

Kidney Tubular Cell Protection; Recent Findings

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Acute renal failure (ARF) or acute kidney injury (AKI) may develop due to numerous factors including obstruction of the urinary tract, toxic substances to kidney and low blood volume^[1-3]. Acute renal failure may lead to numerous complications including metabolic acidosis, uremia and changes in body fluid balance. The diagnosis of acute kidney injury is based mainly on the laboratory findings, such as blood creatinine and urea nitrogen. Management includes treatment of the underlying disorder and supportive care^[4-8]. Recently, attentions are mostly on protection or prevention as well as accelerating the regeneration of tubular cells against injurious insults to the kidney. To study acute kidney injury, various models have been defined for each specific condition. Gentamicin (GM) which is an aminoglycoside antibiotic and is derived from gram-positive bacteria, has a potential for the treatment of aerobic gram-negative infections. Gentamicin is extensively used for induction of ARF in preclinical studies and evaluation of renal protective agents. Gentamicin is usually accumulated in kidney proximal tubular cells which may trigger renal injury, leading to brush border network damage^[9,11]. The kidney toxicity is usually caused by increased free radical production, suppression of antioxidant defense mechanisms as well as acute renal tubular cells necrosis^[9-12], which lead to kidney dysfunction and diminished glomerular filtration rate (GFR). The pathological mechanisms include increase in endothelin-1 augmentation of oxidative stress, upregulation of transforming growth factor-beta (TGF- β), apoptosis, significant increase in

monocyte/macrophage infiltration into the renal cortex or medulla and eventually necrosis^[10-15]. Gentamicin has also been shown to increase the generation of reactive oxygen species (ROS), hydrogen peroxide, superoxide anions and hydroxyl radicals in proximal tubular cells, leading to kidney damage^[9,10]. Therefore, scientists usually focus on the use of various antioxidants for the treatment of gentamicin renal toxicity^[9,10]. In this regards, the role of antioxidants in mitigating the gentamicin renal toxicity protection, tubular effects and integrative glomerular and possible interplay have been described. Oxidative stress is induced by an increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) and/or decrease in body antioxidants. Indeed it is usually described as an imbalance between the level of production and removal of cell oxidants. This imbalance causes a decline in the ability of biological systems in detoxification of the reactive intermediates or repair of the resulting damage. Therefore, in gentamicin administration in should be noted that it might induce severe renal toxicity. The renal toxicity of gentamicin is high enough to be used in the study of drug-induced acute kidney damage. In fact, acute renal toxicity is a common clinical entity with high mortality and morbidity rates which has been attributed to induction of oxidative stress in the kidney^[8-11]. Renal toxicity may also be induced by other complications like diabetes, chronic renal failure or vascular complications, all of which induce oxidative stress and hence put the patients at higher risk of acute renal failure due to ischemic and nephrotoxic insults^[11-15]. Medicinal plants which mostly possess a lot of phytochemicals with antioxidant properties have been recently in the focus of researchers and scientists for treatment and prevention of various oxidative stress-related complications^[8,16,17]. These plants have antioxidant activities due to phytochemicals including phenolic and carotenoid compounds^[16-19]. Phenolic compounds are abundantly presented in herbal medicines and food products and mainly consist of flavonoids, anthocyanins, phenolic acids and tannins with antioxidant activities^[16-21]. These

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compounds and carotenoids have been shown to reduce the risk of several chronic and degenerative complications^[19]. Kidney damage induced by oxidative stress is associated with increased ROS/RNS production which is significantly prevented by these compounds^[8,18-24]. Medicinal plants antioxidants elaborate endogenous antioxidants capacity to protect renal damage by reduction of lipid peroxidation (LPO)^[17-23]. Tocotrienol, a member of vitamin E family with antioxidant activity, supplementation has been shown to increase catalase activity and glutathione level and reduce renal LPO, resulting in proximal tubular injury^[18-24]. Furthermore, it has been able to improve the index of NO₂/NO₃ generation. Tocotrienol has also been shown to protect the renal injury induced by potassium dichromate ^[19-26]. Ligustrazine, an alkaloid extracted from *Ligusticum wallichii* with antioxidant activity, was able to protect the kidneys from ischemia/reperfusion injuries by decreasing ROS generation, reducing MDA, and elevating SOD activity^[20-23]. Troxerutin, abundantly found in tea, coffee, cereal grain and a variety of vegetables and fruits, has been shown to reduce oxidative stress-induced kidney damage^[23-25]. It is able to reduce malondialdehyde level and enhance antioxidant enzyme activities, including catalase, SOD, GPx, and Cu/Zn^[18-26]. As mentioned above, antioxidants mechanism of action is giving electrons to free radicals and trying to turn them neutral. People who intake low vegetables and fruits are at greater risk of developing some complications compared to others. Although free radicals are known to contribute to kidney injury, nephrotoxicity^[26,27], hepatotoxicity, diabetes, heart disease^[19-27], atherosclerosis^[20-28], vision loss and cognition complications^[21-30], and abundant researches, particularly laboratory trials, have shown the beneficial effects of antioxidants against these complications, long term clinical trials do not uniformly confirm this matter. This is especially true for single antioxidant therapy. It seems that the molecules found naturally in grains, fruits and vegetables, usually act to prevent a variety of complications like kidney and liver injuries, but not all antioxidants in different conditions act the same^[26-30]. The result evidences related to the consumption of single antioxidants such as vitamin E or vitamin C are contrary^[16,17, 26-30], however ameliorative effect of vitamin E

against cisplatin-nephrotoxicity in our previous study was observed^[31]. Similarly, ameliorative property of vitamin E and vitamin A on the protection of kidney scarring in children with acute pyelonephritis was also observed by Sobooti et al^[32]. Also, findings about the consumption of antioxidant combinations are not entirely clear. However, it seems that natural products, especially fruits, vegetables and grains are more reliable in protecting kidney complications^[16,17,26-34]. Likewise Ashtiyani et al found, grape seed extract abolishes kidney disturbances following reperfusion in rats in their recent study^[35]. In this regard, the lack of beneficial effect of a single or even a combination of antioxidants is not clear. What is clear is that antioxidants system in the body is complex and antioxidants usually act as parts of complicated networks. Therefore, a single antioxidant cannot do the same as the whole^[8,16,17,30-33]. Although it has been shown that eating grains, fruits, grains and vegetables, which are rich in antioxidants, provides protection against oxidative stress induced complications such as kidney and liver injuries, however, this does not mean that antioxidants will prevent or cure the problem, especially not when they are taken out of their natural context^[8,16,17,30-33].

Oxidative stress contributes to kidney damage by increase of oxidative stress, particularly insufficiency of endogenous antioxidant defense system. Medicinal plants antioxidants have been demonstrated to prevent oxidative induced kidney damage by reduction of lipid peroxidation and increase in scavenging ability of antioxidant defense system. Consumption of medicinal plants antioxidants seem to be important remedies to abrogate pathology of oxidative stress induced kidney injury, but single and even combination of antioxidants do not act the same as whole natural products.

Key words: Acute Renal Failure; Acute Kidney Injury; Medicinal Plants; Oxidative Stress; Reactive Oxygen Species

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