa$ B signaling

systems hence enhancing micro- and macrovascular injury and endothelial dysfunction. The multiple productions of pro-inflammatory mediators can play an important role at diabetic nephropathy. Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) is the one of endothelial pro-inflammatory factor that has cytotoxic effects and induces ROS generation in patients with diabetic nephropathy. In addition, advanced glycation end products (AGEs) have been recognized as one of the multiple factors resulted from hyperglycemia. AGEs formation are able to alter renal mesangial cells function via expressing and activating of pathogenic mediators and aggravating diabetic nephropathy related complications (15).

### Antioxidants and herbal antioxidative components

Any stable substance is able to donate electron(s) or hydrogen to RSs for neutralizing them and prevent from oxidative damage to cellular structure, is called antioxidant. Continuous exposures to various types of RSs lead the cell to promote defense mechanisms for presenting efficient protection against reactive metabolites. One of the most important approaches is composed of components, are called antioxidant and capable effectively to repair an oxidative injury site on macromolecules. Two major groups of antioxidative compounds contain of enzymes and low-molecular-weight antioxidants (LMWA) which may provide maximum protection for biological systems. Antioxidants interact directly or indirectly with RS. Numerous antioxidative enzymes remove directly pro-oxidants and repair or prevent the RS caused damage, but some of them can act indirectly through regenerating and protecting from oxidized antioxidants. There are three most important enzymes that are essential for all oxygen-metabolizing cells, including CAT, SOD and GPx. The SOD converts superoxide anions radicals into molecular oxygen ( $O_2$ ) and hydrogen peroxide, whereas the CAT and peroxidases alter hydrogen peroxide into water and, in CAT case, into water and oxygen.

LMWA can chelate transition metals such as Fe and Cu ions to prevent from participating in the metal-mediated Haber-Weiss reaction. Furthermore, they are responsible for interacting indirectly with RS through scavenging radicals and disrupting their reaction with cellular macromolecules. LMWAs cope RSs if their concentration is adequately high.

These scavengers are localized in cell and regenerated at oxidative condition. They are converted to a radical scavenger by itself while removing the RSs. Radical scavenger can be regenerated to its reduced form by another scavengers which possesses an efficient oxidizing ability.

Dietary sources, mainly, and biosynthetic processes within living systems may provide LMWAs. Histidine dipeptides, glutathione, uric acid, lipoic acid and bilirubin are generated as waste products that also possess antioxidative activities (16).

Most of the reducing agents are derived from dietary sources. There are large numbers of antioxidant molecules

in vegetables, fruit, meat, nutritional supplements and fish including small molecules like tocopherols, flavonoids, polyphenols, carotenoids and ascorbic acid. They possess ability to donate electrons and act as antioxidants. Each of these antioxidative nutrients frequently act synergistically to promote body total antioxidant capacity.

Antioxidants such as phenolics, xanthenes, flavonoids, tannins, coumarins, curcumanoids, lignans and terpenoids are detected in various plant products such as fruits, leaves, seeds, and oils. Therefore, consume of plants containing antioxidative components are recommended to increase protection ability of living systems against oxidative damage.

One of potent antioxidative and radicals scavenger component which persists abundantly in herbal extracts and fruits is ellagic acid that has been detected as an antidiabetic, anti-inflammatory and antioxidative agent. While, it is able to straightforwardly prevent NF- $\kappa$ B pathway across inhibiting the high glucose induced NF- $\kappa$ B activation and synthesis of pro-inflammatory cytokines (TNF $\alpha$ , IL-1 and IL-6) in proximal tubular epithelial cells of rat. Hence decreasing renal cell inflammation and oxidative stress might have ameliorated renal function in diabetic rats (17).

Quercetin exists naturally in a variety of brightly colored plant-based foods such as capers, apple, onion, corn, cocoa, tea, pepper, bean, lovage leave, etc. This flavonoid component has anti-apoptotic, anti-oxidative and anti-inflammatory properties. Recent studies have been showed that quercetin can protect kidney from injury induced by nephrotoxins such as lead by reducing RS generation, renewing the activities of antioxidant enzymes such as Zn/Cu-SOD and GPX, ameliorating DNA oxidative damage and as well as prevention from apoptosis (18).

Anthocyanin is a flavonoid component and water-soluble vacuolar natural pigment that depending on the pH can be red, purple, or blue. Anthocyanins have been confirmed as antioxidative components which are applicable to scavenge active oxygen radicals and prevent carcinogenesis. Purple sweet potato (PSP) is a rich source for anthocyanins. While they have stability and good color tone. Hence they have been used as a source of pigments in food industry. PSP pigments are able to inhibit the activation of I kappa B kinase b (IKKb), and decrease the expression oxidative stress-associated AGE receptor (RAGE), NF- $\kappa$ B and thioredoxin interacting protein (TXNIP) in the upstream of NLRP3 inflammasome, hence they are potentially anti-inflammatory constituents. Considering key role of inflammation in pathological processes of metabolic disorders and PSPC is potential anti-inflammatory and oxidative component, Shan et al have evaluated the effect of PSPC on renal damage induced by high fat diet (HFD) and reported the inhibitory effects of PSPC on NLRP3 signaling pathways in HFD associated kidney injury (19). Marjoram (*Origanum majorana* L.), of *Lamiaceae* family, was known as a happiness symbol at ancient Greek that its growth on the grave would result eternally gladness at the deceased. Usually, the dried leaves and flowering

tops of Marjoram. are consumed as a medicinal plants. It comprises phenolic terpenoids (thymol, carvacrol), phenolic glycosides (arbutin, orientin, thymonin, methyl arbutin, vitexin), flavonoids (diosmetin, luteolin, apigenin), tannins, hydroquinone, phenolic glycosides triacontan, sitosterol, *cis*-sabinene hydrate and acids (oleanolic acid). The antimicrobial and anti-septic properties of marjoram are ascribed to ursolic acid, thymol and carvacrol. Its antioxidative and antitumor properties have recently been determined. Ursolic acid is capable to diminish amyloid beta protein-induced oxidative cell death. Many researchers have reported its alcoholic and aqueous extracts possess radical scavenger and protein glycation inhibitory activities. This vegetable is a potent agent for reducing AGEs generation, thus preventing from aggravation of diabetic kidney disease (20). Likewise, el-Ashmawy et al have suggested its alcoholic, volatile oil and aqueous extracts influence a hepato-renal protection impact against lead induced toxicity (21).

*Salvia*, the largest genus of the *Lamiaceae* family, is defined as very powerful aromatic plants. *Salvia officinalis* L. (sage) has been used as traditional herbal medicine against a variety of diseases. Rosmarinic acid, phenolic acids, carnosic compounds and flavonoids or their derivatives exist in sage extract. It possesses antioxidative (lipid peroxidation inhibitory and radical scavenger impacts), anti-bacterial, anti-inflammatory, fungistatic and virustatic capabilities and as well as insulin sensitizer and hypoglycemic impacts on streptozotocin-induced hyperglycemic rats. Sage has been proposed to have the agonistic activities on peroxisome proliferator-activated receptors- $\gamma$  (PPAR- $\gamma$ ) that attribute to the metabolism of glucose and lipids, therefore can consume as therapeutic agent in hyperlipidemia and type 2 diabetes mellitus (22,23).

Lemon balm (*Melissa officinalis*) is administered in cosmetics, perfumes, food and tea products in many countries, and it has been known as a mild sedative, a spasmolytic and an antibacterial agent. Polyphenolic compounds, such as rosmarinic acid, trimeric compounds and some flavonoids are in lemon balm leaves. Lemon balm essential oils has strong antioxidant activity due to its high contents of tocopherols, neral and geranial volatile oils (strong lemon odors). It is able to enhance glucose uptake (via activating glucokinase) and metabolism of glucose in adipose tissues and liver (through inhibiting phosphoenolpyruvate carboxykinase [PEPCK] and glucose-6-phosphatase and increasing expression of PPAR $\gamma$ , PPAR $\alpha$ , GLUT4 and sterol regulatory element-binding protein [SREBP]-1c), therefore possessing hypolipidaemic and hypoglycaemic effects that can be administered as an antidiabetic modality. These plants have ability to prevent the diabetic nephropathies development (24).

*Asparagus officinalis* L. was named as "the king of vegetables" because it is rich of bioactive components. It contains large amount nutrients such as dietary fiber, oligosaccharides, amino acid derivatives, vitamins and

minerals. In addition, bioactive components, such as lignin, steroidal saponin and flavonoids exist abundantly in it. It has wide range medicinal consumptions including nephropathy treatment, anti-inflammation, antimutagen, antifungal, antibacterial, anti-secretory, antineoplastic and antioxidative, as well as reducer of blood glucose by increasing pancreatic insulin release and so on. Quercetin, rutin, ferulic acid, kaempferol and isorhamnetin are five identified antioxidant compounds of asparagus that can prevent from lipid peroxidation and proteins oxidation (25). Additionally, *A. racemosus* extract has been reported to have beneficial effects in the early diabetic nephropathy treatment while it is effective to reduce important factors related the diabetic nephropathy progression in diabetic rats like creatinine, blood urea nitrogen (BUN), nitrogen amount, hyperglycemia and finally oxidative stress indices. *Achillea millefolium* L. (Asteraceae) is a perpetual plant that has been mostly administered in traditional medicine. Its raw material contains terpenes, alkaloids, bases, coumarins, saponins, tannins, sterols, vitamins, amino and fatty acids, phenolic compounds such as flavonoids (luteolin, rutin, casticin, centaureidin, apigenin, quercetin, acacetin, isorhamnetin, and artemetin) and phenolcarboxylic acids. Its anti-inflammatory, antimicrobial and antioxidative and cytotoxic activities are chiefly ascribed to the phenolcarboxylic acid and flavonoid compound. The anti-diabetic properties of its extracts are related to its antioxidant potential. Also, recent studies have been reported artemetin has antioxidant and anti-inflammatory activities and is capable to lower blood pressure in animal models. It is not only the active compound of achillea plants, but antihypertensive impact of its crude extract certainly is attenuated to artemetin (26).

Pomegranate, or *Punica granatum*, has been administered as a fruit and medicinal agent in South America and Asia. The pomegranate plant contains mannite, alkaloids, ellagic acid, and the bark and rind contain various tannins such as ellagitannins (as punicalagins). Its polyphenols have suitable impacts such as the antioxidative activity, protection of low-density lipoprotein (LDL) from oxidation by their direct interaction with the lipoproteins and indirect effect through their accumulation in arterial phagocytes, reduce blood lipid and glucose concentration through upregulating glucose transporter 4 (GLUT4) into cellular membrane and lower blood pressure. The renal ischemia-reperfusion injury induced oxidative damage is ameliorated by pomegranate bioactive constituents. Their anti-oxidative and anti-inflammatory components are effective to decline the probability of atherosclerosis and vascular disorders in renal failure patients (27).

### Conclusion

Oxidative stress is known as a main pathological process in renal failure which activates various pro-inflammatory cytokines and growth factors, finally leads to glomerulosclerosis, tubulointerstitial fibrosis, tubular cells apoptosis and senescence, as well as deactivated

cellular regenerative pathways. There are natural bioactive components in foods and plants that can protect organs against ROSs. They may be a resourceful and safe therapeutic strategy in improvement and prevention of renal failure.

### Author's contribution

FDS was the single author of the manuscript.

### Ethical considerations

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

### Conflicts of interest

None to be declared.

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