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Original Paper

An Overview on Antioxidant and Anti-inflammatory Properties of Ellagic Acid in Renal Dysfunction

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Background: The pathology of various diseases such as cardiovascular problems, atherosclerosis, inflammation, cancer, diabetes, and renal dysfunction is related to oxidative damage to the cellular components. One of the main mechanisms of kidney dysfunction is oxidative stress which occurs in response to renal ischemia/reperfusion, ultimately leading to acute renal failure. The consuming oxygen by cells produces free radicals in the mitochondria, which are generally Reactive Oxygen Species (ROS). These molecules can damage DNA that contributes to many health problems. Reducing oxidative damage is one of the most important ways to prevent these problems, and antioxidants agents can prevent oxidative stress injuries. Recently, multiple studies have focused on the antioxidant properties of herbal medicines. Ellagic Acid (EA) is a bioactive compound with a wide range of pharmaceutical and industrial applications. The most well-documented effects of EA are its antioxidant and anti-inflammatory properties. Accordingly, the current study aimed to review the previous studies regarding the effectiveness of EA on renal injuries.

Methods: The articles were extracted by researching Scopus, Web of Science, Science Direct, and PubMed databases. The keywords were combinations of “Ellagic acid”, “Renal”, “Kidney”, “Nephrotoxicity”, and “Natural products”.

Results: The reported evidence identified that EA could prevent and treat inflammation and oxidative damage in kidney disorders.

Conclusion: Supported by several presented studies, this review paper has given a view on the useful properties of EA as a novel therapeutic agent in renal diseases.

Keywords: Ellagic acid, Renal, Kidney, Oxidative stress, Antioxidant, Anti-inflammatory

Introduction

Kidney diseases are increasingly identified as the global health problems associated with a tremendous economic burden. With over 17% prevalence worldwide [1], destructive and progressive kidney diseases can result in End-Stage Renal Diseases (ESRD). Also, renal problems are associated with dangerous cardiovascular dysfunction. These are the critical issues that have motivated researchers to find strategies for preventing or treating these conditions [2]. In recent years, the Reactive Oxygen Species (ROS) have been detected as contributing factors in renal injuries [3]. In principle, an imbalance in the generation of ROS and the activity of antioxidant enzymes causes oxidative stress. Free radicals can damage the cell’s main parts by disrupting the structure and function of plasma and intracellular membranes [4]. During renal injuries such as ischemia/reperfusion, glomerulonephritis, or other common renal problems, the oxidative stress leads to a set of metabolic, functional, and structural changes, including energy imbalance, changes in cellular homeostasis, decreased oxidative respiration, enhanced anaerobic respiration, decreased ATP production, and increased ADP and AMP levels [5].

According to the literature, the main mechanisms of oxidative stress pathogenesis in patients with kidney diseases include an increase in the concentrations of some biomarkers such as nucleic acids, lipids, and proteins in circulation and antioxidant defense impairment. Also, in this regard, ROS can contribute to kidney malfunction through glomerular filtration barrier damage caused by inflammation which can lead to hypertension and renal fibrosis [6].

Traditional medicine, as a complementary treatment, provides a healthy and preventive lifestyle and has great potential in

the treatment of various organ dysfunction, including the renal system. In recent decades, herbal therapy and traditional medicine have received much attention due to their lower side effects and high efficacy [7]. Ellagic acid (2,3,7,8-tetrahydroxy-chromeno [5,4,3-cde] chromene-5,10-dione) is a bioactive compound with many medicinal and industrial applications. Ellagic Acid (EA), as a polyphenolic compound, has been found in some fruits, including pomegranates, strawberries, raspberries, walnuts, and grapes [8]. This molecule possesses potent antioxidant and anti-inflammatory properties [9]. Several *in vitro* and *in vivo* experiments have shown that EA has anti-mutation [10], antiviral [11], anti-diabetic [12], and anti-neurodegenerative properties [13]. Also, several studies have examined the prevention and treatment efficacy of EA in renal disorders conditions. Concerning the beneficial properties of EA in kidney dysfunction, the current study aimed to review the available experimental evidence regarding the effectiveness of EA on renal injuries.

Information Sources and Search Strategy

To review the scientific papers, two investigators researched documented articles published from 2000 till now which were indexed in databases of Science Direct, Web of Science, PubMed, and Scopus. The search English keywords were combinations of "Ellagic acid", "Renal", "Kidney", "Nephrotoxicity", and "Antioxidant". The *in vivo*, *in vitro*, and interventional studies in the human population were included. The dissertations, books, abstracts of conferences, patents, and publications evaluated EA's effect on the other organ disorders and were excluded.

Ellagic Acid and Renal Ischemia/Reperfusion Injury

Organ transplantation has been one of the most incredible advances of the last century. One of the most successful organ transplants in humans is kidney transplantation [14]. The unavoidable stages of transplantation and some urological surgeries are ischemia, which occurs with greater destruction of ischemia when blood flow is restored (reperfusion) [15]. Acute Renal Failure (ARF) is a common disorder characterized by a sudden decrease in kidney function and is associated with diminished Glomerular Filtration Rate (GFR) [16]. Elevated plasma urea, creatinine, and decreased urinary excretion are the first findings of the disease [17]. Renal artery occlusion may also occur due to decreased renal blood flow following a cardiac output decrease [18]. Decreased renal blood flow and acute tubular necrosis account for approximately 70% of acute renal failure [19]. Several factors are involved in the pathophysiology of reperfusion injuries, including small vessel damage, endothelial dysfunction, activation of cell death pathways such as necrosis and apoptosis, activation of granulocyte and inflammatory processes, reduction of cell nucleotide stores (formation of ATP and ADP), excerebration of ROS and nitrogen (RNS, NO, ONOO-) which occurred due to activation of neutrophils followed by peroxidation of lipid membranes and hydrolysis of proteins by these active species [20]. In ischemic renal conditions, in the reperfusion and re-oxygenation stage, lesions are caused by free radicals and other oxidative agents [21]. The most important free radical in the biological system is ROS, which included superoxide anion (O^{-2}) and hydroxyl (OH^{-}). The action of free radicals on lipid membranes is lipid peroxidation, membrane protein oxidation, and protein denaturation. Free radicals play a crucial role in the rejection of kidney transplantation, glomerulonephritis, the breakdown of the glomerular basement membrane, and prostaglandins production in the glomerulus [22].

EA, as a well-known antioxidant, is a potent scavenger for peroxyl radicals and other reactive oxygen species. In an animal study done by Bozkurt et al. to evaluate the efficacy of EA against renal Ischemia-Reperfusion (I/R) injuries, the rats were subjected to left renal ischemia (45 min) followed by 60 min of reperfusion. The EA-treated group received 85 mg/kg EA orally, 30 min before the I/R procedure. The obtained results showed the changes in oxidative stress status in response to I/R condition, including enhanced Malondialdehyde (MDA) level and Total Oxidant Status (TOS). They decreased Total Antioxidant Capacity (TAC) in both kidney tissues and blood samples. Although, pretreatment with EA reversed the harmful effects of I/R damage through a significant increase in antioxidant capacity and decrease in oxidative stress indexes. The data suggest that EA effectively reduces tubular necrosis and kidney tissue damage in renal I/R conditions [23]. In another *in vivo* experiment by Hosseini Nejad et al. on the protective effect of EA on renal dysfunction induced by Global Cerebral Ischemic-Reperfusion (GCIR), the I/R model was established using bilateral vertebral and common carotid arteries occlusion for 20 min followed by 30 min reperfusion. Also, the EA-treated group was administrated 100 mg/kg EA 10 days before I/R injuries. In this study, the induction of GCIR caused a significant decrease in GFR and elevated Blood Urea Nitrogen (BUN) and serum creatinine concentration. On the other hand, the results of 10 days pretreatment with EA indicated that EA as a potent antioxidant could prevent disturbances in renal functions through preserving the kidney function indexes caused by GCIR injuries [24].

The responsible mechanisms for the establishment of renal I/R injuries are complicated. However, intense oxidative stress and inflammatory process are considered an inducement for initial renal damage and interstitial fibrosis or repair. Activation of NADPH (Nicotinamide Adenine Dinucleotide Phosphate) oxidase enzyme (NOX) plays a critical role in ROS generation and stimulation of pro-inflammatory factors production. This action facilitates the cascades of NF-kB, which finally lead to the activation of the Janus Kinase (JAK) pathways. JAKs can phosphorylate STATs as a part of the substrates of tyrosine phosphorylation members, which can promote the pro-inflammatory response through increasing inflammatory cytokine production [25]. In this context, an animal study by Liu et al. on underlying mechanisms of protective effects of EA on renal I/R injury, the I/R model was induced by left renal ischemia for 45 min, which followed by 60 min of reperfusion. Other groups received EA in various concentrations (50, 100, and 150 mg/kg), 30 min before I/R procedures. The obtained results revealed that EA attenuated the inflammatory signaling pathway by reducing production and secretion of Interleukin (IL)-6, Tumor Necrosis Factor (TNF)-α, Monocyte Chemoattractant Protein-1 (MCP-1), IL-1β, and oxidative stress indexes, which caused inhibition of renal cell apoptosis. EA administration also resulted in reduced NOX4 level, which is associated with phosphorylation of Janus kinase (JAK)1, JAK2, and Signal Transducer and Activator Of Transcription 1 (STAT1), which proves the renoprotective effect of EA through modulation of NOX4/JAK/STAT signaling pathway [26].

Ellagic Acid and Renal Dysfunction in Diabetic Models

Diabetes mellitus is a chronic metabolic disease characterized by increased blood sugar levels and impaired metabolism of carbohydrates, lipids, and proteins. One of the most critical and severe microvascular complications of diabetes is renal dysfunction induced by nephropathy, which includes various stages [27]. It is estimated that approximately 25% to 30% of patients with type 2 diabetes have diabetic nephropathy [28]. Proteinuria is a major feature of diabetes. The kidney plays a vital role in filtering waste products. Diabetes mellitus is directly related to oxidative stress caused by an increase in oxygen free radicals, hydroxyl, or a decrease in the antioxidant defense system. Oxidative stress caused by diabetes plays a vital role in the development of diabetic nephropathy [29]. Oxidative stress caused by hyperglycemia resulted in damage to the mitochondria, cell death, and kidney tissue injuries [30]. The deficiency of strong antioxidant defenses can activate oxidative stress-dependent signaling pathways. Therefore, one effective way to control the complications of nephropathy caused by hyperglycemia is to use herbal or synthetic antioxidants. In this regard, Chao et al. evaluated the renal-protective effects of EA in diabetic mice model. The diabetes was induced via intraperitoneal administration of streptozotocin for five consecutive days. Other groups received daily EA in 2.5 and 5 g concentration mixed in the diet as a treatment for 12 straight weeks. The results showed that increased kidney content of EA was accompanied by increased plasma insulin and attenuated body weight loss and urine output restriction. EA also dose-dependently elevated creatinine clearance and reduced plasma blood urea nitrogen associated with the diminished plasma level of HbA1c, decreased glycated albumin in urinary samples, and remarkable diminished in the renal activity of aldose reductase and sorbitol dehydrogenase, as well as suppressed mRNA expression of kidney aldose reductase. Moreover, EA administration downregulates pro-inflammatory factors, including Monocyte Chemoattractant Protein 1 (MCP-1), IL-6, IL-1b, and TNF-α in kidney tissue. These data support the anti-inflammatory and renal protective effects of EA supplements to treat diabetic kidney diseases [31]. Also, in a combined *in vitro* and *in vivo* study by Ahad et al. to explore the mechanism that responded to the renal protective effect of EA in diabetic nephropathy rats. Type 2 diabetes was induced using a High-Fat Diet plus Streptozotocin (HFD/STZ), and EA at different doses (20, 40, 60, 80, and 100 mg/k/bw) was applied for 16 consecutive weeks post-induction of the HFD/STZ model. Ellagic acid demonstrated a significant dose-dependent decrease in activation of renal NF-κB, which was associated with suppressed kidney pathology and inhibition of fibronectin and Transforming Growth Factor-Beta (TGF-b) gene expressions in kidney tissues. These results were in line with decreasing serum content of IL-6, IL-1b, and TNF-α. On the other hand, in *in vitro* part, proximal tubular epithelial cells (NRK 52E) were exposed to high glucose medium and treatment by EA that significantly inhibited pro-inflammatory cytokine production in cultured cells. These results prove that EA may have renal protective properties in diabetes patients partly via the antihyperglycemic effect, which was associated with the amelioration of the NF-κB pathway [32].

The Toll-Like Receptors) TLRs (are considered as recognition receptors and upstream of multiple intracellular signaling pathways such as TLR-4/TNF-α. Activation of these receptors in response to inflammatory agents can stimulate the NF-κB and Mitogen-Activated Protein Kinases (MAPK) signaling pathway to produce and secrete pro-inflammatory cytokines leading to inflammation injuries [33]. In this context, *in vivo* and *in vitro* studies by Zhou et al. focused on the antioxidant and anti-inflammatory properties of EA in streptozocin-induced diabetic nephropathy conditions. The kidney NRK-52E cells were obtained from diabetic rats and subjected to various concentrations of EA and TAK-242 (an inhibitor factor for TLR4). The obtained data revealed that EA could improve antioxidant enzyme activities and decrease the levels of TNF-α and serum creatinine to ameliorate the kidney pathology by suppressing the expression of TLR4 and some downstream genes, including *NF-κBp65, HMGB1, IRAK4, TRAF6, IKK-β*. This evidence suggests that EA has efficacy against renal injury through TLR4-HMGB1 and NF-κB pathways [34].

The production of Advanced Glycation End products (AGEs) is one of the destructive processes of diabetes, and the accumulation of these toxic molecules plays a role in the pathogenesis of microvascular complications in diabetes patients such as nephropathy [35]. Raghu et al. studied the properties of EA in the amelioration of renal changes in diabetic rats by targeting non-enzymatic glycation. In this experiment, the rats were administrated streptozotocin to induce diabetic model and also were fed with EA (0.2% and 2%) as a supplementary diet for 12 consecutive weeks. The results demonstrated that EA caused inhibition of the glycation-mediated red blood cell-IgG cross-links and kidney level of N-Carboxymethyl Lysine (CML) and HbA1c accumulation in diabetic rats. This molecular pathway resulted in inhibition of nephrin and podocin expression (podocyte slit diaphragm proteins) and improved renal function in diabetic rats, suggest EA role in the prevention and treatment of diabetic complications [36].

Ellagic Acid and Chemical Nephrotoxicity

Nephrotoxicity is the main renal problem commonly induced by exposure to a drug or toxin that damages the kidney's nephrons. Nephrotoxicity is categorized as acute renal failure [37]. Toxin agents increase oxidative stress by enhancing the production of superoxide anions, hydrogen peroxide, and hydroxyl radicals via renal mitochondria. Free radicals cause peroxidation of membrane phospholipids, DNA strand breakage, and protein denaturation [38]. In this context, some therapeutic drugs such as cisplatin, doxorubicin, and cyclosporine are well-known to induce several side effects like oxidative stress, which could result in chronic health problems where simultaneous administration of natural antioxidants agents has been documented to effective. Accordingly, an *in vivo* and *in vitro* study by Sonaje et al. on antioxidant efficacy of EA-nanoparticle against nephrotoxicity model induced by cyclosporine documented that EA could prevent the nephrotoxicity with decreases in biochemical oxidative stress parameter (like MDA) which is associated with the improvement of the assessment of kidney function (creatinine and BUN), as well as renal histopathology [39]. Another study by Yüce et al. using the same nephrotoxicity model showed that oral administration of EA (10 mg/kg/d) for three weeks resulted in increased Catalase (CAT) and Glutathione Peroxidase (GPx) activity levels as well as Glutathione (GSH) biosynthesis in kidney tissues which were partially associated with ameliorated renal histopathology. These findings suggest that EA supplement can attenuate kidney dysfunction by protecting the lipid peroxidation and increasing the capacity of antioxidant enzymes

in the kidney [40].

Cyclophosphamide, as a well-known alkylating component, is frequently applied in cancer chemotherapy which has some side effects like genotoxicity. It is widely considered an immunosuppressant treatment in rheumatoid arthritis, systemic lupus erythematous, and organ transplantation. The reactive metabolites of cyclophosphamide (phosphoramide and acrolein) are responsible for their destructive cytotoxic effect on the production of reactive oxygen species leading to peroxidative tissue injuries in vital organs like the kidney [41]. In this context, Rehman et al. attempted to evaluate the efficacy of EA against the nephrotoxicity model induced by cyclophosphamide and subsequent genotoxicity. This study assessed biochemical indexes of antioxidant enzymes and renal histopathology for the identification of oxidative stress status. Besides, the genotoxicity was evaluated by measuring DNA fragmentation, micronuclei, and alkaline assay to measure DNA strand breaks. The obtained data supported that EA diminished oxidative stress injuries induced by subsequent and following DNA damage and genotoxicity. This evidence suggests that natural antioxidants like EA have a potential effect against cyclophosphamide-induced kidney damage and genotoxicity [42].

Recently, mercury as an environmental pollutant receives considerable attention. The main toxicity of mercury is related to its oxidative stress, which is possibly caused by the inhibition of antioxidant enzymes or depletion of thiol compounds leading to lipid peroxidation and cell death in the mercury-induced nephrotoxicity. The toxicity of mercury sedimentation in the kidneys results in acute tubular necrosis and nephritic syndrome [43]. Since oxidative stress has been identified to play a critical role in several disorders, the antioxidants capacity is considered a therapeutic agent in combatting diseases. The study by Bharathi and Jagadeesan on antioxidant properties of EA on the renal toxicity induced by mercuric chloride demonstrated that the treatment with EA (5 mg/kg) shows a significant decline in the level of concentration of TBARS (thiobarbituric acid reactive substances) as an index of oxidant content and increase in the antioxidant profile (GPx, SOD, LPO, GSH, CAT) compared to mercury group. This study supports the previous evidence for the efficacy of EA in chemical medications-induced kidney toxicity [44].

Heavy metal contamination is known to be a dangerous health problem. Arsenic as a toxic agent in drinking water or air pollution is considered a major health issue worldwide. Arsenic affects the functions of various vital organs such as the liver and kidneys. The underlying mechanisms of arsenic toxicity in kidneys are not thoroughly clarified. However, oxidative stress is considered one of the main identified and reported mechanisms. The generation of nitric oxide and reactive oxygen species are the causes of renal injuries [45]. Accordingly, an enhanced antioxidant system can be a promising strategy to prevent kidney damage in arsenic exposure conditions. In this context, an *in vivo* study by Mehrzadi et al. focused on the protective potential of EA in renal toxicity induced by arsenic. In this study, the toxicity was established using 10 mg/kg sodium arsenite for 21 days, and also the treatment group was administrated EA (30 mg/kg) for two weeks. Various biochemical assessments in kidney tissues revealed the protective efficacy of EA, which showed improvement of renal histopathological indexes and redox status, such as decreased MDA and increasing antioxidant enzyme genes expression. These observations suggest that EA supplement can be considered a new therapeutic strategy to treat arsenite-induced renal toxicity [46].

Cisplatin (cis-diamminedichloroplatinum) is a synthetic and anti-tumor compound commonly used as an anti-cancer drug in treating organ tumors, such as ovaries, lungs, head, and neck, and testicles. High doses of cisplatin can cause kidney damage. Cisplatin-induced nephrotoxicity often occurs due to the production of free radicals, especially hydroxyl, which causes the peroxidation of lipids, oxidation of proteins and nucleic acids, and the destruction of cell membranes [47]. El-Garhy et al. studied the anti-apoptotic and anti-inflammation properties of EA in nephrotoxic induced by cisplatin. The treatment was administrated using 10 and 30 mg/kg EA for five consecutive days. The preventive effect of EA was demonstrated through decreased BUN, creatinine, and γ-glutamyl transferase levels in serum. Also, it reduced serum endothelin-1, as well as serum and renal nitric oxide, NF-κB, renal caspase-3, TNF-α, hemeoxygenase-1, and MCP-1. These changes were associated with by improvement of kidney histopathology and increased GFR. These findings support the potent anti-inflammatory effect of EA in treating kidney injuries [48]. In line with these findings, another study by Neamatalah et al. reported that EA could preserve the antioxidant capacity through a remarkable decline in organic anion transporter (*OAT1* and *OAT3*) gene expression, which caused inhibition of kidney tubular dilatation, necrosis, and degeneration [49].

Clinical use of gentamicin as an aminoglycoside antibiotic causes side effects despite its therapeutic effects. These antibiotics cause acute renal failure with a prevalence of 10% to 20%. Multiple studies have shown that oxidative stress is involved in gentamicin-induced renal toxicity. Gentamicin increases the production of superoxide anion, hydrogen peroxide, and hydroxyl radicals by renal mitochondria [50]. Sepand et al. studied the kidney mitochondrial dysfunction and apoptosis in response to gentamicin-induced nephrotoxicity. The administration of EA (10 mg/kg) for ten consecutive days resulted in significantly enhanced caspase-3 and the ratio of *Bax/Bcl2* genes expression, which was associated with decreasing plasma creatinine and urea levels and ameliorated oxidative stress marker in kidney tissue. Ellagic acid administration also prevented mitochondrial injury through the mitochondrial membrane potential inhibition and mitochondrial free radical's generation [51].

Conclusion

Taken together, the available *in vitro* and *in vivo* studies on the effects of EA in renal disorders demonstrated that this antioxidant could decrease fibrosis, inflammation, oxidative stress, and histopathology while improving renal function and structure. Treatment of nephrotoxicity, necrosis, and corpuscle cells with EA diminished structural changes and reactive oxygen production through improving antioxidant and mitochondrial activities. The health benefits of EA are well-documented, and the molecular toxicity makes it a promising strategy for therapeutic use against renal disease. This evidence supports that EA supplementation has a protective efficacy in patients with chronic renal disease by preserving GFR and kidney functional indexes. However, additional animal and clinical studies are

necessary to clarify the effects of EA on kidney disorders.

Conflicts of Interest

The authors declared no conflict of interest.

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