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Letter to the Editor

Mechanistic Impacts of Medicinal Plants in Diabetic Kidney Disease

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Dear Editor-in-Chief

Herbal medicines have been traditionally used for the treatment of diabetes mellitus (1). Some medicinal plants contain compounds that can be effective in impaired glucose tolerance. Recent pre-clinical and clinical trials have also demonstrated their beneficial effects on diabetes associated complications, especially on diabetic nephropathy (2-7). Although some plants have been shown to have toxic effects (8), hut several species with beneficial effects on diabetes mellitus and in the prevention of kidney complications in diabetic patients have been identified. These effects have been observed with both bioactive compounds and crude extracts isolated from anti-diabetic plants. In particular, plants such as *Sclerocarya birrea*, *Persea americana*, *Ficus thonningii* and *Helichrysium ceres* have been shown to have renoprotective effects (9-12). Isolated compounds such as oleanolic acid have also been shown to possess renoprotective effects in experimental diabetes in animals. Hence oleanolic acid caused an increase in renal Na^+ excretion in streptozotocin-induced diabetic rats, which was mediated by an improvement in glomerular filtration rate (13).

Initial studies have shown that these plants ameliorated kidney dysfunction in experimentally induced diabetes in rodents. However, the exact effects on human are not clear and should be established. There are various mechanisms by which renoprotection may be achieved, including increase in formation of advanced glycation end-products (AGEs), oxidative stress, and activation of hexosamine flux, causing inflammation and kidney injury. Advanced glycation end-products reduce matrix protein flexibility through cross-link formation of the extracellular matrix proteins. This can cause abnormal interaction with other matrix components. Increase in production of advanced glycation end-products may result in an increase in production of proteins of mesangial cells and macrophages extracellular matrix as well as in endothelial cells.

Alteration in the mesangial cell function is the main cause of decreased renal function in diabetic patients (14). Indeed, when nephropathy progresses, the decline in glomerular filtration rate may be due to expansion of the mesangial matrix. This phenomenon compresses the glomerular capillaries, resulting in reduction in the filtration surface area and impairment in maintaining the normal glomerular capillary hydrostatic pressure (13,14). Sustained hyperglycemia is the main cause of change in kidney function in diabetic patients. Various renoprotective agents have shown to act through antioxidant activity and/or reduction in AGEs production. Additionally, some plants

have shown to cause an improvement in kidney function in experimental diabetes mellitus through inhibition of ET-1 and TGF-β1 and the endothelin-1 receptor A (ETRA) (15). Some medicinal plants interfere with the diluting and concentrating mechanisms of tubular transport processes in the proximal and distal tubules or other components of tubular cell membranes (16,17). Therefore, we may speculate that the compound such as oleanolic acid influence renal fluid and electrolyte handling by alteration of the structural integrity and function of tubular epithelial cells to affect reabsorption and secretion. As it was mentioned, oxidative stress is one of the main causes of kidney dysfunction in diabetic patients as well as renotoxic agents such as gentamicin (18,19). Most of medicinal plants have been shown to act by reduction of oxidative stress (16,17). Oxidative stress is usually induced by increase in reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) and/or decrease in body antioxidants. This imbalance between the level of production and/or removal of cell oxidants causes a decline in the ability of biological systems to detoxify the reactive components or repair of the resulting damages (14-17).

Although renal toxicity other than diabetes may also be induced by other complications such as chronic kidney disease or vascular complications, however, all induced oxidative stress, will put the patients at higher risk of acute renal failure due to ischemic and nephrotoxic insults too (16,17). Medicinal plants which mostly possess antioxidant properties have shown to be effective in the prevention and treatment of oxidative stress-related renal injury. The antioxidant activities of plants have been related to various phytochemicals, however phenolic compounds, especially phenolic acids, flavonoids, anthocyanins and tannins are mostly involved (15-17). These antioxidants elaborate endogenous antioxidants capacity to protect renal damage by reduction of lipid peroxidation. In this regard, the beneficial effect of single or combination of antioxidants is more in human is not clear and need to be established.

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