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Flavonoid–induced nephropathy; increasing awareness

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Abstract

Nephropathy is an extensive range of disorders that there are numerous agents in creating it. The use of herbal products has enhanced significantly in recent years. In addition, high concentrations of metabolites like flavonoids are in close connection with cause renal injury. Flavonoids are the water-soluble pigments and extracted from plants, fruits, leaves and flowers. They are used widely for treatment of different disorders and diseases. In this review we highlighted that flavonoids contain beneficial effects. However, excessive consumption of this compound may induce adverse effects such as toxicities in renal tissue.

Introduction

Nephropathy is a wide range of dysfunction and kidney disease that grows into a serious problem. Several forms of nephropathy cause renal injury kidney such as chronic kidney disease, acute kidney injury, kidney stone, renal papillary necrosis, urothelial cancer, and tubular function defects (1). Oxidative stress appears a vital role in the pathogenesis of kidney and it is well known to contribute to other cause of kidney damage, such as ischemic and toxic renal tubular injury. The renal tissue is susceptible to the injurious effects of reactive oxygen species (ROS) (2). In addition, increase in the production of free radicals causes other pathological disorders such as inflammation, asthma, mongolism, ischemia, neurodegeneration, Parkinson's diseases, and arthritis (3).

Contrast media-induced nephropathy (CIN) as a kidney dysfunction is caused via different risk factors such as diabetes mellitus, anemia, older age, hypotension and the use of high dose of contrast agent (4). Additionally, diabetic nephropathy (DN) is one of the main complications of type 1 diabetes mellitus (T1D) that leads to progress of diabetic kidney disease in patients with T1D and T2D is 25% to 40% and 5% to 40% respectively. The studies demonstrated that diabetic kidney disease occurs following hyperglycemia. Additionally the vascular permeability will increase by hyperglycemia in the renal glomeruli. Additionally, several gene associations for susceptibility to DN for T1D have been suggested. Accumulation of ROS in diabetic kidney disease during oxidative stress is resulting of high glucose concentrations (5).

Core tip
Flavonoids consist various pharmacological effects such as anti-diabetic, anti-inflammatory, antioxidant, anti-allergy and antibacterial efficacy. Additionally, many flavonoids or their overdose induced several types of toxicities and cell damage in the kidney.

Different types of treatment methods appeared for kidney impairment. One of the important methods is natural medicine that has been widely used for the treatment of various diseases. It has been reported that medicinal plants are used for the therapy of DN (6). Flavonoids (as the main herbal compound) possess beneficial effects on various types of nephropathy. For example, flavonoids extracted from the leaves of *Murraya paniculata* inhibit oxidative damage by increasing the activities of SOD and GSH-Px in rats with DN (7). Despite the beneficial effects of flavonoids, several case reports observed with severe flavonoid-induced acute nephropathy. The objective of this paper is to discuss about toxicity due to flavonoids and nephropathy of excessive dosages of flavonoids.

Materials and Methods

In this review article, numerous sources were reviewed through advanced searches in several databases including PubMed/Medline, Scopus, EMBASE, and EBSCO using specific keywords including; Nephropathy, Herbal products, Flavonoid, Toxicity, Flavonoid nephropathy, antioxidant, chronic kidney disease, Oxidative stress, acute tubular necrosis, reactive oxygen species, free radicals, Contrast media-induced nephropathy, diabetic kidney disease, type 1 diabetes mellitus, type 2 diabetes mellitus and diabetic nephropathy or equivalent words.

Flavonoids

Flavonoids are a group of polyphenolic (with low molecular weight) that contain a phenyl benzopyrone structure, in different fruits, vegetables, grains, leaves, flowers and bark. There are different classes of flavonoids that are shown in (Table 1) (8).

They exist in different types of medicine herbals like *Aloe vera, Byrsonima crassa, Cannabis sativa, Butea monosperma, Tephrosia purpurea, Momordica charantia*, *Citrus medica,* and fruits like onion, red wine, buckwheat, red pepper, soya bean, and strawberry (9).

Flavonoids possess various pharmacological activities like anticancer, anti-inflammatory, antioxidant, anti-parasitic, immune-stimulating, antifungal, anti-allergy, antibacterial, antiviral, antidiabetic, antithrombotic, anti-atherosclerotic, and antiulcer effects. Additionally, they have been revealed to have cytotoxicity, estrogenic, osteogenic, and larvicidal and enzyme inhibitor and enhancer activities (10). For example, these compounds affect several types of tumor cells, through apoptosis induction, genes expression decrease, inhibition of cell proliferation, and cell cycle arrest (11).

Anti-oxidative effect of flavonoids

The main action of flavonoids is antioxidant property caused by their molecular structure, that revealed a potent protective effect against hydroxyl, superoxide and proxy-radicals (8,12). Prenylated flavonoids (as a class of flavonoids) to contact against the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical via their strong radical scavenging properties (10). Quercetin and silibin decreased oxidative injury via prevention xanthine oxidase (an important pathway in the oxidative injury to renal tissues) activity. Hesperidin showed that reduced the oxidative stress produced by carbon tetrachloride in rat liver and kidney. The protective effect of silymarin on renal cells is by reducing oxidative damage (13).

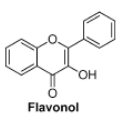
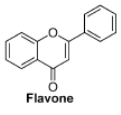
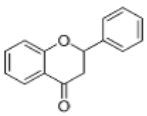
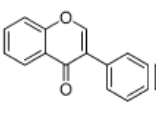
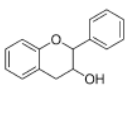
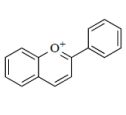
Khanra et al demonstrated the presence of flavonoids and other compounds in *Abroma augusta L.* (Malvaceae) leaf extract can reduce the intracellular ATP and NAD concentrations and inhibit the activation of oxidative stress in renal and myocardial tissues of experimental rats (14).

Flavonoid- induced nephropathy

Recently, the administration of medicine herbal has increased and some of constituents present in herbal are known to induce several types of toxicities in a variety of organ systems such as cardiac, hematologic, hepatic, endocrine, and renal. Several researches revealed the herbal product was involved 50% of acute kidney injury and about 150 patients developed to progressing renal fibrosis. Nephrotoxicity is created by numerous herbal product that can refer to glue thistle (*Atractylis gummifera*), cranberry juice (*Vaccinium macrocarpon*), coneflower (*Echinacea*), and *Cassia obtusifolia*.

. Flavonoids are potent antioxidants and can be effective in treating inflammation. Current biomedical concentration has been on the beneficial activities of flavonoids however, toxicity due to excessive consumption can result in significant morbidity and mortality in patients. For example, flavonoid isolated from Chinese yew (*Taxus celebica*) plant is used as therapeutic agent for diabetes mellitus. However, studies showed consumption of 120 to 150 g of Chinese yew plant causes acute tubular necrosis (ATN) in kidney and the flavonols and alkaloids present in cat's claw (*Uncaria tomentosa*) plant induce acute interstitial nephritis (AIN) (1,15,16). Other study indicated *Cupressus funebris* Endl is as potential sources of flavonoid that its overdoses can increase the occurrence of acute renal failure, acute hepatic failure, autoimmune hemolytic anemia, and thrombocytopenia (17). The result of a research has confirmed quercetin (as a flavonoid) possess a potential anticancer effect on

Table 1. Classification and structure of flavonoids

Class	Flavonol	Flavone	Flavanone	Isoflavone	Flavanol	Anthocyanidin
Flavonoid	Quercetin Kaempferol Myricetin Tamarixetin	Luteolin Luteolin glucosides Rutin Chrysin Apigenin	Naringin Naringenin Taxifolin Hesperidin	Daidzin Genistin	Catechin Epicatechin Epigallocatechin	Cyanidin Apigenidin
Structure						

a number of human cancer cell lines, however, the dose-limiting toxicity of quercetin was returned nephrotoxicity (16).

Conclusion

Recently, the administration of herbal products is being used in treatment of different diseases. However, the consumption of high concentration of herbal compounds may induce types of toxicities in organ systems such as kidneys. Flavonoids as one of herbal products indicated beneficial effects, however, the excessive concentration can appear adverse effects on kidney tissue. The present study has only investigated some of flavonoids nephrotoxicity, therefore more researches should target on the current topic.

Authors' contribution

BY searched the data and prepared primary draft. SP and AH edited the manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors declare that there are no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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