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Therapeutic effects of curcumin on kidney disease; an updated review of the current knowledge

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Abstract
Curcumin is the essential ingredient of turmeric and one of the most potent antioxidants. It also has several biological capabilities, including anti-inflammatory, anticarcinogenic, anticoagulant, antidiabetic, antiviral, antibacterial, and antifungal effects. Therefore, curcumin has a significant potential for the treatment and control of various diseases. In kidney disorders like chronic kidney disease (CKD) and diabetic nephropathy (DN), the mechanism of kidney damage is associated with oxidative stress and inflammation. Curcumin, which has antioxidant and anti-inflammatory abilities, can alleviate kidney damage and treat kidney diseases. In patients with kidney disorders, progression to end-stage renal disease (ESRD) is critical because it increases their mortality rate. It has also been proved that curcumin could diminish such progression due to its antioxidant and anti-inflammatory potential, improving the survival rate. Besides, it has numerous nephroprotective effects that are summarized in this review.

Keywords: Curcumin, Chronic kidney disease (CKD), Turmeric, Nephroprotective, Kidney, end-stage renal disease

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Introduction

Turmeric is a traditional herbal treatment and a standard food flavor. It consists of three curcuminoid compounds responsible for its yellow color, including demethoxycurcumin, bisdemethoxycurcumin and diferuloylmethane (curcumin). The only difference in their structure is related to the methoxy groups on their aromatic rings. Curcumin is an essential component of turmeric, which has antioxidant and anti-inflammatory effects. Several investigations have been carried out about its therapeutic effects on different diseases such as kidney disorders, diabetes, arthritis, fatty liver, cancer, atherosclerosis and neurological disorders (1). However, ingesting curcumin by itself may not result in health benefits because of its poor bioavailability. Nevertheless, various components like piperine, a compound of black pepper, can increase its bioavailability and enhance its efficacy.

In a meta-analysis-review study, Rolfe et al analyzed the information from 65 systematic reviews on the administration of turmeric/curcumin and its therapeutic effects on 20 non-communicable diseases (2). In addition, another review summarized the previous in vivo studies conducted about the anti-diabetic effects of curcumin. They concluded that curcumin improved the homeostasis of glucose and declined insulin resistance, resulting in the treatment of diabetes. It also explains the effect of curcumin administration on the animals' kidney function (3).

According to the World Health Organization (WHO), kidney diseases were among the top ten causes of death globally in 2019 (4). Hence, appropriate therapeutic strategies with the highest nephroprotective effects should be conducted to cure kidney disorders. Numerous studies have evaluated the beneficial effects of curcumin on kidneys. Including the study by Trujillo et al, which explained the nephroprotective effects of curcumin in kidney disorders (5). The efficacy of curcumin administration was recently proved in reducing renal injury due to rhabdomyolysis (6). Additionally, Molina-Jijón et al represented the protective impact of curcumin against renal injury due to the induction of hexavalent chromium [Cr (VI)] compound potassium dichromate K2Cr2O7 in rats (7).

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Implication for health policy/practice/research/ medical education

In kidney disorders, both the mechanism of kidney damage and progression to end-stage renal disease (ESRD) are associated with inflammatory factors and oxidative stress. Curcumin, which has antioxidant and anti-inflammatory abilities, can alleviate kidney damage and treat kidney disease.

The safety of curcumin has been shown in numerous animal model studies. However, few systematic studies about the pharmacology and toxicology of curcumin in humans have been performed.

Method of search

In this review, we analyzed several articles from the international scientific library databases to evaluate the therapeutic efficacy of curcumin in kidney diseases. We searched PubMed/Medline, Scopus and Google Scholar, using the following keywords; curcumin, end-stage renal disease, chronic kidney disease, turmeric, nephroprotection and kidney.

Nephroprotective effects of curcumin

The mortality rate due to kidney diseases has risen from 813 000 to 1.3 million between 2000 and 2019 (4). Therefore, a natural and safe therapeutic approach with the highest nephroprotective effects should be employed to prevent and cure kidney disorders. It has been indicated that curcumin could be a promising medication for nephrology disorder according to its potential as an anti-inflammatory and anti-oxidative treatment with few proven side effects.

Curcumin's nephroprotective effects are related to the reduction of oxidative stress and a loss of balance between reactive oxygen species (ROS) activation and antioxidant systems. It also prevents the degradation of nuclear factor erythroid-derived 2 (Nrf2), as the primary regulator of the antioxidant response, which consequently increases various antioxidant enzymes such as superoxide dismutase and glutathione peroxidase. It also can control the inflammatory process by declining the inflammatory transcription factors such as tumor necrosis factor-alpha (TNF-α) and nuclear factor kappa B (NF-κB) (5).

Various studies have investigated the nephroprotective ability of curcumin on different kinds of kidney disorders, including chronic kidney disease (CKD), diabetic nephropathy (DN), glomerulonephritis, acute kidney injury (AKI), medications/toxins-induced nephropathy and kidney damage due to rhabdomyolysis (5-8).

Nephroprotective effects of curcumin in chronic kidney disease

Chronic kidney disease previously called chronic renal failure (CRF), is a global public health problem through which the kidneys gradually lose their function, resulting in the accumulation of uremic toxins in the body. CKD, which is an inflammatory disease, is defined as either renal injury or glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 for more than 3 months, irrespective of cause (8,9). The progression of CKD to end-stage renal disease (ESRD) is the main problem for CKD patients because it raises mortality rates, the costs of healthcare and the need for dialysis or transplantation (10). Therefore, proper therapeutic approaches should be conducted to suppress or delay the progression of CKD to ESRD.

Curcumin can directly protect the renal tubules epithelial cells from oxidative stress by attenuating reactive species such as ROS and reactive nitrogen species (5,9).

Likewise, curcumin activates cytoprotective proteins, regulated by the Nrf2, resulting in an indirect antioxidant reaction against oxidative stress, which has an essential role in CKD progression to ESRD (5). It also activates Nrf2 and suppresses CKD progression by decreasing oxidative stress and inflammatory response (5,6). In a study by Soetikno et al, curcumin reduced renal fibrosis in rats with subtotal nephrectomy (a well-characterized model of CKD) through Nrf2 activation (11).

The nephroprotective effect of curcumin is also due to the maintenance of function and redox balance of mitochondria and inflammatory cytokines reduction (interleukin-1β [IL-1β], IL-6 and TNF-α) (5,6). Recently, Ali et al administrated curcumin to the adenine-induced CKD rat models for five weeks. They found the nephroprotective effects of curcumin were related to declining inflammation and oxidative stress through modulation of the transcription factor Nrf2 (12).

Recent studies proved both direct and indirect antioxidant effects of curcumin. In another study by Correa et al, the cardio-protective effects of curcumin in uremic rats were also related to both mechanisms of direct and indirect antioxidant effects (13).

One of the anti-inflammatory effects of curcumin is the inhibition of NF-κB activation, which regulates cell proliferation and inflammation (14). In addition, curcumin can downregulate transcription factors like cyclooxygenase-2 (COX-2) and signal transducer and activator of transcription 3 (1,15). In addition, Ghosh et al proved the anti-inflammatory effect of curcumin on improving kidney function in rats with CRF by neutralizing the effect of TNF-α on NF-κB and peroxisome proliferator-activated receptor gamma. Their study also indicated that curcumin administration in those rats caused a significant reduction in proteinuria, blood urea nitrogen (BUN) and plasma creatinine compared to enalapril (16). Ghosh et al, in another study, administered curcumin and enalapril together in rats with CRF and showed the nephroprotective efficacy of curcumin by its anti-inflammatory mechanism (17).

Recent evidence showed that high intestinal permeability in CKD leads to the leakage of pro-inflammatory biomolecules from the intestines into circulation. Therefore, it is indicated that curcumin

modifies intestinal permeability and consequently declines the level of circulatory inflammatory molecules. This result explains the anti-inflammatory effects and advantages of curcumin on CKD (9). Besides, curcumin therapy in rats could improve acute or chronic nephritis and immune-induced renal damage by reduction of proteinuria, BUN, crescent formation, glomerulonephritis and tubulointerstitial disease and also renal infiltration by lymphocytes (18,19). Curcumin has been administered in lupus nephritis studies and showed significant effects on alleviating proteinuria, hematuria, and renal arterial blood pressure (18,19). Moreover, curcumin supplementations were also found to reduce the IgG immune complex deposition in mice with lupus nephritis and decrease the renal inflammation notably (8).

Renal and tubulointerstitial fibrosis, are the final pathway in progressive forms of CKD which consists of four stages, including priming, activation, execution and progression (20). Curcumin can play a protective role for kidneys against fibrosis in the priming and activation phases of renal fibrosis (21).

In a previous clinical trial in which non-diabetic and DN Mexican patients received curcumin supplements for eight weeks which showed no significant change in the treatment of proteinuria, estimated GFR (eGFR) and lipid profile by curcumin. Although curcumin in this study was not beneficial for antioxidant enzymes or Nrf2 activities, it effectively reduced oxidative stress in those patients (22). Currently, other clinical trials also evaluate the effects of curcumin supplementation on Nrf2 expression, oxidative stress, inflammation and renal function in CKD patients (23,24).

Curcumin in hemodialysis patients

Uremic pruritus is a common complication of CKD, especially in hemodialysis patients, affecting patients' morbidity and mortality. Thereby, appropriate anti-pruritic therapeutic approaches with no side effects may improve the quality of life of such patients. Additionally, a double-blind placebo-controlled trial assessed the anti-pruritic effects of turmeric on 100 hemodialysis patients suffering from uremic pruritus. Their study demonstrated the beneficial effects of turmeric in uremic pruritus in ESRD patients by decreasing high-sensitivity C-reactive protein (hs-CRP) (25).

In CKD patients undergoing hemodialysis, gut microbiota produces uremic toxins, including p-cresyl sulfate (PCS), indoxyl sulfate (IS) and indole 3-acetic acid (IAA), all of which are harmful to the body. Prebiotics, however, can regulate the gut environment and suppress toxin production. Various studies have investigated the prebiotic effects of curcumin in CKD patients (26,27). For instance, in a randomized, double-blind trial on 28 patients with CKD on hemodialysis, the effects of curcumin supplementation on the production of uremic toxins from gut microbiota were assessed. This investigation demonstrated that curcumin juice reduced the PCS plasma levels without statistical differences in IS and IAA levels (26). Consequently, curcumin supplements as a prebiotic can modulate the gut environment and inhibit uremic toxins production.

Nephroprotective effects of curcumin in diabetic nephropathy

End-stage renal disease induced by DN is a widespread condition associated with high mortality and morbidity. It is assumed that proteinuria and transforming growth factor-β (TGF-β) may contribute to ESRD progression in patients with DN. Previous studies investigated the therapeutic effects of turmeric on DN through TGF-β suppression or reducing proteinuria. For instance, in a placebo-controlled trial, the effects of turmeric on serum and urinary TGF-β, TNF-α, IL-8 and proteinuria for four weeks on 40 patients with type-2 DN were evaluated. The study showed that turmeric can be administered as safe adjuvant therapy for DN patients with overt proteinuria. In this study, a significant reduction in proteinuria, TGF-β and IL-8 without substantial change in serum creatinine level in the turmeric group was seen too (28).

Accordingly, Lu et al evaluated the nephroprotective effects of curcumin in DN patients in a study in which curcumin was taken to db/db mice with DN for 16 weeks. They found that curcumin improved renal histological changes by protecting against glomerular expansion and ameliorated renal hypertrophy. It also revealed that curcumin corrected renal function since its diminished albuminuria (29). In addition, they suggested that the inhibition of NLRP3 inflammasome, as an essential factor in inflammation and tissue damage in CKD, AKI and fibrosis, mediates the nephroprotective effects of curcumin (29). In another study, the nephroprotective effects of curcumin against kidney damage from oxidative stress induced by a combination of diabetes mellitus and nicotine exposure in rats were assessed. It was shown that curcumin might improve nicotine-induced DN progression by regulating the mRNA expression levels of essential genes important in the progression of DN (30). In the study by ALTamimi et al, the nephroprotective effect of curcumin in diabetes mellitus induced by streptozotocin in rat models was determined. They expressed curcumin's protective role through the mechanisms of Nf-κB and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase suppression, Nrf2 activation, and downregulating protein kinase C isoform β-II (PKCβII) /p66Shc pathway (31).

Nephroprotective effects of curcumin in acute kidney injury

Acute kidney injury is characterized by an acute loss of renal function and has significant consequences such as prolonged hospital stays, accelerated CKD and increased mortality. Recently, studies regarding a safe therapeutic

option to prevent and recover AKI have attracted much attention, while curcumin seems to be an appropriate option. One of the studies was an investigation by Wu et al, which showed curcumin nephroprotective effects in rhabdomyolysis-induced AKI in rats. They explained the mechanism of curcumin in kidney function improvement in AKI was oxidative stress suppression through regulating the adenosine monophosphate-activated protein kinase and Nrf2/HO-1 signaling pathways. Additionally, curcumin improved AKI and cell apoptosis by activating the PI3K (phosphatidylinositol-3 kinase)/protein kinase B (Akt) pathway (32).

Cardioprotective effects of curcumin in CKD

A substantial increase in cardiovascular risk manifesting as heart failure, arrhythmias, coronary artery disease and sudden cardiac death accompanies CKD, resulting in a higher mortality rate. Therefore, cardioprotection approaches are crucial in the management of CKD to enhance patients' survival.

High levels of ROS production in chronic diseases like ESRD accelerated the prevalence of atherosclerosis and other chronic complications (33). Boaz et al found that the mean serum malondialdehyde (MDA) level, a marker of oxidative stress, was significantly higher in the CKD population on hemodialysis with cardiovascular disorders (CVD) than in those without CVD (34). As a result, increased oxidative stress is assumed to be the potential mechanism of CVD in CKD patients (35).

Cardiovascular disorders are a serious complication and a crucial leading cause of death in patients with ESRD on hemodialysis. Thus, cardioprotective approaches should be taken in such patients to improve their survival. Hemodialysis patients have an imbalance between oxidative and antioxidative markers because of the bio-incompatibility of dialysis membranes as an essential source of ROS and losses of antioxidants (33). Hemodialysis patients are also exposed to inflammation, characterized by plasma levels of acute-phase proteins such as CRP (36). A number of clinical trials investigated the cardioprotective effects of curcumin in hemodialysis patients. For example, a clinical trial evaluated the effects of curcumin on oxidative stress markers in 50 hemodialysis patients for eight weeks (37). This trial showed that curcumin decreased MDA, increased catalase enzyme and improved plasma albumin (37).

Protection against CVD in CKD rats was found as an effect of curcumin induction by suppressing oxidative stress-related mechanisms, cell death and mitochondrial dysfunction (35). Bugyei-Twum et al administered theracurmin, a novel by-product of curcumin, to treat cardiovascular complications in CKD rats. They explained the essential role of inflammation in CKD and the development of cardiovascular complications, in particular, damages mediated by NLRP3. Theracurmin had cardioprotective effects by the reduction of cardiac fibrosis and NLRP3 inflammasome activation (38).

Bioavailability of curcumin

Despite the beneficial effects of curcumin, the significant restriction in its clinical administration is low-bioavailability. The primary reasons for this problem are low gastrointestinal tract absorption due to poor solubility in water and rapid metabolism and clearance from the body. Besides, curcumin is chemically unstable in contact with alkaline pH, oxygen, ultraviolet (UV) and visible light (39). As a consequence, various approaches have been taken to increase its bioavailability. One way is using adjuvants like piperine which blocks curcumin's metabolic pathway to boost its absorption. Another strategy could be using nanoparticles like "nano-curcumin," which has the same antioxidant and anti-inflammatory effects as curcumin, though more bioavailability. Using liposomes, phospholipids and micelles are other examples of increasing the bioavailability of curcumin, studies have shown that phospholipid and micelle complexes enhance the absorption of curcumin in the gastrointestinal tract, resulting in higher serum concentration, lower excretion and increased bioavailability (15,40-42).

High bioavailable turmeric/curcumin analogs

The results of systematic reviews recommended that bioavailability-enhanced preparations for turmeric or curcumin could be valuable for treating several diseases. The microparticle curcumin, a natural health product that has both anti-inflammatory and antifibrotic properties, is more bioavailable than curcumin and may be an effective treatment for patients with CKD. In a multicenter clinical trial by Weir et al, the effect of microparticle curcumin on the improvement of albuminuria and eGFR was proved (43). Moreover, the beneficial effects of curcumin and chitosan-encapsulated curcumin on blood sugar, heart, and kidney injuries in the streptozotocin-induced type-1 diabetes in mice were compared in a study. It was revealed that curcumin encapsulated by chitosan was more effective in blood glucose reduction, increasing insulin level and treating heart and kidney damage than curcumin (44). In a study on mice with systemic lupus erythematosus and Sjogren's syndrome, ultra-soluble curcumin (USC) with a 35-fold increase in solubility, showed advantageous benefits as a potential medication (45).

In a recent study, a novel curcumin analog (B06) was administrated to diabetic rats and then a significant decline in inflammatory mediators in the serum, heart, kidney and renal macrophage infiltration was observed. It consequently showed a therapeutic effect on diabetic complications through an anti-inflammatory mechanism (46). Another curcumin analog (C66), with higher efficacy than the plant curcumin, was also used in diabetic nephropathic mice and showed nephroprotective effects (47).

Side effects of curcumin

The administration of curcumin has been proven to be safe in several animal studies and clinical trials. However, some mild and not life-threatening side effects, including diarrhea, rash, yellow stool and headache, have been reported in humans (48). Although the safety and efficacy of curcumin have been proved, conducting more systematic studies about the pharmacology and toxicology of curcumin in humans is required.

Conclusion

In kidney disorders, both the mechanism of kidney damage and progression to ESRD are associated with inflammatory factors and oxidative stress. However, growing evidence from its large efficacy on oxidative-stress-related damages to the kidney and its remarkable protective effect on other tissues like cardiac cells is of utmost interest. In the present study, we reviewed those mechanisms and curcumin's nephroprotective abilities, suggesting that it could be a promising medication in the future for patients with kidney disorders.

Authors' contribution

Conceptualization: TS, LS.
Methodology: TS, LS.
Validation: TS, LS.
Research: LS, TS, NA.
Resources: LS, TS.
Writing—original draft preparation: TS, LS.
Writing—reviewing and editing: HRJ, NA, FK, HVR, KA, TS, LS.
Visualization: LS, TS.
Supervision: TS, LS.
Project Management: TS.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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

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