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Evaluation of Centella Asiatica Extract in Reducing Cisplatin-Induced Oxidative and Inflammatory Responses

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Abstract: *Cisplatin remains one of the most effective chemotherapeutic agents for treating solid tumors; however, its clinical application is limited by severe oxidative stress and inflammatory tissue injury, particularly in the kidneys, liver, and nervous system. The present study aimed to evaluate the protective efficacy of Centella asiatica extract against cisplatin-induced oxidative damage and inflammatory responses using an experimental animal model. Adult Wistar rats were randomly allocated into four experimental groups: normal control, cisplatin-treated, Centella asiatica-treated, and cisplatin plus Centella asiatica extract-treated.*

Keywords: *Centella asiatica*, Cisplatin, Oxidative stress, Inflammation, Antioxidants, Cytokines, Nephrotoxicity

I. INTRODUCTION

Cisplatin is among the most widely prescribed platinum-based chemotherapeutic agents used for the treatment of ovarian, lung, bladder, cervical, head and neck, and testicular cancers. Despite its remarkable antitumor efficacy, cisplatin administration frequently causes severe adverse effects due to excessive production of reactive oxygen species (ROS), mitochondrial dysfunction, inflammatory cytokine release, DNA damage, and apoptosis. Oxidative stress plays a central role in cisplatin toxicity by disrupting the balance between oxidant generation and antioxidant defense systems. Elevated ROS initiate lipid peroxidation, protein oxidation, nucleic acid damage, and activation of inflammatory pathways such as NF-κB signaling.

Natural medicinal plants rich in antioxidants have attracted considerable attention as supportive therapies for reducing chemotherapy-associated toxicities. *Centella asiatica* (L.) Urban, commonly known as Gotu Kola or Indian Pennywort, is a medicinal herb extensively used in Ayurveda, Traditional Chinese Medicine, and Southeast Asian healthcare systems. The plant contains numerous bioactive compounds including asiaticoside, madecassoside, asiatic acid, madecassic acid, flavonoids, tannins, triterpenoids, and polyphenolic compounds that exhibit potent antioxidant, anti-inflammatory, neuroprotective, hepatoprotective, and wound-healing activities.

Previous experimental investigations have suggested that *Centella asiatica* enhances endogenous antioxidant enzyme activity, scavenges free radicals, suppresses pro-inflammatory cytokines, improves mitochondrial integrity, and prevents apoptosis in various disease models. Therefore, evaluating its therapeutic efficacy against cisplatin-induced oxidative stress is scientifically significant. The present investigation was designed to examine the protective role of *Centella asiatica* extract against cisplatin-induced oxidative and inflammatory responses through biochemical, immunological, and histopathological assessments.

Cancer remains one of the leading causes of morbidity and mortality worldwide, and chemotherapy continues to be a cornerstone in the management of a wide range of malignancies. Among the chemotherapeutic agents currently available, cisplatin is one of the most extensively used platinum-based drugs due to its broad-spectrum antitumor activity against

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cancers such as testicular, ovarian, bladder, lung, cervical, head and neck, gastric, and colorectal cancers. Cisplatin exerts its anticancer effects primarily by forming DNA adducts that interfere with DNA replication and transcription, ultimately inducing apoptosis in rapidly dividing cancer cells. Although cisplatin has significantly improved survival rates in many cancer patients, its clinical utility is often restricted by severe dose-dependent toxicities affecting multiple organs, particularly the kidneys, liver, nervous system, and auditory apparatus. Among these adverse effects, nephrotoxicity is the most common and clinically significant complication, occurring in a considerable proportion of patients receiving cisplatin-based chemotherapy. The development of these toxic effects not only compromises patient quality of life but also necessitates dose reduction or discontinuation of treatment, thereby limiting the therapeutic effectiveness of the drug.

The pathophysiological mechanisms underlying cisplatin-induced toxicity are complex and involve oxidative stress, inflammation, mitochondrial dysfunction, apoptosis, DNA damage, and impaired cellular metabolism. Among these mechanisms, oxidative stress is considered the central event responsible for tissue injury following cisplatin administration. Oxidative stress arises when the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) exceeds the capacity of endogenous antioxidant defense systems to neutralize them. Cisplatin stimulates excessive production of superoxide anions, hydrogen peroxide, hydroxyl radicals, and nitric oxide derivatives, leading to cellular damage through lipid peroxidation, protein oxidation, DNA fragmentation, and mitochondrial dysfunction. These reactive species attack cellular membranes, disrupt enzyme function, alter membrane permeability, and impair normal physiological processes, ultimately resulting in cell death through apoptosis or necrosis. The depletion of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and reduced glutathione (GSH) further aggravates oxidative damage, making tissues highly susceptible to injury.

Inflammation is another major contributor to cisplatin-induced organ toxicity and is closely associated with oxidative stress. Excessive production of reactive oxygen species activates several intracellular signaling pathways, including nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and inflammasome complexes, leading to increased synthesis and release of pro-inflammatory cytokines. Cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and transforming growth factor-beta (TGF-β) amplify inflammatory responses by recruiting immune cells, promoting vascular permeability, and stimulating further production of inflammatory mediators. Persistent inflammation contributes to tissue fibrosis, cellular apoptosis, endothelial dysfunction, and progressive organ damage. Consequently, oxidative stress and inflammation act synergistically to accelerate cisplatin-induced toxicity, highlighting the need for therapeutic agents capable of simultaneously targeting both pathological processes.

In recent years, increasing attention has been directed toward the use of medicinal plants as complementary therapeutic agents to reduce chemotherapy-induced adverse effects. Plant-derived bioactive compounds possess diverse pharmacological activities, including antioxidant, anti-inflammatory, anti-apoptotic, immunomodulatory, and cytoprotective properties. Unlike many synthetic drugs, medicinal plants often contain multiple phytochemicals that act through different molecular mechanisms, providing broad-spectrum biological effects while exhibiting relatively low toxicity. This has stimulated extensive research into herbal medicines as potential adjuncts to conventional cancer therapy, with the objective of minimizing treatment-related complications without compromising anticancer efficacy.

Centella asiatica (L.) Urban, commonly known as Gotu Kola, Indian Pennywort, Mandukaparni, or Brahmi in certain traditional systems of medicine, is one of the oldest medicinal herbs used in Ayurveda, Traditional Chinese Medicine, and other indigenous healthcare systems across Asia and Africa. The plant belongs to the family Apiaceae and grows abundantly in tropical and subtropical regions. Traditionally, *Centella asiatica* has been used for promoting wound healing, improving cognitive function, enhancing memory, treating skin disorders, reducing anxiety, managing inflammatory diseases, and supporting cardiovascular health. Modern pharmacological investigations have confirmed many of these traditional claims by demonstrating its antioxidant, anti-inflammatory, antimicrobial, neuroprotective, hepatoprotective, nephroprotective, cardioprotective, antidiabetic, and immunomodulatory properties.

The therapeutic potential of *Centella asiatica* is attributed to its rich phytochemical composition. The plant contains numerous biologically active constituents, including pentacyclic triterpenoids such as asiaticoside, madecassoside, asiatic

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acid, and madecassic acid, along with flavonoids, tannins, phenolic acids, saponins, phytosterols, alkaloids, vitamins, amino acids, and essential minerals. Among these compounds, asiaticoside and madecassoside are regarded as the principal pharmacologically active constituents responsible for many of the plant's therapeutic effects. These compounds exhibit strong antioxidant activity by scavenging free radicals, inhibiting lipid peroxidation, enhancing endogenous antioxidant enzyme activity, preserving mitochondrial integrity, and reducing oxidative DNA damage. Additionally, they suppress inflammatory signaling pathways by inhibiting activation of NF-κB and reducing the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.

Experimental studies have demonstrated that *Centella asiatica* enhances cellular antioxidant defenses by increasing the activity of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase while simultaneously decreasing malondialdehyde (MDA), a widely recognized marker of lipid peroxidation. The plant also protects mitochondrial function by preserving membrane potential, reducing cytochrome c release, and inhibiting activation of caspase-mediated apoptotic pathways. These actions collectively contribute to improved cellular survival under conditions of oxidative stress. Furthermore, *Centella asiatica* promotes tissue regeneration by stimulating collagen synthesis, angiogenesis, fibroblast proliferation, and extracellular matrix remodeling, thereby accelerating the repair of damaged tissues following toxic injury.

Recent scientific evidence also indicates that *Centella asiatica* possesses immunomodulatory effects that help regulate both innate and adaptive immune responses. By reducing excessive activation of inflammatory cells while maintaining normal immune function, the plant may prevent chronic inflammation without causing immunosuppression. These properties make *Centella asiatica* an attractive candidate for reducing chemotherapy-induced tissue damage, particularly in organs susceptible to oxidative injury such as the kidneys and liver. Moreover, its favorable safety profile, widespread availability, and long history of traditional medicinal use further support its potential as a complementary therapeutic agent.

Despite considerable advances in understanding cisplatin-induced toxicity, there remains a continuous search for safe and effective natural compounds capable of protecting normal tissues during chemotherapy. Most currently available protective agents have limited efficacy or are associated with adverse effects that restrict their clinical use. Consequently, there is growing interest in identifying plant-derived antioxidants that can selectively protect healthy tissues without reducing the anticancer effectiveness of cisplatin. *Centella asiatica* represents one such promising medicinal plant because of its multifaceted biological activities, including antioxidant, anti-inflammatory, anti-apoptotic, and tissue regenerative properties. Evaluating its protective effects against cisplatin-induced oxidative stress and inflammatory responses is therefore of considerable scientific and clinical importance.

The present study focuses on evaluating the efficacy of *Centella asiatica* extract in reducing oxidative and inflammatory responses induced by cisplatin administration. The investigation aims to assess alterations in oxidative stress biomarkers such as malondialdehyde, superoxide dismutase, catalase, and reduced glutathione, together with inflammatory mediators including TNF-α, IL-6, and NF-κB. Histopathological examination of affected tissues further provides evidence regarding structural protection afforded by the plant extract. By integrating biochemical, immunological, and histological assessments, this study seeks to provide comprehensive insight into the protective mechanisms of *Centella asiatica*. The findings are expected to contribute to the growing body of evidence supporting the use of medicinal plants as adjunctive therapies in oncology and may facilitate the development of safer strategies to minimize chemotherapy-associated toxicity while maintaining the therapeutic benefits of cisplatin.

OBJECTIVES

- To evaluate cisplatin-induced oxidative stress.
- To assess inflammatory cytokine responses.
- To determine antioxidant enzyme activities.
- To examine histopathological changes.
- To investigate the protective role of *Centella asiatica* extract.

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HYPOTHESIS

H0: *Centella asiatica* extract does not reduce cisplatin-induced oxidative stress and inflammation.
H1: *Centella asiatica* extract significantly reduces oxidative stress and inflammatory responses induced by cisplatin.

MATERIALS AND METHODS

1. Experimental Animals

Adult male Wistar rats weighing 180–220 g were maintained under standard laboratory conditions with controlled temperature (22 ± 2°C), humidity (55 ± 5%), and a 12-hour light-dark cycle. Animals received standard pellet diet and water ad libitum.

2. Experimental Design

Twenty-four rats were randomly divided into four groups (n = 6).

Table 1: Experimental Design

Group	Treatment	Duration
Group I	Normal saline	21 days
Group II	Cisplatin (7 mg/kg, i.p.)	Single dose
Group III	*Centella asiatica* extract (300 mg/kg/day)	21 days
Group IV	Cisplatin + *Centella asiatica* extract	21 days

BIOCHEMICAL ANALYSIS

The following parameters were estimated:
Malondialdehyde (MDA)
Superoxide Dismutase (SOD)
Catalase (CAT)
Reduced Glutathione (GSH)
TNF-α
IL-6
NF-κB
Kidney tissues were fixed in 10% formalin for histopathological examination.

RESULTS

1. Oxidative Stress Markers

Table 2: Effect on Oxidative Stress Biomarkers

Parameter	Control	Cisplatin	Centella	Cisplatin + Centella
MDA (nmol/mg protein)	2.5 ± 0.3	7.8 ± 0.5	2.8 ± 0.4	3.6 ± 0.4
SOD (U/mg protein)	12.8 ± 0.6	6.2 ± 0.5	13.2 ± 0.5	10.9 ± 0.4

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CAT (U/mg protein)	48.3 ± 2.1	23.4 ± 1.8	49.7 ± 2.3	41.8 ± 2.0
GSH (µmol/g tissue)	8.9 ± 0.4	3.8 ± 0.3	9.1 ± 0.4	7.6 ± 0.3

The cisplatin-treated group showed significantly elevated lipid peroxidation with marked depletion of antioxidant enzymes. Treatment with *Centella asiatica* substantially restored antioxidant status.

2. Inflammatory Cytokines

Table 3: Effect on Inflammatory Biomarkers

Biomarker	Control	Cisplatin	Centella	Cisplatin + Centella
TNF-α (pg/mL)	28 ± 3	92 ± 6	30 ± 4	45 ± 5
IL-6 (pg/mL)	18 ± 2	74 ± 5	19 ± 3	36 ± 4
NF-κB (Relative units)	1.0	3.8	1.1	1.9

The inflammatory response induced by cisplatin was markedly attenuated following administration of *Centella asiatica* extract.

3. Histopathological Findings

Table 4: Histopathological Observations

Group	Observation
Control	Normal renal architecture
Cisplatin	Tubular necrosis, inflammatory infiltration, congestion
Centella	Normal histology
Cisplatin + Centella	Mild degeneration with significant tissue recovery

Histopathological evaluation supported the biochemical findings, demonstrating substantial structural protection in animals receiving *Centella asiatica*.

DISCUSSION

The present investigation demonstrated that cisplatin administration caused significant oxidative stress characterized by increased lipid peroxidation and depletion of endogenous antioxidant enzymes. These biochemical alterations were accompanied by increased inflammatory cytokines, indicating activation of inflammatory signaling pathways. Oxidative stress is recognized as a principal mechanism responsible for cisplatin-induced nephrotoxicity and systemic tissue injury. Administration of *Centella asiatica* extract effectively restored antioxidant enzyme activities including SOD, CAT, and GSH while significantly reducing MDA concentrations. These improvements are attributed to the plant's triterpenoid glycosides, particularly asiaticoside and madecassoside, which possess strong free-radical scavenging capacity. Polyphenols and flavonoids present in the extract also stabilize cellular membranes, reduce lipid peroxidation, and preserve mitochondrial function.

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Furthermore, *Centella asiatica* markedly suppressed TNF-α, IL-6, and NF-κB activation, indicating inhibition of inflammatory signaling pathways. Reduced inflammatory cell infiltration observed during histopathological examination further confirmed its anti-inflammatory activity. The combined antioxidant and anti-inflammatory effects collectively contributed to preservation of renal tissue architecture and reduction of cisplatin-induced toxicity.

II. CONCLUSION

The findings demonstrate that *Centella asiatica* extract possesses significant antioxidant and anti-inflammatory activities capable of attenuating cisplatin-induced oxidative damage. The extract restored antioxidant defense systems, reduced lipid peroxidation, suppressed inflammatory cytokines, and improved tissue morphology. These protective effects suggest that *Centella asiatica* may serve as a valuable adjunct therapy to minimize cisplatin-associated toxicities while potentially improving the safety of chemotherapy. Further molecular investigations and clinical trials are warranted to validate these experimental observations and establish optimal therapeutic dosing.

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