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NEPHROTOXIC POTENTIAL OF *CURCUMA LONGA* AND CURCUMIN: CELLULAR PATHWAYS, OXIDATIVE STRESS, AND CLINICAL RELEVANCE

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ABSTRACT

Nephrotoxicity, defined by damage to the kidney caused by the administration of toxic substances like drugs, chemicals, or heavy metals, continues to be an important clinical problem. The kidneys function to provide homeostasis, filter the blood, and excrete waste products of metabolism, but their large blood flow and active transport processes render them particularly susceptible to toxic insults. Traditional therapeutic strategies in the management of nephrotoxicity are not only limited but tend to concentrate on symptom management alone without preventing or reversing the injury. This has spurred investigations of natural products, with medicinal plants in the forefront as a source of nephroprotective agents. One such plant is Curcuma longa, popularly referred to as turmeric, whose bioactive ingredient curcumin has antioxidant, anti-inflammatory, and anti-apoptotic activities. The phytochemical composition of *Curcuma longa* consists of curcuminoids, volatile oils, and various phenolic compounds. The major bioactive constituent, curcumin, has been widely studied for its pharmacological activity. Its nephroprotective effect is largely due to its capacity to neutralize oxidative stress, the mechanism of action of nephrotoxicity. Most of the nephrotoxic substances, including cisplatin, gentamicin, and toxins in the environment, produce reactive oxygen species (ROS) that interfere with cell membranes, cause DNA damage, and impair mitochondrial activity. Curcumin inactivates these free radicals by activating endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. This not only decreases oxidative injury but also maintains cellular homeostasis.

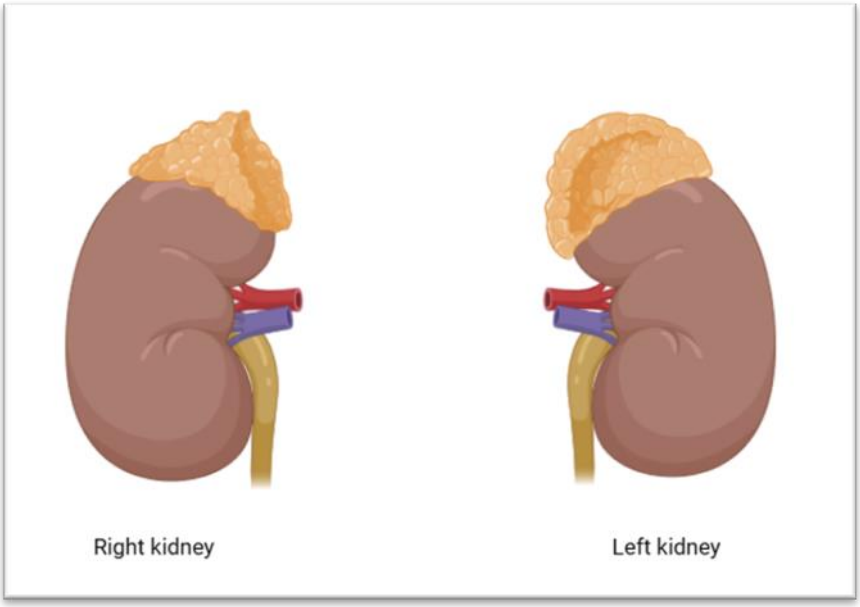
Besides its antioxidant properties, curcumin demonstrates potent anti-inflammatory activities. Nephrotoxicity has a tendency to activate inflammatory cascades by cytokines including tumour necrosis factor-alpha (TNF-α), interleukins, and nuclear factor-kappa B (NF-κB) signaling. Chronic inflammation enhances renal tissue damage, contributing to fibrosis and chronic kidney dysfunction. Curcumin has been found to inhibit NF-κB activation, thus inhibiting the release of pro-inflammatory mediators. This action plays an important role in diminishing structural and functional injury in the kidneys. In addition, curcumin regulates apoptotic processes by preventing caspase activation and saving renal tubular epithelial cells from apoptosis. Collectively, these activities underscore curcumin's multi-faceted involvement in preventing nephrotoxic injury. Experimental and clinical research add confirmatory evidence for these protective actions. In animal models of cisplatin-induced nephrotoxicity, curcumin supplementation has been correlated with lower serum creatinine and blood urea nitrogen levels, which are markers of enhanced renal function. Histopathological examinations also establish decreased tubular necrosis and integrity of kidney structure. Comparable findings have been seen in gentamicin-induced nephrotoxicity models, where curcumin suppressed renal oxidative stress and inflammation. Although clinical data in humans are still very limited, initial studies indicate that curcumin supplementation may enhance antioxidant levels and might even decrease nephrotoxic side effects of chemotherapeutic agents. In spite of its promising potential, clinical use of curcumin is hampered by its low bioavailability, extensive metabolism, and minimal systemic bioavailability. To overcome these drawbacks, numerous formulations like curcumin nanoparticles, liposomes, and curcumin-phospholipid complexes have been designed with enhanced pharmacokinetic profiles and amplified nephroprotective effects. Future research on optimized delivery systems is essential for converting preclinical evidence into successful therapy for patients with risk for nephrotoxicity.

KEYWORDS: Renal health, Curcumin, Drug-induced kidney injury, Good health and wellbeing, Anti-oxidant therapy, etc.

INTRODUCTION

Kidney is a critical organ that is in charge of homeostasis through the elimination of metabolic waste, maintaining electrolyte balance, and fluid volume regulation in the body.[1,2] Any form of dysfunction can have severe implications on health. Nephrotoxicity refers to a situation in which exposure to toxic substances results in structural or functional damage of

the kidney.[3,4] This toxicity is often evident as decreased glomerular filtration, tubular impairment, or even AKI, which if not treated can progress to chronic kidney disease.[5,6] Nephrotoxicity is clinically important because it not only adds to morbidity and mortality but also makes therapeutic management more complex, particularly in patients on treatment with drugs that have renal side effects.[7,8]



- **Definition and Relevance of Nephrotoxicity:**

Nephrotoxicity is the damage to the kidneys by toxic chemicals, drugs, or toxins in the environment. It may either be reversible or irreversible, as it depends on how much exposure there has been and whether the kidney is capable of replacing the damaged cells. The relevance of nephrotoxicity is that it is quite common and affects healthcare. For instance, nephrotoxicity is one of the top reasons for drug withdrawal and dose restriction in clinical use. In addition, kidney injury is usually asymptomatic in its initial phases and so is hard to diagnose until considerable harm has been done. Detection and prevention of nephrotoxicity at an early stage are thus critical in the protection of renal function.[9]

- **Common Etiology of Nephrotoxicity**

A number of agents can cause nephrotoxicity and tend to come in three large categories, which include drugs, heavy metals, and environmental toxins.

i. Drugs – Most drugs that are used therapeutically have been noted to damage the kidneys. Antibiotics like aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic drugs like cisplatin, and some antivirals are some of the best-

characterized nephrotoxic drugs. They commonly exert their action through oxidative stress, damage to mitochondria, or through direct damage to renal tubular epithelial cells. Owing to the vast utilization of these agents, drug-induced nephrotoxicity is still the most prevalent clinical problem.[10]

ii. Heavy Metals – Heavy metal exposure, such as cadmium, mercury, and lead, is a significant etiological factor in nephrotoxicity. The metals accumulate in renal cells and interfere with normal physiological functions, resulting in proteinuria, necrosis of the tubules, and renal clearance impairment. Occupational exposure, polluted water, and inadmissible disposal of industrial waste are key sources of heavy metal-induced renal damage.[11]

iii. Environmental and Natural Toxins – Environmental toxins, plant toxins, and mycotoxins also play an important role in nephrotoxicity. Aflatoxins, aristolochic acid, and certain pesticides have been shown to induce renal impairment. Unregulated consumption of herbal medicines and exposure to polluted food or water in most developing countries add to the risk of toxin-induced nephrotoxicity.[12]

- **Need for Nephroprotective Agents:**

Considering the inevitable exposure to nephrotoxic agents in the form of drugs and environmental pollutants, there is an increasing demand for useful nephroprotective strategies. Traditional therapeutic approaches predominantly are limited to drug withdrawal or symptom management but seldom provide protection against continued injury at the cellular level. This lack has prompted the investigation of natural products and phytochemicals with possible nephroprotective effects.[13]

One of them is Curcuma longa, or turmeric. It is being traditionally utilized in medicine due to its anti-inflammatory, antioxidant, and detoxifying effects. The bioactive substance curcumin has been scientifically studied for its potential to combat oxidative stress, inhibit inflammation, and regulate signaling pathways associated with cellular survival and repair. Such processes are directly applicable in the scenario of nephrotoxicity, wherein oxidative stress and inflammation are pivotal to the pathogenesis of renal damage.[14]

Thus, the function of Curcuma longa in nephrotoxicity is important not only therapeutically but also to create preventive measures for renal injury. With increasing kidney diseases

burden worldwide, studies on natural nephroprotective drugs such as turmeric offer a viable option for less harmful, more potent interventions.[15]

Overview

- Botanical Description and Traditional Uses:

The perennial plant Curcuma longa, also referred to as turmeric, is a member of the Zingiberaceae family. Originally from South and Southeast Asia, it is currently grown for commercial purposes in China, India, and other tropical nations. This plant has long leaves that have a strong scent, and it usually reaches a height of one meter. The most significant component of the plant is the rhizome, which has medicinal, dyeing, and spice properties. The striking yellow-orange hue of turmeric is attributed to its rhizome. Usually, it is dried and then finely powdered.[16,17]

Turmeric has been valued for centuries in traditional medicine systems such as Ayurveda, Siddha, and Traditional Chinese Medicine. It has been used to treat various health conditions, including digestive issues, respiratory infections, liver problems, and inflammatory disorders. In addition, it has been traditionally applied as a topical antiseptic for treating wounds and skin infections. Beyond its medicinal applications, turmeric holds cultural and spiritual significance, particularly in Indian rituals and cuisine, where it symbolizes purity and healing. Its long-standing use highlights the recognition of its therapeutic benefits long before modern scientific studies confirmed its biological activity.[18,19]

- **Phytochemical Composition**

The pharmacological activity of Curcuma longa can largely be attributed to its abundant phytochemical content. The major bioactive compounds present in the plant are curcuminoids, volatile oils, and other phenolic compounds.[20,21]

i. Turmeric gets its yellow hue from phenolic chemicals called curcuminoids. Minor curcuminoids include demethoxycurcumin and bisdemethoxycurcumin, whereas curcumin is the most important curcuminoid. These three compounds account for most of the biological activities of turmeric, including antioxidant, anti-inflammatory, and anticancer activities.[22]
ii. Volatile Oils – Turmeric has essential oils responsible for its scent and pharmacological activities. Prominent components of the volatile oil fraction are turmerone, atlantone, and

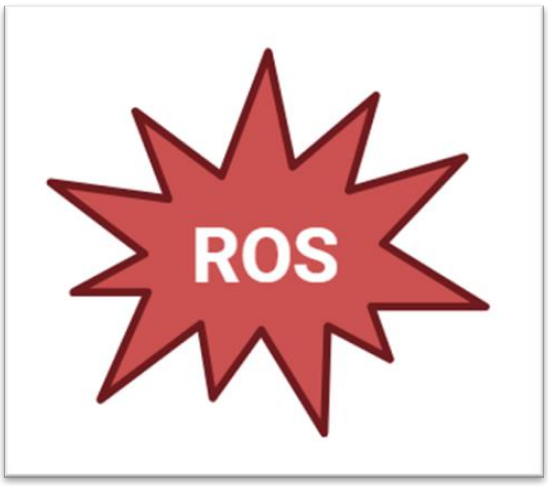
zingiberene. These chemicals have antimicrobial, anti-inflammatory, and immunomodulatory activities, contributing to the therapeutic diversity of turmeric.[23]

iii. Phenolic and Other Constituents – Turmeric also possesses phenolic acids, flavonoids, and proteins, which supplement its pharmacological profile. The constituents synergistically interact with curcuminoids to further augment antioxidant activity and confer protective functions against cell injury.[24]

The intricate phytochemical composition of Curcuma longa enables it to target multiple signaling pathways implicated in disease progression, thereby constituting a potential natural remedy for therapeutic and preventive interventions.[25, 26]

- Significance of Curcumin as the Predominant Bioactive Ingredient:

Among the varied phytochemicals of turmeric, curcumin is the most widely researched and pharmacologically active. It is a hydrophobic polyphenol yielding turmeric its distinctive yellow colour and being the major contributor to its pharmacological activity. Numerous biological effects, including anti-inflammatory, anti-cancer, anti-microbial, and antioxidant qualities, are exhibited by curcumin. Its ROS scavenging ability and induction of endogenous antioxidant defences are especially significant in disorders such as nephrotoxicity, where the disease is characterized by oxidative stress contributing to renal injury. Curcumin also modulates several signaling pathways like NF-κB, Nrf2, and apoptotic pathways, thus dampening inflammation and supporting cell repair mechanisms.[27,28]



In nephrotoxicity, curcumin has been demonstrated to safeguard renal tissue against drug-induced, heavy metal-induced, and toxin-induced injury. Experimental studies illustrate the ability of curcumin to inhibit lipid peroxidation, preserve renal tubular integrity, and reduce

fibrosis. Its pleiotropic effects render it an appealing option for nephroprotection, given the shortcomings of traditional pharmacological treatment.[29,30]

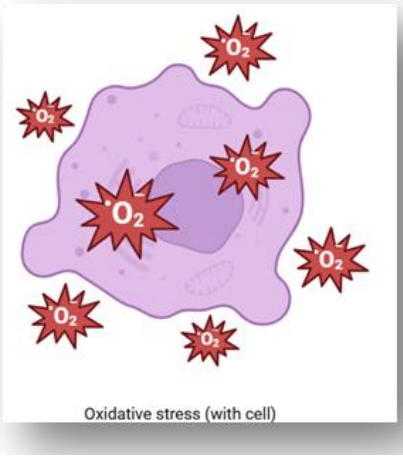
Another notable characteristic of curcumin is its safety profile. In spite of its low bioavailability, attempts to increase its absorption and therapeutic effects by formulation with nanoparticles, liposomes, as well as adjuvants like piperine have been made. This has new doors opened for its use in the clinic.[31, 32]

In aggregate, curcumin is the keystone of Curcuma longa's medicinal activity. Its triple-level biological actions not only justify historical usage of turmeric but also make it a potential natural candidate for the treatment of nephrotoxicity and other oxidative stress disorders.[33,34]

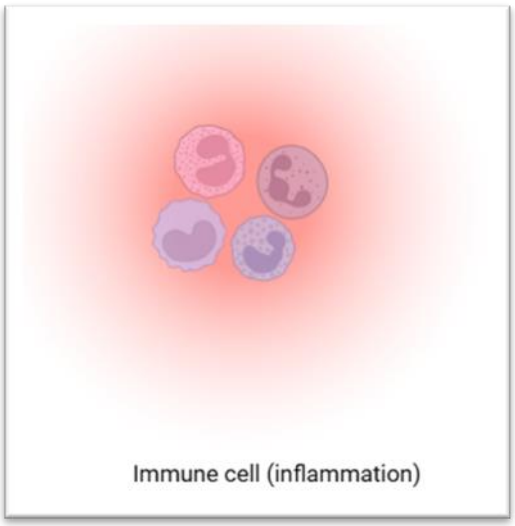
Pathophysiology of Nephrotoxicity:

- Mechanisms of Kidney Damage: Kidneys are very sensitive to toxic damage because they receive a large blood volume, have active reabsorption mechanisms, and high metabolic rates. Nephrotoxicity is caused by a variety of mechanisms, and some of the most important ones include oxidative stress, inflammation, apoptosis, and fibrosis.[35]

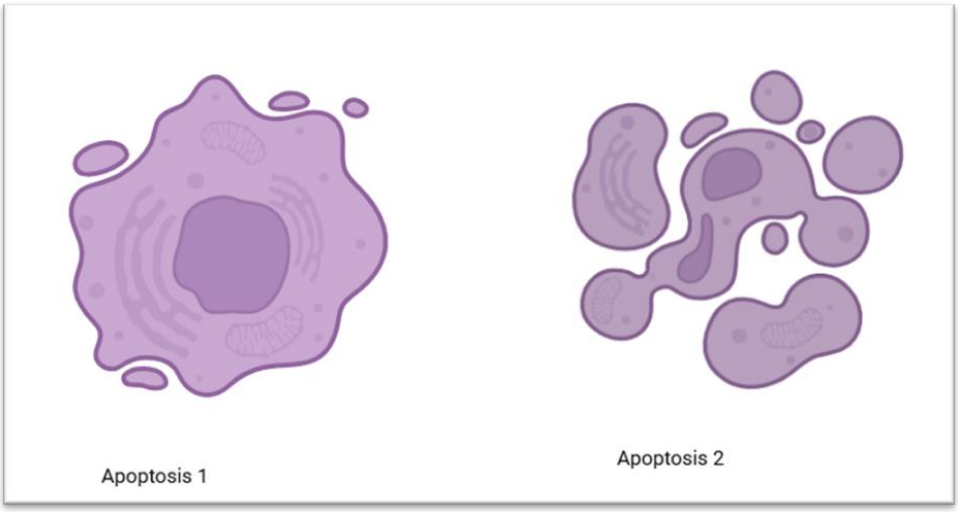
i. Oxidative Stress: One of the most critical mechanisms of nephrotoxicity is oxidative stress. The kidneys, and more specifically the proximal tubular cells, are extremely susceptible to harm from reactive oxygen species (ROS) due to their high metabolic activity. Overproduction of ROS overpowers the antioxidant defence system, causing lipid peroxidation, protein oxidation, and DNA damage. Not only does this compromise cellular integrity but also mitochondrial function, which further enhances oxidative injury. Oxidative stress contributes to acute and chronic kidney damage to a large extent, irrespective of the nephrotoxic agent.[36]



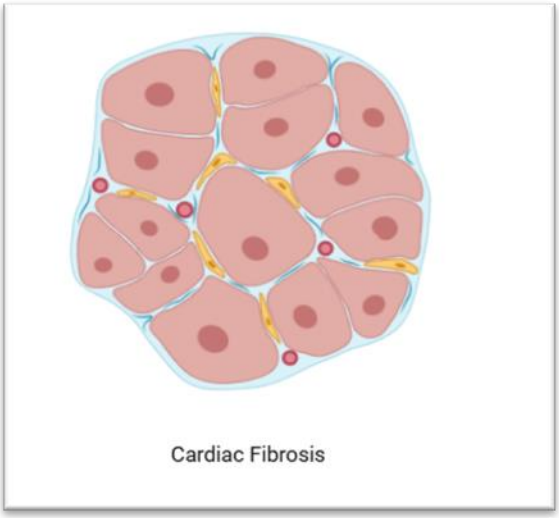
ii. Inflammation: Nephrotoxic insults also activate pro-inflammatory signaling pathways, in particular NF-κB and release of cytokines. Infiltration of immune cells like macrophages and neutrophils into renal tissues exacerbates injury by generating further ROS and pro-inflammatory mediators. Chronic inflammation leads to structural remodelling of renal tissue, promoting the progression from reversible acute injury to irreversible chronic kidney disease (CKD).[37]



iii. Apoptosis: A second key mechanism is induction of programmed cell death. Nephrotoxins trigger the intrinsic and extrinsic pathways of apoptosis, leading to tubular epithelial cell loss. Mitochondrial impairment, activation of caspases, and DNA fragmentation are typical findings of apoptosis in nephrotoxicity. Although apoptosis is a protective response by eliminating damaged cells initially, hyperactivation leads to extensive tubular atrophy and renal dysfunction.[38]



iv. Fibrosis: Fibrosis is the common end pathway of chronic nephrotoxicity. Chronic oxidative stress, inflammation, and apoptosis stimulate fibroblasts and promote the deposition of extracellular matrix proteins. This results in glomerulosclerosis and tubular interstitial fibrosis, both of which impair renal structure and function. Once fibrosis has occurred, renal injury is mostly irreversible, emphasizing the need for early treatment.[39]



- **Examples of Nephrotoxic Agents:**

A number of drugs and environmental substances are established causes of nephrotoxicity.

i. Cisplatin: Cisplatin, a platinum drug, is the most extensively researched nephrotoxic chemotherapeutic agent. Although potent against solid tumors, its application is restricted by dose-limiting nephrotoxicity. Cisplatin results in renal tubular cell death, mitochondrial damage, and the generation of ROS. Cisplatin also initiates inflammatory processes, aggravating kidney damage. Nephrotoxicity is a limiting factor despite supportive maneuvers in long-term use.[40]

ii. Gentamicin: Gentamicin, an aminoglycoside antibiotic, is also a significant nephrotoxic compound. Gentamicin is sequestered in renal proximal tubule cells and causes lysosomal disruption, oxidative injury, and apoptosis. Gentamicin nephrotoxicity is mediated by acute tubular necrosis, which can cause acute kidney injury. In light of the fact that gentamicin is a life-saving antibiotic, attempts to modulate its nephrotoxicity are of primary interest in pharmacological research.[41]

iii. Environmental Toxins: Apart from drugs, environmental toxins including heavy metals (cadmium, mercury, lead) and herbal toxins (e.g., aristolochic acid) are major causes of nephrotoxicity. Heavy metals deposit in the renal cortex, interfering with normal

enzymatic processes and triggering oxidative stress. Aristolochic acid contained in certain traditional herbal remedies is a well-known nephrotoxin that causes interstitial fibrosis and urothelial cancer. These incidents depict the wide range of nephrotoxic agents across clinical and environmental contexts.[42,43]

Pharmacological Properties

Nephrotoxicity, caused by drugs, environmental toxins, or toxins, is an important cause of acute kidney injury (AKI) and chronic kidney disease (CKD). The pathologic mechanisms are oxidative stress, inflammation, apoptosis, and fibrosis, which together compromise renal function and structure. With such multiple pathological pathways, natural compounds with multi-targeted therapeutic action are increasingly of interest for nephroprotection. Curcuma longa (turmeric), which is used widely in traditional medicine, has shown strong pharmacological potential in safeguarding kidneys against toxic injury. Its bioactive molecule, curcumin, possesses antioxidant, anti-inflammatory, anti-apoptotic, and anti-fibrotic properties, thus emerging as an ideal nephroprotective agent.[44,45]

i. Antioxidant Potential: Oxidative stress is the pivotal mechanism of nephrotoxicity. Damage to lipids, proteins, and DNA caused by an excess of reactive oxygen species (ROS) eventually compromises renal tubular function. Antioxidant defences like glutathione (GSH), catalase, and superoxide dismutase (SOD) are frequently reduced during nephrotoxic damage, making the kidney susceptible.

Curcumin, the major curcuminoid of Curcuma longa, possesses powerful antioxidant activity via two main mechanisms: direct scavenging of ROS and enhancement of endogenous antioxidant mechanisms.[46,47]

a. ROS Scavenging: Curcumin possesses a polyphenolic backbone with hydroxyl groups that can scavenge free radicals like superoxide anion, hydroxyl radicals, and peroxynitrite. This inhibits lipid peroxidation and protects renal cell membranes from damage.[48,49]
b. Augmenting Endogenous Antioxidants: Curcumin activates the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which controls antioxidant response elements. Activation of Nrf2 enhances antioxidant enzyme expressions such as SOD, glutathione peroxidase, and heme oxygenase-1. Through the enhancement of these endogenous antioxidants, curcumin enhances the ability of the kidney to withstand oxidative stress.[50]

ii. Anti-inflammatory Effects

Inflammation is a key cause of nephrotoxicity. Nephrotoxic compounds induce inflammatory cascades by activating nuclear factor-kappa B (NF-κB), a transcription factor involved in cytokine production. This results in upregulation of pro-inflammatory mediators such as tumour necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). Chronic inflammation worsens renal injury and speeds fibrosis.[51,52]

Curcumin has potent anti-inflammatory activities that reverse these processes directly:

a. NF-κB Inhibition: Curcumin inhibits NF-κB activation by blocking the phosphorylation and degradation of its inhibitory protein, IκBα. This inhibits NF-κB translocation into the nucleus, diminishing transcription of inflammatory cytokines.[53,54]
b. Curcumin modulates cytokines by increasing anti-inflammatory cytokines like IL-10 and decreasing circulating and renal tissue levels of TNF-α, IL-1β, and IL-6. This balances the immune response, preventing tissue damage.[55,56]

iii. Anti-apoptotic Activity

Apoptosis, or programmed cell death, is a key process involved in kidney damage caused by toxins.

Cisplatin and gentamicin cause cell death by damaging mitochondria, leading to the release of cytochrome c and the activation of caspases. Excessive cell death in the renal tubular epithelial cells leads to kidney dysfunction and structural damage.[57]

Curcumin helps protect the kidneys by regulating the pathways that lead to cell death:

a. Caspase Inhibition: Curcumin reduces the activity of caspases, particularly caspase-3 and caspase-9, which are key proteins in the process of cell death.[58]
b. Mitochondrial Protection: Curcumin helps maintain the integrity of mitochondria, preventing the release of cytochrome c and ensuring the production of ATP. This stops the process of cell death that occurs through mitochondria.[59]
c. Modulation of Bcl-2 Family Proteins: Curcumin increases the levels of proteins that prevent cell death, such as Bcl-2, while reducing the levels of proteins that promote cell death, like Bax. This changes the balance in favour of cells staying alive.[60]

By working through these pathways, curcumin prevents too much cell death and protects the renal tubular cells, which are essential for filtering and reabsorbing substances in the kidney.

Studies on rats treated with cisplatin show that curcumin has a protective effect by reducing cell death in the tubular cells.[61]

iv. Anti-fibrotic Properties

Fibrosis is the last step of long-term kidney damage. It happens when the body makes too many extracellular matrix (ECM) parts, such collagen.

Transforming growth factor-beta 1 (TGF-β1) is a major factor that causes fibrosis by activating fibroblasts and increasing ECM buildup. Continuous fibrosis leads to scarring of the glomeruli, shrinkage of the tubules, and loss of kidney function that cannot be reversed.[62]

Curcumin helps prevent fibrosis by influencing these processes:

a. Inhibition of TGF-β1: Curcumin reduces the production of TGF-β1 and it signaling pathways, which stops the activation of fibroblasts.[63]
b. Inhibition of ECM Accumulation: Curcumin prevents the build-up of collagen and fibronectin in the kidneys, slowing the progression of fibrosis.[64]

Experimental and Preclinical Evidence:

Nephrotoxicity is a serious harmful consequence of many of the commonly applied therapeutic drugs, including cisplatin, aminoglycoside antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs). The pathologic alterations of nephrotoxicity involve tubular necrosis, glomerular damage, oxidative stress, and inflammatory cell infiltration. Growing evidence documents the therapeutic potential of natural substances in mitigating renal injury. Among them, Curcuma longa (turmeric), and most specifically its active ingredient curcumin, has shown protective potential against drug-induced nephrotoxicity in experimental and preclinical models. The current report discusses evidence from animal models, histopathological data, biomarker studies, and dose-dependent effects of curcumin treatment.[65, 66]

i. Findings from Animal Models of Drug-Induced Nephrotoxicity

Animal research has given considerable information regarding the nephroprotective effect of Curcuma longa. In rodent models subjected to nephrotoxic drugs like cisplatin, gentamicin, and Adriamycin, curcumin supplementation was linked with decreased renal impairment. The

protective actions have been ascribed to its very potent antioxidant and anti-inflammatory actions.[67]

In cisplatin-induced nephrotoxicity models, curcumin lowered the serum creatinine and blood urea nitrogen (BUN) levels remarkably, reflecting enhanced renal function. In addition, curcumin treatment lowered lipid peroxidation markers like malondialdehyde (MDA) and raised antioxidant enzyme activities like superoxide dismutase (SOD) and catalase. In gentamicin-induced models, curcumin attenuated not only oxidative stress but also inhibited the release of proinflammatory cytokines like tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6).[68, 69]

These observations indicate that curcumin prevents both functional and structural renal damage caused by nephrotoxic drugs. Notably, its effectiveness for diverse nephrotoxic agents points towards a wide spectrum of protective effects.[70]

ii. Histopathological Changes and Biomarker Evaluation:

Histopathology has been a key method for evaluating how curcumin helps protect the kidneys from toxic damage.

In models where animals were not treated, their kidneys showed severe damage, including damaged kidney tubes, loss of the layer of cells lining the tubes, shrinkage of small blood vessel clusters, and an increase in harmful immune cells. However, in animals that received curcumin, there was a clear improvement. The structure of the kidney tubes was better preserved, there was less cell death, and the number of harmful immune cells was reduced.[71]

In models where kidneys were damaged by the drug cisplatin, the tissue samples showed nearly normal kidney tube structures with very little cell swelling in animals that had been given curcumin beforehand. Similarly, in animals treated with gentamicin, curcumin helped reduce the severity of damage to the kidney tubes and kept the small blood vessel structures intact.

Biomarker tests support these findings.[72]

Curcumin was found to lower levels of substances that show oxidative stress, such as malondialdehyde (MDA) and nitric oxide. It also increased the levels of glutathione (GSH), an important protective substance in kidney tissue. Additionally, curcumin lowered the levels

of blood markers that show kidney damage, such as creatinine, blood urea nitrogen (BUN), and cystatin C. Urine markers, like N-acetyl-β-D-glycosaminidase (NAG) and kidney injury molecule-1 (KIM-1), which signal early kidney damage, were also reduced in animals treated with curcumin. These results show that curcumin helps protect the kidneys in several ways, improving both how the kidneys function and their appearance under a microscope.[73]

iii. Dose-Dependent Effects of Curcumin

The protective effects of curcumin appear to depend on the dose used.

In preclinical studies, various doses were tested, usually between 50 mg/kg and 200 mg/kg of body weight in animals. Lower doses (up to 50 mg/kg) offered some protection, mainly by reducing oxidative stress but with only a small improvement in how well the kidneys worked. Intermediate doses (100 mg/kg) had more noticeable effects, including a significant drop in blood markers of kidney damage like creatinine, BUN, and visible tissue damage. At higher doses (150–200 mg/kg), curcumin showed strong protection for the kidneys, often matching or even surpassing the effectiveness of standard kidney-protecting drugs.[74]

However, the dose-dependent response also suggests there is a point were increasing the dose no longer provides more benefit, indicating that the protective effect has reached its maximum. Importantly, curcumin was very safe at these tested doses, with little to no harmful side effects in the animals. The relationship between dose and effect highlights the need for better methods to deliver curcumin so that its protective benefits can be maximized without using higher than necessary amounts.[75]

iv. Mechanistic Insights:

Curcumin's nephroprotective action is mediated through various mechanisms. Its strong antioxidant action lowers reactive oxygen species (ROS) and lipid peroxidation, thus inhibiting oxidative damage to tissue. Curcumin's anti-inflammatory actions, mediated by the inhibition of NF-κB signaling and inhibition of proinflammatory cytokines, are responsible for lowered renal inflammation. Curcumin also modulates apoptosis by increasing the anti-apoptotic proteins (Bcl-2) and lowering the pro-apoptotic markers (Bax, caspase-3), which synergistically inhibit tubular cell death. The compound also maintains mitochondrial function, thereby adding renal protection.[76]

Clinical Evidences in Humans

Nephrotoxicity is still an important issue in clinical practice, especially among patients who are being treated with chemotherapeutic drugs, antibiotics, or those with long-standing comorbidities like diabetes and hypertension. Although preclinical evidence of effective nephroprotective action of Curcuma longa (turmeric) and its bioactive molecule curcumin has been impressive, its implications in the clinical arena have been slow to accrue. Human trials have started evaluating the effectiveness of curcumin supplementation to prevent or reduce nephrotoxicity, with emphasis placed on renal biomarkers, oxidative stress, and pro-inflammatory mediators. The present report summarizes existing clinical evidence, placing emphasis on current findings and existing gaps in research.[77]

i. Trials With Curcumin Supplementation in Nephrotoxic Patients:

Various clinical trials have compared the role of curcumin among patients with nephrotoxic conditions, such as those undergoing chemotherapy, diabetic nephropathy patients, and patients with chronic kidney disease (CKD).[78]

a. Cisplatin-treated patients with cancer: There are a few small-scale clinical trials that have investigated curcumin supplementation in patients with cancer who receive cisplatin, an often-used chemotherapeutic drug notorious for its nephrotoxicity. Initial results indicate that curcumin could prevent impairment of renal function during chemotherapy, with decreases in serum creatinine and enhancements in global renal tolerance. Still, sample sizes are limited and dosing regimens differ significantly among studies.[79]
b. Diabetic nephropathy: Randomized controlled trials (RCTs) in diabetic patients with incipient nephropathy have shown improvement in proteinuria and decrease in markers of kidney damage after curcumin supplementation. Studies have mentioned the effects of benefits on urinary albumin excretion and GFR stabilization, indicating a possible renoprotective effect in metabolic nephropathy.[80]
c. Chronic kidney disease (CKD): In clinical trials in CKD patients, curcumin supplementation has been shown to reduce inflammatory mediators and oxidative stress, both of which are key contributors to progression of renal injury. Quality-of-life measurements have been improved, and renal function decline has slowed, although the degree of benefit is variable across studies.[81]
d. Haemodialysis patients: Certain interventional studies have given curcumin to haemodialysis patients to minimize systemic dialysis-related oxidative stress and

inflammation. Results are decreases in proinflammatory cytokines and oxidative markers, but proof of direct benefit on long-term renal outcomes is restricted.[82]

ii. Effects on Renal Biomarkers, Oxidative Stress, and Inflammation

a. Renal Biomarkers

Human trials routinely measure classic renal function indicators like serum creatinine, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR). Clinical trials in patients with diabetic nephropathy and CKD show small improvements in these markers with curcumin supplementation. For example, declines in proteinuria and eGFR stabilization have been noted, reflecting protective effects on glomerular and tubular function. In chemotherapeutic nephrotoxicity, initial findings indicate curcumin can decrease the severity of renal injury, but these need to be confirmed.[83]

b. Oxidative Stress

Oxidative stress is a key pathogenic process in nephrotoxicity, and various trials have quantified markers including malondialdehyde (MDA), advanced oxidation protein products (AOPPs), and antioxidant enzyme activities. Supplementation with curcumin has been found to decrease MDA levels and enhance endogenous antioxidants like superoxide dismutase (SOD) and glutathione (GSH). In patients with CKD and dialysis, these are especially significant, as oxidative imbalance hastens disease progression and aggravates cardiovascular risk.[84]

c. Inflammation

Inflammatory mediators such as TNF-α, interleukin-6 (IL-6), and C-reactive protein (CRP) are increased in nephrotoxic conditions and CKD. Clinical trials repeatedly show that curcumin supplementation decreases these proinflammatory biomarkers. In diabetic nephropathy, decreases in CRP and cytokine levels are associated with improvement in proteinuria and renal function. In patients undergoing dialysis, curcumin has been linked to decreased systemic inflammation, possibly with an overall better prognosis. These anti-inflammatory actions correlate with preclinical evidence, strengthening the mechanistic rationale for curcumin's nephroprotective effects.[85]

iii. Limitations and Gaps in Existing Clinical Data

While promising, the clinical evidence for curcumin in nephrotoxicity is still limited by a number of factors:

a. Small numbers: Most studies are pilot or small-scale with less than 100 participants, constraining statistical power and generalizability.
b. Heterogeneity of study populations: Clinical trials vary extensively in patient populations, from cancer patients being treated with nephrotoxic chemotherapy to diabetic nephropathy or CKD patients. Such diversity makes it difficult to compare and impacts the ability to define standard protocols.[86]
c. Formulation and dosage variability: Curcumin's low bioavailability is a major hindrance. Various research employs different formulations—native curcumin, nanoparticle preparations, or curcumin in conjunction with bioenhancers like piperine. Heterogeneous dosing regimens complicate the establishment of maximal therapeutic doses.
d. Short trial lengths: Most trials have relatively short lengths (8–24 weeks), which is too short to evaluate long-term renoprotective effects or the progression of disease. Chronic nephrotoxicity usually takes years to occur, and brief trials might be biased toward underestimating curcumin's potential benefits.[87]
e. Short trial lengths: Most trials have relatively short lengths (8–24 weeks), which is too short to evaluate long-term renoprotective effects or the progression of disease. Chronic nephrotoxicity usually takes years to occur, and brief trials might be biased toward underestimating curcumin's potential benefits.[88]
f. Safety and tolerability data: Curcumin is safe in general, but big trials are yet to be conducted to assess its long-term safety in patients with renal impairment, especially when used in combination with other drugs.[89]

Challenges and Limitations:

Curcuma longa (turmeric) and its active compound curcumin have been well investigated due to their antioxidant, anti-inflammatory, and nephroprotective activities. Preclinical and early clinical research indicate the therapeutic potential of curcumin in preventing nephrotoxicity caused by chemotherapy drugs, antibiotics, and metabolic diseases like diabetes. Nonetheless, some limitations hold it back from clinical application. Major drawbacks are poor bioavailability, high metabolism and low systemic absorption, and safety issues at increased doses. This review critically appraises these limitations and their therapeutic implications for the use of curcumin in nephrotoxicity.[90]

i. Poor Bioavailability of Curcumin:

Poor bioavailability of curcumin is one of the most well-known limitations of curcumin. While curcumin shows excellent pharmacological activities in vitro, curcumin's efficacy in vivo is limited because of difficulties in reaching adequate plasma and tissue levels.

Curcumin is lipophilic and has very poor aqueous solubility, so the absorption from the gastrointestinal tract is poor. Even when taken in relatively high oral doses, only a small amount of curcumin finds its way into systemic circulation in an active state. This renders it impossible to deliver therapeutic levels to the kidneys where its nephroprotective effect is most required.

Various methods have been formulated to improve bioavailability, ranging from curcumin nanoparticles to liposomal curcumin, phospholipid complexes, and co-treatment with bioenhancers such as piperine in black pepper. Piperine has, for example, been found to enhance curcumin bioavailability by 2000% according to human studies. In spite of these, the extensive use of these formulations in the clinic is limited, partly as a consequence of variability in quality, standards of manufacturing, and the approval from regulatory authorities.

Therefore, low bioavailability is the key barrier, hindering curcumin from being able to consistently attain therapeutic effectiveness in nephrotoxicity control.[91]

ii. Rapid Metabolism and Low Systemic Absorption

As a supplement to its poor absorption, curcumin is metabolized and systemically eliminated quickly, further limiting its pharmacological potential. After being absorbed in the intestine, curcumin becomes rapidly exposed to first-pass metabolism in the intestinal mucosa and liver. It is largely metabolized into conjugated forms including glucuronides and sulphates, which are less biologically active than free curcumin.

These metabolites are excreted quickly in bile and urine, with very low concentrations of active curcumin remaining in circulation. Both animal and human studies have found consistently low plasma levels of curcumin even with high oral doses. For instance, following oral dosing with 2 g of curcumin, plasma levels are commonly reported in the nanomolar to low micromolar range well below the levels that produce significant therapeutic effects in cell culture experiments.

For nephrotoxicity, this is a significant drawback. Because the kidney is a main target organ, curcumin's rapid clearance shortens the time window for exerting beneficial effects. In addition, the poor systemic absorption hinders the capacity to maintain effective concentrations at the site of renal damage.

Measures to overcome this barrier involve creating structural analogues of curcumin with enhanced stability, prodrug formulations, and utilization of adjuvants to retard metabolism. Although these efforts hold promise, clinical data proving their superiority in nephroprotection are still limited.[92]

iii. Safety Concerns with High Doses

Another key limitation of curcumin is its safety when taken in large amounts.

Because curcumin is not well absorbed by the body and is quickly eliminated, some research has tested very high doses to improve its effectiveness. These doses can range from 4 to 12 grams per day in human studies. Although curcumin is usually considered safe and well-tolerated in moderate amounts, recent findings suggest that taking it in such high doses may pose some risks, particularly for people with kidney problems.

Some reported side effects include digestive issues like nausea, diarrhoea, and stomach discomfort.

In rare cases, very high doses of curcumin have been linked to liver damage, which raises questions about its long-term safety. Also, curcumin has blood-thinning properties, which can increase the risk of bleeding when taken with other medications that also thin the blood. This is especially important for patients with chronic kidney disease, who are often on multiple medications.

Regarding kidney-related risks, giving high doses of curcumin to people with already reduced kidney function could be dangerous.

Some of its breakdown products may build up in kidney tissues, even though this has not been thoroughly studied. Additionally, curcumin can affect the enzymes and systems in the body that process medications, which may lead to interactions with other drugs that are harmful to the kidneys or commonly used by people with chronic kidney disease.

Another issue is the lack of clear and consistent guidelines for how much curcumin should be taken.

Different studies use varying amounts and forms of curcumin, making it hard to determine a safe and effective dose. Until more long-term safety information is available, it is important to use high-dose curcumin with caution, especially in people who are more vulnerable, such as those with chronic kidney disease or who are undergoing dialysis.[93]

iv. Implications for Clinical Translation:

The combined drawback of poor bioavailability, very fast metabolism, and safety issues at higher doses severely restricts the clinical use of curcumin in nephrotoxicity. Although preclinical evidence proves consistent protective action, clinical trials frequently experience modest or variable benefit, most likely as a result of these pharmacokinetic and safety limitations.

Overcoming these drawbacks calls for novel approaches. New curcumin formulations with enhanced pharmacokinetics, like nanoparticle-based curcumin, micelles, and liposomal carriers, are promising answers but must be rigorously clinically tested. Of equal significance is the provision of standardized dosing schedules, monitoring for safety, and extended trials to define curcumin's therapeutic status in nephrotoxicity.[94]

Advancements in curcumin delivery

Curcumin, the major bioactive constituent of Curcuma longa (turmeric), has been investigated thoroughly for its antioxidant, anti-inflammatory, and nephroprotective effects. Preclinical research has repeatedly established that curcumin is capable of modulating drug-induced and metabolic nephrotoxicity through down-regulation of oxidative stress, inhibition of proinflammatory cytokines, and preservation of renal tissue from structural injury. Clinical translation has been restricted due to poor solubility, low oral bioavailability, fast metabolism, and systemic clearance. These restrictions hinder curcumin from achieving therapeutic levels at the site of action, especially the kidneys.[95]

New drug delivery advancements have been aimed at creating new curcumin formulations to enhance pharmacokinetics, bioavailability, and optimal therapeutic effect. Of these, nanoparticles, liposomes, and phospholipid complexes are the most promising options. These delivery systems are addressed in this report and discussed for their application in

nephroprotection, highlighting enhanced pharmacokinetics and hoped-for therapeutic impact.[96]

i. Novel Formulations

a. Nanoparticle-Based Curcumin

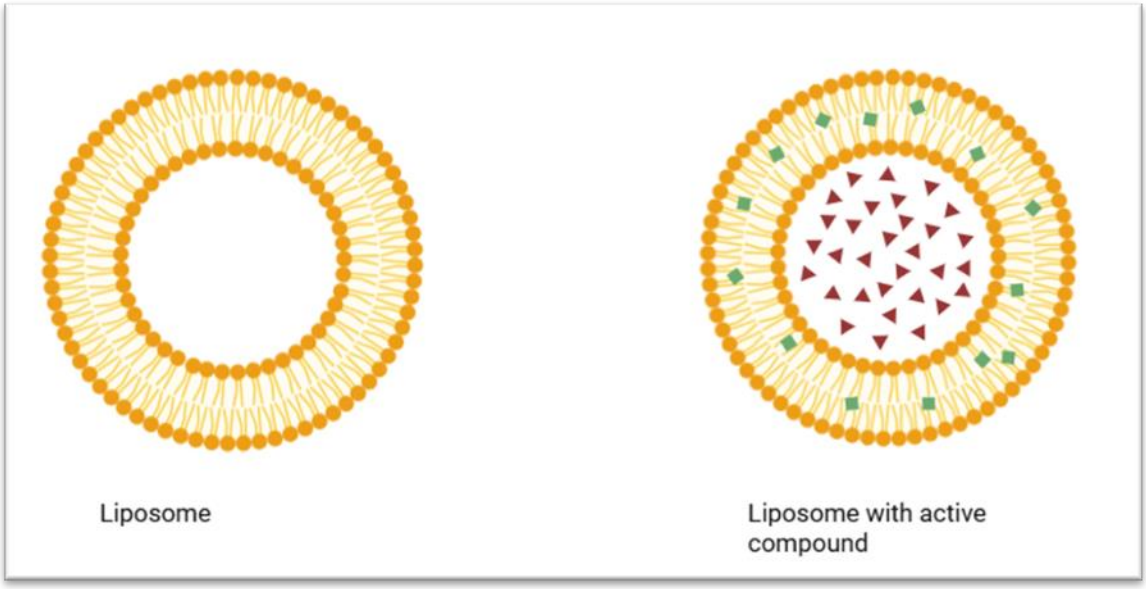
Nanoparticle formulations have been one of the most successful approaches to overcome the poor solubility and extensive metabolism of curcumin. By downsizing particles to the nanometre scale, nanoparticles enhance surface area, increase solubility, and allow for enhanced gastrointestinal absorption. Polymeric nanoparticles, solid lipid nanoparticles, and nano capsules have been created to encapsulate curcumin and shelter it against degradation.

Curcumin nanoparticles in preclinical studies exhibited enhanced antioxidant and anti-inflammatory efficacy than free curcumin. In models of cisplatin-induced nephrotoxicity, curcumin nanoparticles decreased serum creatinine, BUN, and indicators of oxidative stress more efficiently. Histopathological analysis also indicated better maintenance of renal tubular architecture. The greater renal bioavailability of nanoparticle-formulated curcumin permits steady release and extended circulation time, rendering it a good solution for clinical nephroprotection.[97]

b. Liposomal Curcumin

Liposomes are phospholipid bilayer vesicles of spherical form capable of enclosing hydrophobic and hydrophilic molecules. Liposomal curcumin is particularly beneficial in providing greater stability, increased solubility, and delivery to targeted tissues. Liposomal formulations are resistant to enzymatic degradation of curcumin and aid in its entry into the cell membrane.

In curcumin research for nephrotoxicity, liposomal curcumin has been more effective in protective action against renal oxidative damage and inflammation than unformulated curcumin. Animal studies illustrate that liposomal curcumin more potently inhibits proinflammatory cytokines TNF-α and IL-6, which results in decreased tubular necrosis and renal function preservation. Additionally, delivery systems of liposomes can be designed for sustained or targeted release, enhancing further therapeutic responses to chronic nephrotoxic diseases.[98]



c. Phospholipid Complexes (Phytosomes)

Phospholipid complexes or Phytosomes are another innovative approach towards the bioavailability enhancement of curcumin. Herein, curcumin molecules interact with phospholipids, most notably phosphatidylcholine, to make them more lipophilic and enhance permeability through membranes. This Favors gastrointestinal absorption and enhances systemic exposure.

Phytosomes-based curcumin products have shown considerably elevated plasma levels and prolonged half-life versus free curcumin. Curcumin Phytosomes in experimental models of nephrotoxicity enhanced renal function, lowered lipid peroxidation, and increased activity of antioxidant enzymes more powerfully than standard curcumin. These complexes have also been tested in initial human studies and proved to be more tolerable and bioavailable, and therefore a promising candidate for translation into nephroprotective therapy.[99]

ii. Enhanced Pharmacokinetics

The most important objective of new curcumin formulations is to evade the pharmacokinetic obstacles of free curcumin. Free curcumin has poor solubility, less absorption, fast metabolism, and fast excretion, which lead to very low plasma and tissue levels. The new delivery systems improve these issues immensely:

a. Nanoparticles promote solubility and stability with improved rates of absorption and extended circulation.

b. Liposomes safeguard curcumin from metabolic degradation by facilitated targeted and sustained release.

c. Phospholipid complexes enhance membrane permeability and systemic bioavailability, thereby providing more stable bioavailability.

d. Together, these formulations show enhanced pharmacokinetic properties, such as elevated maximum plasma concentration (Cmax), increased area under the curve (AUC), and prolonged half-life. This enables therapeutic concentrations of curcumin to be achieved in renal tissues, where curcumin may exert its antioxidant and anti-inflammatory protection against nephrotoxic injury.[100]

iii. Therapeutic Efficacy in Nephrotoxicity

These advances in curcumin delivery systems have been reflected in enhanced therapeutic efficacy in experimental nephrotoxicity models. Such comparative analysis indicates that new formulations always perform better than free curcumin in suppressing renal damage markers, maintaining histological integrity, and enhancing survival rates in nephrotoxicity conditions.

For example, nanoparticle curcumin showed better renoprotection in cisplatin- and gentamicin-induced models of nephrotoxicity, reducing serum creatinine and BUN significantly while improving antioxidant defence mechanisms. Liposomal curcumin delivered better anti-inflammatory responses, successfully suppressing cytokine-induced renal injury. Phytosomes preparations gave better renal biomarker profiles and histological integrity in chronic models such as diabetic nephropathy and chemically induced kidney damage.

While there are still limited human clinical data, these encouraging preclinical results highlight the therapeutic promise of advanced curcumin delivery. As these delivery technologies move toward clinical use, they could potentially be a useful adjunctive approach for the preservation of renal function in patients at risk of nephrotoxicity.[101]

Future Perspectives

Nephrotoxicity, caused by drug, toxin, and metabolic disease exposure, is a major etiology of acute and chronic kidney damage. Therapeutic management today involves early recognition, dose modification, and supportive therapy, yet these measures are often insufficient to entirely protect or correct renal damage. Curcuma longa (turmeric) and its bioactive molecule

curcumin have been studied in depth for their nephroprotective effects. Preclinical findings show antioxidant, anti-inflammatory, and anti-apoptotic activities, with preliminary clinical evidence indicating modest renal biomarker improvements. In spite of this development, various lacunas still exist in the knowledge and utilization of curcumin in the management of nephrotoxicity.[102]

i. Need for Large-Scale Clinical Trials

Most clinical trials assessing curcumin in nephrotoxicity and its associated renal disorders are small, heterogeneous, and short-term. These are limitations that limit the strength of evidence and the application of preclinical results into day-to-day practice. Large-scale, multicentre randomized controlled trials (RCTs) are a priority that future studies need to consider to prove the efficacy and safety of curcumin in nephrotoxicity. Major considerations for such studies are:

a. Standardized formulations: Due to the low bioavailability of curcumin, well-characterized formulations like nanoparticles, liposomes, or phospholipid complexes with superior pharmacokinetics need to be utilized in clinical trials. Standardization will enable replicability and comparison between studies.
b. Sufficient sample sizes and variety: Use of larger and more heterogeneous patient groups, such as those with chemotherapy-induced nephrotoxicity, diabetic nephropathy, chronic kidney disease (CKD), and dialysis-dependent patients, will yield more universally applicable results.
c. Long-term results: Trials need to be longer than short periods (typically 8–24 weeks) to measure meaningful outcomes like progression to end-stage renal disease (ESRD), dialysis commencement, hospitalization, and mortality.
d. Safety monitoring: Long-term therapy with curcumin at therapeutic levels needs close monitoring for safety, especially in patients with compromised renal clearance or those on complex medication regimens.[103]

ii. Potential for Incorporating Curcuma longa into Nephroprotective Regimens:

With its diversified mechanisms of action, curcumin has potential to be included in current nephroprotective regimens. Its antioxidant, anti-inflammatory, and mitochondrial-protective action complements present therapeutic strategies, which are mostly supportive and nonspecific.

a. Adjunctive Therapy in Drug-Induced Nephrotoxicity: In chemotherapy, especially with drugs such as cisplatin, nephrotoxicity continues to be a dose-limiting side effect. Supplementation with curcumin may be added as an adjuvant to minimize oxidative and inflammatory damage and potentially permit more therapeutic doses of chemotherapy without jeopardizing renal safety. The same uses might be extrapolated to aminoglycoside antibiotics or NSAIDs, where nephrotoxicity tends to impose limitations on prolonged therapy.
b. Insertion in CKD and Diabetic Nephropathy: In patients with CKD or diabetic nephropathy, curcumin may be added to current regimens in combination with renin–angiotensin–aldosterone system (RAAS) inhibitors, sodium–glucose cotransporter-2 (SGLT2) inhibitors, and other renoprotective agents. Its capacity to suppress proteinuria, decrease inflammatory cytokines, and maintain glomerular function renders it as an adjuvant therapy candidate to attenuate disease progression.
c. Synergy with Lifestyle and Nutritional Approaches: As a plant compound that is increasingly used in traditional medicine and diets, curcumin may also be included in nutritional and life-style interventions for renal protection. Its role as a nutraceutical could provide a suitable option for patients who look for natural adjuncts to conventional medical treatment.

To become successful, however, standardized dosing, formulation, and safety profiles must be proven through clinical validation.[104]

iii. Role in Preventive Versus Therapeutic Approaches

An important future issue is whether Curcuma longa is optimally suited as a prevention or treatment agent for nephrotoxicity.

a. Preventive Role

With its mechanisms of minimizing oxidative stress and inflammation, curcumin would best work when given before or concurrently with nephrotoxic exposures. For example, pre-treatment of curcumin in preclinical models of cisplatin nephrotoxicity substantially reduces renal injury. In practice, curcumin may be investigated as a prophylactic agent in patients undergoing nephrotoxic chemotherapy or long-term antibiotic treatment. Likewise, in high-risk populations for CKD progression, curcumin may be administered early to defer onset or slow decline.

b. Therapeutic Role

Curcumin's therapeutic application also reaches patients with established nephrotoxicity or chronic renal damage. For diabetic nephropathy and CKD patients, curcumin supplementation has already demonstrated modest proteinuria and inflammatory marker improvements. Its therapeutic function may involve diminishing residual inflammation, maintaining renal function, and enhancing quality of life.

Yet, current evidence supports curcumin as potentially more effective as a preventive than a curative treatment, because irreversible structural damage in established renal disease may be less likely to occur. This makes comparative trials of curcumin's preventive versus therapeutic effects critical.[105]

CONCLUSION

Sustained preclinical and promising clinical evidence underscores the protective action of Curcuma longa (turmeric) and its bioactive compound curcumin in modulating nephrotoxicity. Animal model experiments uniformly show the decreases in oxidative stress, inflammation, and apoptosis with curcumin treatment, resulting in maintained renal function and enhanced histopathology. Curcumin specifically decreases serum creatinine, blood urea nitrogen (BUN), and proteinuria, and increases antioxidant defence mechanisms like glutathione and superoxide dismutase. Histological observations reveal decreased tubular necrosis, lesser glomerular damage, and less inflammatory infiltration in nephrotoxic agent-exposed kidneys such as cisplatin and gentamicin.

Clinical trials, while few, corroborate these results. Diabetic nephropathy patients, patients with chronic kidney disease (CKD), and patients on nephrotoxic chemotherapy have yielded modest but encouraging enhancements in renal biomarkers, oxidative stress indices, and inflammatory markers with curcumin supplementation. Overall, this literature suggests that Curcuma longa has wide-spectrum nephroprotective activity by its antioxidant, anti-inflammatory, and anti-apoptotic properties.

With its pleiotropic mechanisms and benign safety profile at moderate doses, Curcuma longa has potential as an adjuvant therapy for nephrotoxicity. Its use in combination with nephroprotective regimens might fulfil several roles:

a. Adjunctive use with nephrotoxic drugs – Curcumin might diminish renal damage from chemotherapy agents or aminoglycosides, thereby permitting continued effective drug therapy without dose-limiting toxicity.
b. Supportive therapy in diabetic nephropathy and CKD – Curcumin's capacity for diminishing proteinuria, inflammatory cytokines, and oxidative damage makes it a potential agent to be used along with conventional treatments for slowing the progression of disease.
c. Preventive intervention – The best time to use curcumin might be early on, as prophylactic treatment, especially in those individuals at high risk of drug-induced renal injury or metabolic disease.

Notably, Curcuma longa is also consistent with patient demand for plant and natural therapies, rendering it a promising adjunct in integrative medicine strategies. Nevertheless, its application should be seen as complementary and not substitutive, since existing evidence fails to establish curcumin as an independent therapy.

In spite of promising findings, a number of challenges need to be overcome before Curcuma longa can be confirmed as a proven nephroprotective treatment. The low bioavailability and high turnover of curcumin are still major hurdles. New formulations like nanoparticles, liposomes, and phospholipid complexes have demonstrated enhanced pharmacokinetics, yet additional validation in human populations is essential.

Priorities for future research involve:

a. Large-scale randomized controlled trials (RCTs): Standardized formulations from multiple centres and sufficient sample sizes should be used to validate efficacy.
b. Dose protocols and long-term safety: Optimal dosing protocols must be determined by studies, especially for patients with reduced renal clearance.
c. Clinical endpoints: Upcoming trials must use hard renal endpoints such as the rate of progressing to end-stage renal disease (ESRD), initiation of dialysis, and mortality, as opposed to using biomarkers alone.
d. Preventive versus therapeutic uses: Contrastive investigations must determine whether curcumin is more efficacious in preventing renal damage or in treating established nephrotoxicity.[106]

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