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Agents-induced nephrotoxicity and catcheins

Tahereh Farkhondeh [1], Saeed Samarghandian [2,*], Mahshid Sedaghat [3]
[1] Cardiovascular Diseases Research Center, Birjand University of Medical Sciences, Birjand
[2] Department of Basic Medical Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran
[3] Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran

*corresponding author e-mail address: ***samarghandians1@nums.ac.ir*** | Scopus ID 6507632790

ABSTRACT
The present review was performed to gather the available literature on the nephroprotective effects of catechins against toxic agents. Several studies have demonstrated the therapeutic effects of catechins versus nephrotoxic agents such as cisplatin, cyclosporine A, tamoxifen, FK506, gentamicin, ethylene glycol, calcium, oxalate monohydrate, cadmium, ferric nitrilotriacetate, hydrogen peroxide, contrast medium, fructose, glucose, melamine vanadium, ochratoxin A, streptozotocin. However, more investigations should be done to indicate the nephroprotective effects of catechins against toxic agents in humans.
Keywords: *catechins; toxic agents; antioxidant; kidney; nephrotoxic.*

1. INTRODUCTION
Nephrotoxicity is toxicity in the kidneys induced by toxic agents and some drugs through activation of oxidative stress, inflammatory responses, and apoptosis pathways [1]. Due to kidneys receive many vessels, it may concentrate various drugs and toxic chemicals within the renal cortex and medulla rejoins [2]. Almost all of the nephrotoxic agents bind to the brush border receptors of the renal proximal convoluted tubules and concentrate within proximal tubular cells [3]. Imbalance between oxidant-antioxidant system is the main mechanism of renal injury [3]. Herbs rich in flavonoids have been detected as an important therapy for renal failures because of their antioxidant and anti-inflammatory effects [4-6]. Tea leaves consist of several kinds of catechin such as (−)-epicatechin (EC) (-)-epicatechin gallate (ECG), (−)-epigallocatechin (EGCand), (−)-epigallocatechin gallate (EGCG). Almost 10 types of catechins have been extracted from tea during tea processing [7]. Respectively, the total concentration of catechins in black tea, oolong tea, and green tea is 11.7–55.3, 58.0–183.9 mg/g [5], and 74.8–105.7 mg/g mg/g [8]. Polyphenols of green tea (GTP) may be studied as a treatment substance for recovering of kidney injuries [8]. The current study aimed to review the investigation from 1990 to present related to the therapeutic functions of catechins in the amelioration of renal failures.

2. NEPHROPROTECTIVE EFFECTS OF CATECHINS
2.1. Cisplatin
Cisplatin (CP), an anticancer drug, induces nephrotoxicity through oxidative stress, nitrosative stress, inflammation, apoptosis responses [8, 9]. The protective effects of coenzyme Q10 and EGCG have been investigated in rats received a nephrotoxic dose of CP. Administration of antioxidant decreased the contents of serum creatinine (Cr) and blood urea nitrogen (BUN) in animals exposed to CP. The only antioxidants or in different combinations decreased malondialdehyde (MDA) and also increased catalase (CAT), glutathione (GSH), glutathione peroxidase (GPx), and superoxide dismutase (SOD) levels and the dose of selenium, copper ions, and zinc in renal tissue. The study indicated that the effects of EGCG and coenzyme Q10 against CP-induced nephrotoxicity were similar, whereas the administration of the low doses of the two antioxidants was highly effective on the ameliorating oxidative stress in the animal kidney [10]. It was also detected that EGCG and CoQ10 prevented the CP-induced renal damage through improving oxidative/nitrosative, inflammation and apoptotic responses in the animal kidney [11]. Sahin et al., 2010 indicated that EGCG treatment improved the alterations associated with CP-induced nephrotoxicity by elevating the levels of heme oxygenase-1 (HO-1) and NF-E2-related factor-2 (Nrf-2) with decreasing the nuclear factor-kappa B (NF-kB p65) and 4-hydroxynonenal (HNE) levels. EGCG treatment also raised the antioxidant enzymes (CAT, SOD, GPx) activities and also the contents of glutathione (GSH) in the kidney of rats. The study suggested that EGCG prevented nephrotoxicity caused by CP through modulating Nrf2/HO-1 and NF-kB signaling pathways [12]. ECG administration ameliorated CP-induced oxidative stress, inflammation and apoptosis and histopathological alteration in the kidney of rats. The study suggested that ECG ameliorated renal dysfunction induced by CP due to down-regulation effects on the mitogen-activated protein kinase (MAPK) pathway [13]. EGCG prevented CP-induced nephrotoxic effects by ameliorating apoptotic pathways including death receptor Fas (Fas-L), activated extrinsic pathway, and the expressions of BAX (Bax) and B-cell lymphoma 2 (Bcl-2) in mice kidney [14]. Chen et al., 2015 indicated that EGCG prevented CP-induced nephrotoxicity in mice by decreasing the phosphorylated extracellular signal- They modulated GRP78 (glucose-regulated protein 78), kinase (p-ERK), caspase-12 expression, suggested that EGCG might be effective against kidney damage induced by CP through

preventing endoplasmic reticulum (ER) stress-caused apoptosis [15]. It was indicated that EC prevented the CP-caused renal damage by protecting mitochondria in the mice. The study indicated that CP caused mitochondrial damage via decreasing in the mitochondrial succinate dehydrogenase activity, complex IV protein, and mitochondrial fragmentation as well as inducing cytochrome c release in mouse proximal tubular cells. However, EC administration ameliorated the modifications in the mitochondrial function by decreasing oxidative stress and ERK activity. The study indicated that EC may be effective to treat renal failures by modulating mitochondrial function [16].

2.2. Cyclosporine

Cyclosporine A (CyA) is the immunosuppressant drug that is effective for improving organ transplantation and autoimmune diseases [17]. However, the renal injury is an important side effect of CsA that is featured by the interstitial fibrosis, tubular atrophy, and progressive renal dysfunction [17, 18]. It has been indicated that EGCG protected renal function against CsA by decreasing oxygen-free radicals [19]. Catechin administration decreased the lipid peroxidation and also increased GSH levels induced by CsA in the mice kidney [20]. EC treatment also improved the nephrotoxicity of CyA modulating oxidant-antioxidant system in rat kidney [21].

2.3. Tamoxifen

Tamoxifen (TMX) is an anti-cancer drug that is effective against breast cancer [22]. Catechin decreased the level of GSH, cytochrome P450 (CYP), ascorbic acid (AsA), and the activities CAT, SOD, GST, glutathione reductase (GR) and GPx and glucose-6-phosphate dehydrogenase (G6-PD) in the kidney. The study indicated that catechins supplementation prevented renal toxicity by modulating oxidative stress [22].

2.4. FK506

FK506 (tacrolimus) is one of the most immunosuppressive drugs that cause nephrotoxicity. EGCG and EGC were effective against cytotoxicity induced by FK506, however; EC and catechin did not increase the viability of kidney cells. Additionally, the nephron-protective effects of EGCG and EGC were caused by reducing the levels of cytochrome c and caspase-3 in FK506-treated LLC-PK1 cells. The study suggested that catechins prevented the nephrotoxicity induced by FK506 via ameliorating the apoptotic pathway in LLC-PK1 cells [23, 24].

2.5. Gentamicin

Gentamicin is one of the main aminoglycoside drugs that are suitable for inhibiting various gram-negative bacterial infections [25]. The nephron-protective effect of catechin hydrate against has been investigated gentamicin in rats. Gentamicin administration increased the serum Cr and BUN levels and also changed the structure of glomeruli and tubules via inducing oxidative stress. However, catechin treatment reversed all changes induced by gentamicin in rat kidney. The study suggested that catechin prevented gentamicin-induced nephrotoxicity by modulating oxidative stress in the kidney [25].

2.6. Ethylene glycol

The nephroprotective effect of EGCG against ethylene glycol and its probable mechanism has been studied in an animal model of nephrolithiasis. The findings indicated that ethylene glycol increased BUN, Cr, urine oxalic acid (Ox), calcium, and renal osteopontin (OPN) expression in rats. However, EGCG treatment ameliorated these alterations in animals. Additionally, ECCG treatment improved renal pathological modifications and OPN expression. The study suggested that EGCG prevented the synthesis of calcium oxalate nephrolithiasis in the rats and protected renal functions [26].

2.7. Calcium oxalate monohydrate

Calcium oxalate monohydrate (COM, the chemical formula CaC2O4) is a calcium salt of an oxalic acid that is involved in the formation of human kidney stones. The effect of catechin on the calcium crystallization has been investigated in the NRK-52E cells. The findings indicated that catechin administration might protect NRK-52E cells against COM induced nephrotoxicity by ameliorating the membrane potential of mitochondria change and the cytochrome c, cleaved caspase 3, SOD and, 4-HNE expression [27].

2.8. Cadmium

Cadmium (Cd), accumulation in the kidney generates ROS and then leads to inflammation, oxidative stress, apoptosis, and glomerular dysfunction [28]. The nephron-protective effects of EGCG against CdCl2 have been studied. The findings indicated that EGCG attenuated the CdCl2-induced kidney damage via ameliorating oxidative stress responses, the activities of kidney antioxidant enzyme, E-cadherin content, generation of phosphorylation-Smad3 (pp-Smad3), α-smooth muscle actin (α-SMA), Smad3, and transforming growth factor-β1 (TGF-β1),. Furthermore, EGCG suppressed the expression of microRNA-21 (miR-21) and miR-192 and induced the levels of miR-29a/b/c. The study suggested that EGCG attenuated Cd-induced chronic kidney damage by modulating inflammation, oxidative stress, and apoptosis responses in animal models [29].

2.9. Ferric nitrilotriactate

The impact of catechin on Ferric nitrilotriacetate (Fe-NTA)-caused nephrotoxicity in male rats has been investigated. The findings indicated that catechin pretreatment decreased renal dysfunction, MDA, and also increased antioxidant content and normalized the morphological alterations in the rat kidney. The study suggested the beneficial impact of catechin on Fe-NTA-caused nephrotoxicity in animal models that be related to its antioxidant effects [29].

2.10. Hydrogen peroxide

The nephroprotective effects of catechin microencapsulation against H_2O_2 induced DNA damage in glomerular mesangial cells (GMCs) have been investigated. The findings indicated that catechin microencapsulation enhanced the GMCs ability to repair DNA damage by modulating oxidative stress [30]. It has been shown that diets containing catechin against H_2O_2 induced nephrotoxicity. For this reason, the kidney of rats supplemented with dietary catechin was exposed to H_2O_2. The results indicated that kidney from rats with diets containing larger quantities of catechin had protective effects against H_2O_2 toxicity [31].

2.11. Glucose

Researchers have indicated that the EGCG has nephroprotective aspects on human kidney cell damage induced by high glucose. EGCG reduced high glucose (HG)-induced IL-6 and TNF-α generation in human embryonic kidney (HEK) cells. EGCG reduced HG-induced protein expressions in HEK cells and the receptor of advanced glycation end products (RAGE) mRNA. Additionally, EGCG reduced the production of ROS in HEK cells

and enhanced superoxide dismutase production. It was found that EGCG prevented the progression of diabetic nephropathy by ameliorating inflammation and oxidative stress responses [32].

2.12. Melamine

The therapeutic aspects of catechin against melamine-cyanuric acid mixture (MCM)-caused crystallization using *in-vivo* and *in-vitro* models have been studied. Findings indicated that catechin decreased the crystal formation induced by MCM in conditioned media. *In-vivo* research, catechin inhibited the MCM-induced apoptosis and expression of the protein in rats. Catechin also decreased the MDA and urinary 8-isoprostane (8-IP) as well as raised the activitiy of antioxidant enzymes including SOD in MCM-treated rats. Catechin decreased renal crystals content and kidney damage. The findings suggested that catechin prevented renal crystallization by preventing ROS production, phospho-P38, apoptosis, and osteopontin signaling in rats [33].

2.13. Vanadium

The study conducted by Soussi et al., 2017 has reported that oxidative stress in kidney induced by ammonium metavanadate (AMV) and EGCG protected rat kidney. The obtained findings indicated that AMV elevated the lipid peroxidation levels in the kidney and also decreased the activities of antioxidant enzymes. According to the histological analysis, AMV induced glomerular hypertrophy and tubular dilatation in the rat kidney. However, administration of EGCG improved all the above modifications induced by AMV. The data proposed that EGCG ameliorated AMV -induced oxidative stress in rat kidney [34].

2.14. Ochratoxin A

The impact of catechins (ECG and EGCG) on ochratoxin A (OTA)-caused cytotoxicity was studied in the LLC-PK1 cells (a pig kidney cell line). Cytoprotective effects of the catechins against OTA-induced cell damage by decreasing ROS production have been observed. The study indicated that the radical scavenging capacity of catechin has the main role in the protective effects against OTA-induced cytotoxicity [35].

3. CONCLUSION

The present review showed the therapeutic aspects of catechins versus nephrotoxic agents in experimental models; however; clinical trial studies should be done to demonstrate the antidotal effects of catechins in human intoxications.

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