

Comparative Analysis of the Most Effective Medicinal Plant Extract for Protection Against Cisplatin-Induced Toxicity

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Abstract: *Cisplatin is one of the most effective chemotherapeutic agents used for the treatment of several solid tumors, but its clinical application is frequently limited by toxicity, particularly nephrotoxicity. Cisplatin-induced renal injury is associated with oxidative stress, mitochondrial dysfunction, inflammation, apoptosis, DNA damage, and tubular injury. Medicinal plants and their bioactive constituents have attracted considerable attention because many possess antioxidant, anti-inflammatory, anti-apoptotic, and cytoprotective properties.*

Keywords: Cisplatin, nephrotoxicity, medicinal plants, curcumin, silymarin, *Nigella sativa*, ginger, green tea, oxidative stress, renal protection.

I. INTRODUCTION

Cisplatin is a platinum-based anticancer drug widely used against several malignancies, including cancers of the testis, ovary, lung, bladder, head and neck, and other solid tumors. Despite its strong antitumor activity, its clinical utility is restricted by toxic effects on normal tissues. Among these adverse effects, nephrotoxicity is particularly important because cisplatin accumulates in renal tubular cells and can produce acute kidney injury. Contemporary evidence indicates that cisplatin-induced kidney injury involves several interconnected mechanisms, including DNA damage, mitochondrial dysfunction, oxidative stress, endoplasmic-reticulum stress, inflammatory signaling, vascular injury, and apoptosis (Tang 2023).

Approximately 20–35% of patients receiving cisplatin may develop acute kidney injury, depending on treatment conditions, cumulative dose, hydration status, patient characteristics, and other risk factors (Fang 2021). The kidney is particularly vulnerable because cisplatin is transported into proximal tubular cells, where reactive oxygen species and inflammatory mediators contribute to cellular damage. Oxidative stress causes lipid peroxidation, protein oxidation, mitochondrial dysfunction, and depletion of endogenous antioxidants. In parallel, inflammatory mediators such as tumor necrosis factor- α and other cytokines intensify renal tubular damage.

The search for protective compounds that can reduce cisplatin toxicity without interfering with its anticancer action has therefore become an important area of pharmacological research. Medicinal plants are promising because their extracts contain multiple phytochemicals capable of simultaneously targeting oxidative stress, inflammation, apoptosis, and cellular antioxidant defense. Reviews of natural products have identified flavonoids, polyphenols, phenolic acids, terpenoids, saponins, and other plant-derived compounds as potential protective agents against cisplatin-induced renal injury (Fang 2021).

OBJECTIVES OF THE STUDY

- To examine the mechanisms responsible for cisplatin-induced toxicity, particularly renal toxicity.
- To evaluate the protective effects of selected medicinal plant extracts against cisplatin-induced damage.

- To compare curcumin, silymarin, ginger, *Nigella sativa*, and green tea based on antioxidant, anti-inflammatory, anti-apoptotic, biochemical, and histological effects.
- To assess the experimental and clinical evidence available for each medicinal plant.
- To identify the medicinal plant preparation with the strongest overall evidence of protective activity.
- To identify limitations and research gaps requiring further investigation.

II. MATERIALS AND METHODS

1. Research Design

The present study was designed as a comparative narrative literature analysis rather than a new experimental investigation. Published research concerning medicinal plant-derived preparations used against cisplatin-induced toxicity was evaluated and synthesized.

2. Literature Period

The principal literature considered for the comparative analysis was published between 2010 and 2023, with emphasis on studies directly investigating cisplatin toxicity and plant-derived protective interventions.

3. Selected Medicinal Plants

Five major candidates were selected:

Curcuma longa – curcumin

Silybum marianum – silymarin

Zingiber officinale – ginger extract

Nigella sativa – aqueous/ethanolic extract and seed oil

Camellia sinensis – green tea polyphenols

4. Comparative Parameters

The studies were compared according to:

serum creatinine and blood urea nitrogen;

oxidative-stress markers;

antioxidant enzymes;

inflammatory mediators;

apoptosis-related mechanisms;

histopathological protection;

hepatoprotective activity where reported;

evidence from animal and human studies;

consistency of reported effects;

translational potential.

Because the published studies use different species, doses, extraction methods, cisplatin doses, treatment schedules, and outcome measures, the present paper does **not** treat the reported results as directly pooled quantitative data.

COMPARATIVE ANALYSIS OF MEDICINAL PLANT EXTRACTS

Table 1. Comparative characteristics of selected medicinal plants against cisplatin-induced toxicity

Medicinal plant	Major active constituents	Principal protective mechanisms	Experimental evidence	Human evidence	Overall assessment
<i>Curcuma longa</i>	Curcuminoids, especially curcumin	Antioxidant, anti-inflammatory, anti-apoptotic, modulation of inflammatory cytokines	Strong	Emerging clinical evidence	Highest overall evidence
<i>Silybum marianum</i>	Silymarin, silybin, silychristin,	Antioxidant, inhibition of lipid peroxidation,	Strong	Mixed clinical	High experimental potential but

	silydianin	anti-inflammatory		evidence	inconsistent clinical findings
<i>Nigella sativa</i>	Thymoquinone, volatile oils, phenolics	Antioxidant, anti-inflammatory, anti-apoptotic, enhancement of thiol defenses	Strong	Limited	Promising preclinical candidate
<i>Zingiber officinale</i>	Gingerols, shogaols, phenolic compounds	Antioxidant, anti-inflammatory, anti-apoptotic	Moderate–strong	Limited	Promising experimental protection

1. Curcumin from *Curcuma longa*

Curcumin is one of the most extensively investigated plant-derived compounds for protection against cisplatin toxicity. It is a major polyphenolic constituent of turmeric (*Curcuma longa*) and possesses antioxidant and anti-inflammatory properties. Experimental studies have demonstrated that curcumin can reduce renal oxidative injury and inflammatory signaling.

Ueki (2013) investigated curcumin in a mouse model of cisplatin-induced nephrotoxicity. Curcumin administration reduced serum TNF- α and renal TNF- α and MCP-1 concentrations, reduced ICAM-1 expression, and attenuated renal dysfunction and tubular necrosis. These findings suggest that curcumin protects the kidney not simply through direct antioxidant activity but also by suppressing inflammatory pathways.

The importance of curcumin is strengthened by clinical evidence. Mehrab (2023) conducted a randomized, double-blind, placebo-controlled clinical trial involving 82 patients receiving cisplatin. Nano-curcumin administration was associated with improvements in BUN and other renal parameters, while differences in the urinary NGAL-to-creatinine ratio suggested a potential protective effect against tubular injury. The intervention was reported to be well tolerated.

2. Silymarin from *Silybum marianum*

Silymarin is a complex mixture of flavonolignans obtained from milk thistle (*Silybum marianum*). Its major components include silybin, silychristin, and silydianin. Silymarin has strong antioxidant and membrane-stabilizing properties and has traditionally been investigated for hepatoprotection.

A study by Abdelmeguid (2010) demonstrated substantial protection against cisplatin-induced renal morphological changes in rats, particularly when silymarin was administered before cisplatin exposure. The findings suggested that pretreatment was more effective than post-treatment in limiting renal structural injury.

Importantly, silymarin has also been evaluated in humans. Momeni (2015) conducted a clinical trial involving 60 patients receiving cisplatin and reported lower BUN and serum creatinine in the silymarin group after follow-up.

3. *Nigella sativa*

Nigella sativa, commonly known as black seed, contains thymoquinone and several other bioactive constituents. Its potential against cisplatin-induced renal toxicity has received considerable experimental attention.

In animal studies, aqueous-ethanolic *Nigella sativa* extract improved serum urea and creatinine abnormalities and improved kidney function in cisplatin-treated rats. Dose-dependent effects were reported, particularly at 200 mg/kg in some experimental protocols (Samarghandian 2016).

A later study of *Nigella sativa* oil reported significant attenuation of cisplatin-induced increases in serum creatinine and BUN, preservation of renal brush-border membrane enzymes, improvement of antioxidant parameters, and reduction of histopathological kidney damage (Khan 2017).

4. Ginger Extract from *Zingiber officinale*

Ginger (*Zingiber officinale*) contains phenolic compounds such as gingerols and shogaols with antioxidant and anti-inflammatory properties. Its potential against cisplatin-induced nephrotoxicity has been demonstrated experimentally.

Ali (2013) investigated ginger extract in cisplatin-treated male rats and observed marked renal injury in animals receiving cisplatin alone. Ginger administration reduced serum creatinine and BUN and improved histological and

ultrastructural renal changes. The study also examined Bax, an important pro-apoptotic protein, suggesting that ginger may influence apoptosis in addition to oxidative injury.

These findings indicate that ginger may provide multidimensional protection. Nevertheless, compared with curcumin and *Nigella sativa*, fewer studies have examined standardized ginger preparations against cisplatin toxicity, and clinical evidence remains limited.

III. DISCUSSION

The comparative evidence demonstrates that cisplatin-induced toxicity is not caused by a single biochemical pathway. Consequently, medicinal plants with multiple pharmacological mechanisms may provide greater protection than compounds acting exclusively through one pathway. The major mechanisms identified across the literature include oxidative stress, inflammation, apoptosis, mitochondrial dysfunction, and renal tubular injury (Tang 2023).

Curcumin appears particularly attractive because it simultaneously addresses several of these mechanisms. Experimental evidence demonstrates suppression of inflammatory mediators such as TNF- α and MCP-1 and reduction of renal tubular necrosis. Its antioxidant properties further provide protection against reactive oxygen species and oxidative damage. The availability of randomized clinical evidence from 2023 gives curcumin an additional advantage over most other plant-derived candidates. The clinical study did not establish curcumin as a definitive standard treatment, but it provided preliminary evidence that nano-curcumin could reduce markers associated with cisplatin-induced renal injury.

IV. FUTURE RESEARCH DIRECTIONS

Future research should focus on standardized extracts with well-characterized phytochemical profiles. Direct comparative experiments should administer equivalent doses of curcumin, silymarin, *Nigella sativa*, ginger, and green tea under identical cisplatin exposure conditions.

Further research should investigate renal biomarkers such as serum creatinine, BUN, NGAL, kidney injury molecule-1, glutathione, malondialdehyde, superoxide dismutase, catalase, inflammatory cytokines, and apoptotic proteins. Molecular studies should additionally investigate Nrf2/ARE, NF- κ B, MAPK, mitochondrial pathways, and apoptosis-related signaling.

Clinical trials should be adequately powered and should determine whether these interventions reduce nephrotoxicity without decreasing cisplatin's antitumor efficacy. Standardized nano formulations or other delivery systems may also improve the bioavailability of poorly absorbed phytochemicals such as curcumin.

V. CONCLUSION

Cisplatin remains an important anticancer drug, but nephrotoxicity and other systemic toxicities limit its therapeutic use. The literature published between 2010 and 2023 demonstrates that several medicinal plants and their bioactive constituents can attenuate cisplatin-induced renal damage through antioxidant, anti-inflammatory, anti-apoptotic, and cytoprotective mechanisms. Curcumin, silymarin, *Nigella sativa*, ginger, and green tea all demonstrate promising protective effects in experimental models.

Among the evaluated candidates, curcumin from *Curcuma longa* shows the strongest overall evidence profile, primarily because of its broad multimechanistic activity and the availability of human clinical evidence by 2023. Silymarin represents another important candidate but has produced inconsistent clinical findings. *Nigella sativa* demonstrates strong preclinical potential, whereas ginger and green tea remain promising experimental interventions requiring further clinical validation.

The evidence does not yet justify replacing established clinical approaches to cisplatin nephrotoxicity with any medicinal plant extract. Instead, these agents should be regarded as promising candidates for development of adjunctive nephroprotective strategies. Large, standardized, randomized clinical trials are required to determine whether the

encouraging experimental effects translate into meaningful clinical protection while preserving cisplatin's anticancer efficacy.

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