Acta Persica Pathophysiologica

Curcumin and kidney protection; current findings and new concepts

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ARTICLE INFO

Article type:
Review

Article history:
Received: 23 December 2015
Accepted: 21 January 2016
Published online: 9 Mach 2016

Keywords:
Curcumin
Acute renal failure
Antioxidant
Nephrotoxicity

ABSTRACT

According to various epidemiological data, renal failure, either acute or chronic is a serious health and economical problem throughout the world. Curcumin as a member of ginger family (Zingiberaceae), is one of three curcuminoids present in turmeric and the necessity to develop kidney protective modalities sets the eyes in compounds such as curcumin, which has been used in the traditional medicine, specifically because its protective effects against kidney damage. It has been recognized that curcumin is a bifunctional antioxidant; it applies antioxidant activity in a direct and an indirect ways through scavenging reactive oxygen species and provoking an antioxidant response. Curcumin by its bifunctional antioxidant has the capability to react directly with reactive species and to stimulate up-regulation of several antioxidant and cytoprotective proteins. Thus, according to previous studies curcumin due to its properties, was effective to ameliorate the kidney damages and in this review, we will try to explain these abilities of curcumin.

Review

Core tip: Curcumin is a free radical scavenger due to its antioxidant capacity and many experimental investigations reported its ameliorative effect in acute and chronic kidney disease such as diabetic kidney disease, nephrotoxicity and renal ischemia.

Please cite this paper as: Nasri H, Abedi-Gheshlaghi Z, Rafieian-Kopaei M. Curcumin and kidney protection; current findings and new concepts. Acta Persica Pathophysiol. 2016;1:e01.

Introduction

Chronic renal failure is a complication defined as progressive disturbance of kidney function over time and is characterized by abolishing the ability of the body to remove soluble waste resulting in the accumulation of "uremic toxins" (1-3). While, acute kidney injury is commonly described as a sudden decline in kidney function, its clinical manifestation appears as a reversible acute rise in nitrogen waste products, measured as blood urea nitrogen and serum creatinine levels, over a period of hours to weeks (1-3). Now, it is well detected that chronic renal failure is an inflammatory illness and uremic toxins have the main role in creating the inflammatory milieu (1,2). Kidney fibrosis is generally considered as activation and proliferation of interstitial area and by excessive synthesis and aggregation of extracellular matrix components, containing fibronectin and collagen. Likewise, the phenotypic changes that attribute to acute renal failure comprise inflammatory response and oxidative stress. Slowing the rate of progression of chronic renal failure and promoting the recovery of acute kidney injury is a critical part of the management of these two disease (2-4). Oxidative stress describes an imbalance between formation of reactive oxygen species and antioxidative defense mechanisms (1-5). Uremia is associated with increased oxidative stress, and treatment of uremic individuals by hemodialysis or peritoneal dialysis has been proposed to particularly attribute to oxidative stress and diminished antioxidant levels in these groups. Loss or insufficiency of antioxidant activity might also attribute to augmented oxidative stress in uremia (1-8).

Materials and Methods

This review article discusses kidney related aspects of curcumin including its protective properties in acute and chronic renal disease and diabetic nephropathy. We report the available evidences of clinical outcomes of clinical or experimental investigations with this drug. For this review, we used a variety of sources by searching through PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was conducted using combinations of the following key words and or their equivalents; acute kidney injury, curcumin, antioxidant, nephrotoxicity and chronic renal failure.

Oxidative stress generation in kidney

Curcumin is a phenolic substance with chemical formula C21H20O6 which is extracted from Curcuma longa

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rhizomes is frequently used in various parts of the world (1,7-10). Furthermore, it is one of curcuminoids present in turmeric and is responsible for the yellow color of turmeric. Curcuminoids are a rich source of phenolic compounds and curcumin as the major component of turmeric has been shown antioxidant, anti-tumor, antimicrobial, anti-inflammatory and antimutagenic activities. Curcumin is soluble in acetone, ethanol and dimethylsulfoxide but insoluble in water and ether. In addition, it is rapidly conjugated and metabolized and its chemical structure for the first time, was identified in 1910 by Lampe and Milobedzka (1,7-10). Several studies have shown the ability of curcumin to prevent lipid peroxidation as a significant key in process of many diseases. In addition, curcumin is a free radical scavenger due to its antioxidant capacity and many experimental investigations reported the ameliorative effect of curcumin in acute and chronic kidney problems (1,5-12). Therefore, the aim of this study is to explain the protection effects of curcumin against kidney problems. It is well recognized that reactive oxygen species like hypochlorous acid (HOCl), or hydrogen peroxide (H_2O_2) and free radicals like superoxide (O_2^-), hydroxyl radical (OH^-), and nitric oxide (NO^-), are constantly formed in vivo (1-14). Hence, the findings of reactive oxygen species by itself does not yet outline oxidative stress, however, in a condition where antioxidative protection mechanisms are weakened, cause the imbalance between formation of reactive oxygen species and protection mechanisms which generates oxidative stress (12-16). Kidney sources for reactive oxygen species are vascular cells, activated macrophages, various glomerular cells. The balance in formation of reactive oxygen species and antioxidative protective mechanisms depends on the activity of enzymes like catalase, NO-synthase, superoxide dismutases and glutathione peroxidase. This stability, by the way, is rather fragile, hard to predict, and intensely dependent on environmental situation. Various cellular enzymes, comprising mitochondrial lipoxygenase, oxidases, cyclooxygenase, myeloperoxidase, xanthine oxidase, NADPH oxidase and in the case of L-arginine or tetrahydrobiopterin depletion, NO-synthase have been recognized as cellular sources of reactive oxygen species formation (1-16). Reactive oxygen species are also considered to contribute to the pathogenesis of ischemia-reperfusion damage (1-4,15-18). Likewise, oxidative stress mediates an extensive range of kidney impairment, from acute kidney disease, hyperlipidemia, rhabdomyolysis, obstructive nephropathy and glomerular injury which lead to chronic kidney disease and hemodialysis (12-18). Endogenous complexes in cells can be classified as enzymatic antioxidants and non-enzymatic antioxidants (12-18). The non-enzymatic antioxidants are also separated to nutrient antioxidants and metabolic antioxidants. Nutrient antioxidants, which belong to exogenous antioxidants, are compounds that cannot be produced in the body and should be provided by foods or supplements (10-19).

Moreover, due to their impact on cell cycle regulation, oxygen radicals may attribute to hypertrophy of tubular cells (38-40). Moreover, oxidative stress has role as a significant cofactor attributing to endothelial dysfunction, atherosclerosis, inflammation and glomerulosclerosis (16-20). When, reactive oxygen species are released by the mitochondrial respiratory chain can damage biomolecules like proteins, lipids and nucleic acids (11-19). To prevent the injury, antioxidant protection has evolved to remove most of these oxidant agents (1-7). Even when a balance between oxidative injury and protective mechanisms is usually reserved, there are some specific conditions in which the excessive production of free radicals, or deficiencies in antioxidant protection, results in the appearance of oxidative stress (15-21). While renal diseases patients live under predominantly various pro-oxidative situations, thus, they might be particular profit of antioxidant therapy (12-20). For many years, there have been investigations based on the application of natural compounds herbal-derived as potential therapeutic substances for various illnesses in humans (10-22).

Kidney protective effect of curcumin

It has been recognized that curcumin is a bifunctional antioxidant; it applies antioxidant activity in a direct and an indirect way through scavenging reactive oxygen species and provoking an antioxidant response. In summary, curcumin by its bifunctional antioxidant has the capability to react directly with reactive species and to stimulate an up-regulation of several antioxidant and cytoprotective proteins. Curcumin is able to scavenge superoxide anion (O_2^-), H_2O_2, singlet oxygen, peroxynitrite, hydroxyl radicals ($^{\cdot}OH$), nitric oxide and peroxyl radicals ($ROO^{\cdot}$) (2-28). Additionally, aspects such as the presence of phenolic groups in the structure of curcumin describe its capability to react with reactive nitrogen species and reactive oxygen species and it may probably be one of the mechanisms by which curcumin treatment keeps the epithelial cells of kidney tubules from oxidative damage induced by H_2O_2. Moreover, indirect antioxidant ability of curcumin is described by its capability to stimulate the expression of cytoprotective proteins like superoxide dismutase, glutathione reductase, catalase (14-26), glutathione peroxidase (1,16-25), glutathione-*S*-transferase, and γ-glutamylcysteine ligase (14-24). Likewise, it has been detected that curcumin can enhance the concentration and synthesis of reduced glutathione in various cells containing astrocytes and neurons by induction of γ-glutamylcysteine ligase. In fact, recent investigations have shown that antioxidant activity may be exerted in various in vitro and in vivo models such as preventing lipid peroxidation in a variety of cells like erythrocytes, brain, liver, liposomes and macrophages, where peroxidation is brought by Fenton's reagent, in addition to hydrogen peroxide (H2O2), 2,2'-azo-bis(2-amidino-propane) hydrochloride (AAPH) and metals (15-29). Kidney fibrosis is largely identified by activation and proliferation of interstitial renal fibroblasts and by

extreme synthesis and accumulation of extracellular matrix substances, comprising fibronectin and collagen (25-38). Recent studies have revealed that treatment by curcumin decreases the collection of type I collagen and fibronectin in the kidneys of animals with unilateral ureteral obstruction. Activation of rat kidney interstitial fibroblasts was induced by transforming growth factor β. Curcumin treatment inhibited fibroblast proliferation and the cell cycle was arrested in the G1 phase. Curcumin treatment upregulated the expression of peroxisome proliferator-activated receptor gamma (30-38).

Diabetic kidney disease is one of the major causes of end-stage kidney failure (35-40). Diabetic kidney disease is defined by the presence of hyperfiltration, glomerular hypertrophy, mesangial matrix expansion, and increased expression of extracellular matrix proteins, tubular albuminuria (31-42). It involves several profibrotic factors like connective tissue growth factor and transforming growth factor β (1,38-45). The influence of curcumin on diabetic kidney disease has been detected by attenuation of proteinuria and improvement of creatinine clearance in rats. Accordingly, curcumin decreases oxidative stress by reducing levels of subunits of nicotinamide adenine dinucleotide phosphate oxidase that catalyzes the synthesis of $O_2^{-\cdot}$. Furthermore, it has increased the activity of the antioxidant enzyme glutathione peroxidase (31-42). More recent investigations have shown that the kidney protective property of curcumin was related to the down-regulation of the profibrotic cytokines vascular endothelial growth factor, transforming growth factor β, and osteopontin and extracellular matrix proteins fibronectin and collagen IV. Besides, it was detected a reduction in the development of structural injury detected by lower glomerulosclerosis index, tubules and interstitial fibrosis and arteriolopathy. These properties, may be in part, conducted by inhibition of protein kinase C-β (40-45). On the other hand, the protective influence of curcumin in diabetic kidney disease has also been related to the prevention of renal triglyceride buildup (40-48). More recent studies on administration of curcumin in diabetic kidney disease showed reduction of inflammatory kidney response by the attenuation of proinflammatory cytokines like tumor necrosis factor-alpha and monocyte chemoattractant protein-1. Additionally by attenuation of kidney macrophage infiltration, expression of the profibrotic cytokine TGF-β, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) could ameliorate the diabetic kidney disease (1-6,30-39).

Acute renal failure is a public health problem with an annual mortality rate which exceeds those of breast and prostate carcinoma, cardiac failure, and diabetes (42-50). After a toxic injury or an ischemic episode, dysfunction and the loss of renal tubular epithelial cells play a central role in the evolution of acute renal failure. In response to an injurious insult, tubular cells fail cytoskeletal integrity and cellular polarity, due to the dislocation of membrane proteins resulting in the disruption of cell-matrix and cell-cell integration (31-45). Central to tubular damage is mitochondrial dysregulation, established in a reduction in cell respiration and ATP production. Mitochondrial activities rest on a complex molecular machinery delicately tuned and balanced through regulatory proteins of the two opposing processes fission and fusion (48-52). The influence of curcumin on acute renal failure has been detected, too. In this condition, curcumin was able to significantly attenuate the reduction of serum glutathione peroxidase and the increase of the malondialdehyde concentration, nitric oxide and protein carbonyl content in kidney (50-53). Importantly, the kidney protective property of curcumin is associated to maintenance of function and redox balance of mitochondria. These findings contribute to the protecting property of curcumin in the kidney to the diminution of the master regulator of antioxidant response nuclear factor erythroid-derived 2, attenuation of inflammatory response, inhibition of mitochondrial dysfunction, preservation of antioxidant enzymes and inhibition of oxidative stress (25-31). One study by Bayrak et al, showed the protective effect of curcumin against ischemia/reperfusion injury in rat kidneys. In this study, treatment with 200 mg/kg of curcumin daily for 7 days, significantly attenuated the levels of nitric oxide, protein carbonyl and malondialdehyde content in kidneys and urea, glutathione peroxidase and cystatin C levels in serum (12-18, 50-64).

Nephrotoxicity induced by chemicals

Kidney is a common target for toxicity, due to some chemical. A number of researchers have reported that curcumin can attenuate the renal injuries induced by some chemicals such as heavy metals. Heavy metal is a term that refers to any metallic chemical element and has a relatively high density and is toxic or poisonous at low concentrations. Several studies indicated the ameliorated effects of curcumin on heavy metals-induced nephrotoxicity such as cadmium, mercury and chromium. Cadmium can increases lipid peroxidation and induces oxidative stress in a biological system may be due to alterations in the antioxidant defense system (58-65). One experimental study showed the protective role of curcumin on cadmium-induced nephrotoxicity in rats. In this study male Wistar rats were treated once daily by oral gavage for 5 days and divided into 4 groups including control rats, cadmium acetate (200 mg/kg), curcumin (250 mg/kg) and in group four, rats pretreated with 250 mg/kg of curcumin for 1 hour before administration with cadmium acetate. Cadmium caused an increase in level of renal lipid peroxidation and reduced glutathione. Also the hydropic swelling and hypertrophy of proximal tubular cells were observed in renal cortex of rats which treated with cadmium. The results revealed that pretreatment with curcumin reduced both biochemical and histological alterations induced by cadmium (66). Mercury as a heavy silvery-white metal can induced nephrotoxicity via an increase in oxidative stress parameters including glutathione and lipid peroxidation levels and change in

level of catalase, superoxide dismutase and glutathione peroxidase activities in kidney. Treatment with curcumin (80 mg/kg/d) for 3 days was effective for protection against mercury-induced oxidative stress parameters and serum biochemical changes in the kidney of rats. Moreover, the concentration of mercury in the tissues was decreased after the pre/post-treatment with curcumin (66).

Potassium dichromate ($K_2Cr_2O_7$) is an inorganic chemical reagent, most commonly used as an oxidizing agent. As with all hexavalent chromium compounds, it is harmful to health and can induces nephrotoxicity in animals and humans. Molina-Jijón et al (67) showed that use of curcumin was effective in protecting of $K_2Cr_2O_7$-induced renal oxidant damage by a mitochondrial pathway. In this study male Wistar rats, were divided into 10 groups. The treatment with curcumin was including 3 different schemes, 1) complete treatment with 100, 200, and 400 mg/kg of curcumin 10 days before and 2 days after $K_2Cr_2O_7$ injection, 2) pretreatment with 400 mg/kg of curcumin for 10 days before $K_2Cr_2O_7$ injection and 3) posttreatment with 400 mg/kg of curcumin 2 days after $K_2Cr_2O_7$ injection. Then Rats were sacrificed 48 hour after $K_2Cr_2O_7$ or vehicle injection to evaluate mitochondrial and renal function and oxidant stress. At the end of this study, complete treatment and pretreatment with curcumin ameliorated histological damage, renal dysfunction, oxidant stress and decrease in antioxidant enzyme activity in mitochondria and kidney, which were induced by $K_2Cr_2O_7$. Likewise, pretreatment with curcumin attenuated the mitochondrial dysfunction including changes in ATP content, oxygen consumption, mitochondrial membrane potential and calcium retention. Furthermore, curcumin pretreatment induced the nuclear translocation of the nuclear factor-E2-related factor 2 (Nrf2) and increased the activity of glutathione S-transferase, superoxide dismutase and glutathione reductase (67).

Sodium fluoride is an inorganic chemical compound with the formula NaF that can induces nephrotoxicity. Curcumin at the doses of 10 and 20 mg/kg body weight (intraperitoneally) revealed nephroprotective effects in a model of rats study. In this study, the pretreatment with curcumin one week before the administration of fluoride (600 ppm) was effective in normalization of serum urea, serum creatinine and blood urea nitrogen. Also, curcumin prevented the decreasing of antioxidant enzyme including catalase and superoxide dismutase and increasing in level of renal lipid peroxidation (68).

Conclusion

According to various epidemiological data, renal failure, either acute or chronic, is a serious health and economical problem throughout the world. The necessity to develop kidney protective modalities sets the eyes in compounds such as curcumin, which has been used in the traditional medicine, specifically because of its protective effects against kidney damage. In addition, curcumin is a free radical scavenger due to its antioxidant capacity and many experimental investigations reported the ameliorative effect of curcumin in acute and chronic kidney problems such as diabetic kidney disease, nephrotoxicity and renal ischemia.

Authors' contribution

HN and ZAG wrote the primary draft. MRK edited the final manuscript.

Conflicts of interest

The authors declare no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by authors.

Funding/Support

None.

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