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Combined Curcumin and G-CSF Therapy Attenuates Cisplatin-Induced Leukopenia and Hepatotoxicity in an Experimental Murine Model

Idress H. Mohamed[1], Bulkasim M. Abdulnabi[2*], Ibtisam S. Abd-Alali[3], Fathia A. F. Abdalarahem[4]
[1,2]Zoology Department, Faculty of Science, Omar Al-Mukhtar University, Al-Beida, Libya.
[3,4]Department of Therapeutic nutrition, Higher Institute of Science and Technology, Al - Beida, Libya.

العلاج المشترك بالكركمين وعامل تحفيز مستعمرات المحببات (*G-CSF*) يخفف من نقص الكريات البيضاء والتسمم الكبدي الناجم عن السيسبلاتين في نموذج تجريبي على الفئران

إدريس حسن محمد[1]، بلقاسم محمد عبد النبي[2*]، ابتسام سعد عبدالعالي[3]، فتحية عبد الرحيم[4]
[2،1]قسم علم الحيوان، كلية العلوم، جامعة عمر المختار، البيضاء، ليبيا
[3،4]قسم التغذية العلاجية، المعهد العالي للعلوم والتكنولوجيا، البيضاء، ليبيا

*Corresponding author: idrissm836@gmail.com

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Abstract:
Despite the potent efficacy of Cisplatin in combating various solid malignancies, its therapeutic utility is often compromised by severe toxic manifestations. Notable clinical constraints include the induction of systemic leukopenia and significant hepatic impairment. The objective of this investigation was to evaluate the potential of a co-administration strategy involving Curcumin and Granulocyte Colony-Stimulating Factor (G-CSF) in providing synergistic cytoprotection against the aforementioned toxicological challenges within a murine experimental framework. A cohort of fifty male albino mice was utilized, following a randomized allocation into five experimental clusters. These included a baseline Control, a group challenged with Cisplatin (7.5 mg/kg, i.p.), and treatment cohorts receiving either Curcumin (200 mg/kg, p.o.), G-CSF (30 µg/kg, s.c.), or a synergistic integration of both agents (Cis+Cur+G-CSF). Therapeutic efficacy was evaluated through hematological profiling, assessment of hepatic functional enzymes (ALT, AST and ALP), and measurement of oxidative stress biomarkers (MDA, SOD and GSH). Cisplatin administration produced marked leukopenia accompanied by significant hepatic oxidative injury. Although treatment with either Curcumin or G-CSF alone conferred partial improvement, the combined regimen produced the most pronounced protective response, with the greatest restoration of WBC counts ($p < 0.001$) and substantial normalization of liver biochemical indices. The evidence presented suggests that the dual administration of Curcumin and G-CSF offers a potential pharmacological paradigm for mitigating the toxic sequelae inherent to platinum-derived chemotherapeutics.

Keywords: Cisplatin toxicity; Curcumin; Granulocyte Colony-Stimulating Factor; chemotherapy-induced leukopenia; drug-induced hepatotoxicity; oxidative stress.

الملخص:
على الرغم من فعالية السيسبلاتين القوية في مكافحة العديد من الأورام الخبيثة، إلا أن فائدته العلاجية غالبًا ما تتأثر سلبًا بآثاره الجانبية السامة الشديدة. ومن أبرز هذه الآثار الجانبية السريرية حدوث نقص عام في عدد كريات الدم البيضاء واضطراب كبير في وظائف الكبد. هدفت هذه الدراسة إلى تقييم إمكانية استخدام استراتيجية الإعطاء المشترك التي تتضمن الكركمين (Curcumin) وعامل تحفيز مستعمرات المحببات (G-CSF) لتوفير حماية خلوية تآزرية ضد التحديات السمية المذكورة آنفًا، وذلك ضمن إطار تجريبي على الفئران. تم استخدام مجموعة من خمسين فأرًا أبيض ذكرًا، بعد توزيعها عشوائيًا على خمس مجموعات تجريبية. شملت هذه المجموعات: مجموعة ضابطة أساسية، ومجموعة خضعت للعلاج بالسيسبلاتين (7.5 ملغم/كغم، حقن داخل الصفاق) ومجموعات علاجية تلقت إما الكركمين (200 ملغم/كغم، عن طريق الفم) أو عامل تحفيز مستعمرات المحببات (G-CSF)(30 ميكروغرام/كغم، تحت الجلد)، أو مزيجًا تآزريًا من كلا العاملين (سيسبلاتين + الكركمين + G-CSF). تم تقييم الفعالية العلاجية من خلال تحليل الدم، وتقييم إنزيمات الكبد الوظيفية (ALT وAST وALP)، وقياس مؤشرات الإجهاد التأكسدي (MDA وSOD وGSH). أدى إعطاء السيسبلاتين إلى نقص ملحوظ في عدد كريات الدم البيضاء مصحوبًا بتلف تأكسدي كبير في الكبد. على الرغم من أن العلاج بالكركمين أو G-CSF منفردًا أدى إلى تحسن جزئي، إلا أن النظام العلاجي المركب حقق الاستجابة الوقائية الأبرز، مع أعلى نسبة استعادة لعدد كريات الدم البيضاء ($p < 0.001$) وتطبيع كبير لمؤشرات وظائف الكبد. تشير الأدلة المقدمة إلى أن الإعطاء المزدوج للكركمين وعامل تحفيز مستعمرات المحببات (G-CSF) يمثل نموذجًا دوائيًا محتملاً للتخفيف من الآثار الجانبية السامة المصاحبة للعلاجات الكيميائية المشتقة من البلاتين.

الكلمات المفتاحية: سمية السيسبلاتين؛ الكركمين؛ عامل تحفيز مستعمرات المحببات؛ نقص الكريات البيضاء الناجم عن العلاج الكيميائي؛ سمية الكبد الناجمة عن الأدوية؛ الإجهاد التأكسدي.

Introduction:

Since its approval by the FDA in the late 1970s, Cisplatin (cis-diamminedichloroplatinum II) has remained a cornerstone in the treatment of solid malignancies because of its potent antineoplastic efficacy. Nevertheless, its therapeutic value is substantially limited by dose-dependent systemic toxicity. Among the most clinically consequential toxic manifestations are hepatotoxicity and severe myelosuppression, particularly leukopenia and neutropenia, both of which can compromise adherence to optimal chemotherapeutic dosing schedules and treatment intensity. The hepatic toxicity induced by Cisplatin is primarily linked to oxidative stress. After accumulating in hepatic tissue, the drug stimulates excessive production of reactive oxygen species (ROS), thereby exhausting intracellular glutathione (GSH) stores and disrupting cellular redox equilibrium. Such oxidative stress triggers the permeabilization of mitochondrial membranes, which subsequently initiates a cascade involving the liberation of cytochrome c and the activation of caspases, ultimately culminating in hepatocyte programmed cell death. Furthermore, the up-regulation of the Nuclear Factor-kappa B (NF-κB) signaling pathway orchestrates the secretion of various pro-inflammatory mediators, notably TNF-α and IL-6, which exacerbate hepatocellular necrotic damage (1,2 and 3).

At the same time, Cisplatin exerts profound toxicity on the hematopoietic system by targeting rapidly proliferating hematopoietic stem cells (HSCs) within the bone marrow. Through DNA cross-link formation, the drug initiates apoptotic signaling pathways that culminate in severe leukopenia and neutropenia. These hematological disturbances markedly increase susceptibility to life-threatening infections and frequently necessitate dose reduction or treatment delay, outcomes that may ultimately favor chemoresistance and weaken therapeutic success (4,5 and 6).

Granulocyte Colony-Stimulating Factor (G-CSF) is currently regarded as the standard supportive intervention for chemotherapy-induced neutropenia because it promotes the proliferation and differentiation of myeloid progenitors through interaction with specific G-CSF receptors. However, despite its hematopoietic efficacy, G-CSF does not possess intrinsic antioxidant or hepatoprotective activity, leaving non-hematopoietic tissues susceptible to Cisplatin-induced injury (7,8 and 9).

In contrast, the polyphenolic compound Curcumin, extracted from Curcuma longa, has gained extensive recognition due to its robust capacity to neutralize oxidative agents and modulate inflammatory responses. Curcumin activates the Nrf2/HO-1 pathway and directly scavenges ROS, thereby exerting substantial hepatoprotective effects. It has also been suggested to function as a chemosensitizer under certain experimental conditions (10,11 and 12).

Although the individual therapeutic advantages of G-CSF and Curcumin are well-documented, the clinical efficacy of their synergistic integration has not yet been thoroughly elucidated. To date, no study has comprehensively examined whether co-administration of these two agents can simultaneously counteract Cisplatin-induced hepatic and hematopoietic toxicity. It was therefore hypothesized that Curcumin may stabilize both the hepatic microenvironment and the bone marrow niche through antioxidant mechanisms, whereas G-CSF may accelerate immune reconstitution through stimulation of

hematopoietic recovery. On this basis, the present investigation was designed to evaluate whether a combined Curcumin/G-CSF regimen could provide a multi-targeted cytoprotective strategy in a controlled murine model of Cisplatin toxicity (13,14).

Materials and Methods:

Chemicals & Reagents:

Cisplatin was purchased from Sigma-Aldrich (St. Louis. MO. USA), whereas highly purified curcumin (>95% purity as confirmed by HPLC) was obtained from Merck KGaA (Darmstadt. Germany). Recombinant human G-CSF (Filgrastim) was provided by F. Hoffmann-La Roche AG (Basel. Switzerland). ELISA-based diagnostic kits used for measuring hepatic enzymes, namely AST, ALT, and ALP, together with oxidative stress-related parameters, were obtained from Biodiagnostic Company (Cairo, Egypt). All additional reagents employed in the present work were of analytical or molecular biology grade.

Animals & Housing:

The study included fifty adult healthy male albino mice (*Mus musculus*) weighing between 25 and 30 g, obtained from the Central Animal House. Prior to treatment, the animals were maintained for a 14-day acclimatization period under controlled environmental conditions, including a regular 12 h light/dark cycle and a room temperature of 22 ± 2°C. Throughout the experiment, animals were allowed free access to chlorine-free drinking water and a standard pellet diet (15).

Experimental Design:

The animals were randomly allocated, using a computerized randomization approach, into five groups of ten mice each. Group I served as the normal control group, whereas Group II received cisplatin only. Group III was treated with cisplatin plus curcumin, while Group IV received cisplatin combined with G-CSF. Group V was assigned to the combined treatment protocol comprising cisplatin, curcumin, and G-CSF. The administered doses were 7.5 mg/kg cisplatin via the intraperitoneal route (i.e.), 200 mg/kg curcumin orally (p. o.), and 30 µg/kg G-CSF by subcutaneous injection (s. c.).

Sample Collection & Analysis:

Twenty-four hours after the last administered dose, on the eleventh experimental day, mice were anesthetized via intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg). Blood specimens were collected by cardiac puncture; one aliquot was placed in EDTA tubes for CBC assessment, and the remaining aliquot was allowed to clot before centrifugation at 3000 rpm for 15 min at 4°C for serum separation. Following sacrifice, liver samples were immediately removed, washed with chilled saline, and split into two portions. The first portion was homogenized in 50 mM phosphate buffer (pH 7.4) for oxidative stress determination, while the second was preserved in 10% neutral buffered formalin for histological processing.

Hematological and Biochemical Analysis:

An automated hematology analyzer (Sysmex Corp., Kobe, Japan) was employed to evaluate hematological indices. The serum concentration of total bilirubin and the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were quantified spectrophotometrically using commercially available colorimetric assay kits according to the protocol of (16).

Oxidative Stress Assessment:

The degree of hepatic lipid peroxidation was determined by assessing malondialdehyde (MDA) concentration. Hepatic antioxidant status was further characterized through the estimation of reduced glutathione (GSH) content and superoxide dismutase (SOD) activity. These biochemical parameters were measured using validated spectrophotometric methods in line with the procedures of (17,18). Each determination was carried out in triplicate to ensure analytical consistency.

Statistical Analysis:

Data are reported as mean ± standard error of the mean (SEM). Intergroup differences were evaluated by one-way analysis of variance (ANOVA), with tukey's honestly significant difference (HSD) test applied as a post hoc procedure for multiple comparisons. Statistical processing was conducted using IBM SPSS Statistics version 25.0. Differences were considered statistically significant when p was less than 0.05, with significance thresholds expressed as *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

Results:

Hematological Parameters:

Cisplatin administration caused severe myelosuppression, as demonstrated by a marked reduction in total white blood cell (WBC) count relative to the control group ($1.625\pm0.38 \times 10^3/\mu L$ versus $5.3\pm1.075 \times 10^3/\mu L$; $p<0.001$). Although both monotherapeutic interventions produced partial hematological improvement, the most pronounced recovery was observed in the Combined therapy group. In that group, total WBC count and the other leukocyte-related parameters approached near-normal values and did not differ significantly from those recorded in healthy controls. Detailed hematological findings

are summarized in Table 1.

Table (1): Hematological parameters following treatment interventions in Cisplatin-challenged mice.

Hematological Parameter	Group I (Normal Control)	Group II (Cisplatin)	Group III (Cis + Curcumin)	Group IV (Cis + G-CSF)	Group V (Combined)
WBC (×10^3/µL)	5.3±1.075	1.625±0.38***	2.425±0.223**	4.5±1.279	5.2±1.082*
Neutrophils (cells/mms)	409±12.764	540.3±12.74***	442.5±8.810*	308±20.245***	462.5±22.76*
Lymphocytes (cells/mms)	490.7±32.9	700.75±11.7***	1245.5±20.7***	1391.5±40.9***	1408±41.8***
Monocytes (cells/mms)	771.5±11.55	532.25±12.4***	726.00±16.7*	822.75±26.4*	1202±28.62***
RDW (×10^4)	30.625±0.83	25.65±2.48**	54.35±0.94***	59.2±3.57***	60.25±3.647***

Data are presented as mean ± standard deviation for ten animals in each experimental group. Abbreviations: Cis, cisplatin; WBC, white blood cell count; RDW, red cell distribution width. Statistical significance compared with the normal control group (Group 1) is denoted as *p ≤ 0.05, **p ≤ 0.01, and ***p ≤ 0.001.

Hepatic Function Markers:

Marked hepatocellular injury was induced by Cisplatin treatment, as reflected by approximately 2–3-fold increases in serum ALT, AST, and ALP activities compared with the corresponding control values. Curcumin monotherapy significantly reduced these enzyme elevations ($p<0.01$). Nevertheless, the most effective biochemical protection was achieved in the Combined therapy group, in which hepatic enzyme activities were maintained at levels comparable to physiological norms. These observations are presented in Figures 1, 2 and 3.

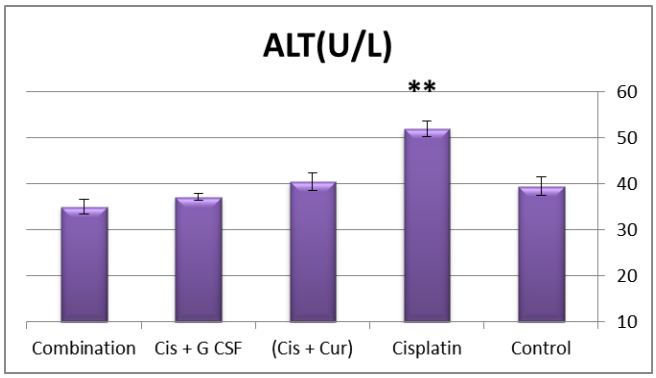

Figure (1): Fluctuations in serum Alanine Aminotransferase (ALT) levels among the various experimental cohorts. The symbol ** denotes a statistically significant variance (p≤0.01) when comparing the Cisplatin-intoxicated mice against the baseline Normal Control.

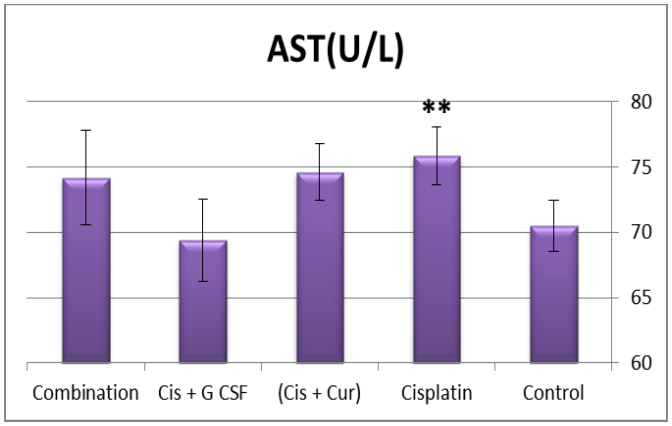

Figure (2): Fluctuations in Serum Aspartate Aminotransferase (AST) levels among the various experimental cohorts. The symbol ** denotes a statistically significant variance (p≤0.01) when comparing the Cisplatin-intoxicated mice against the baseline Normal Control.

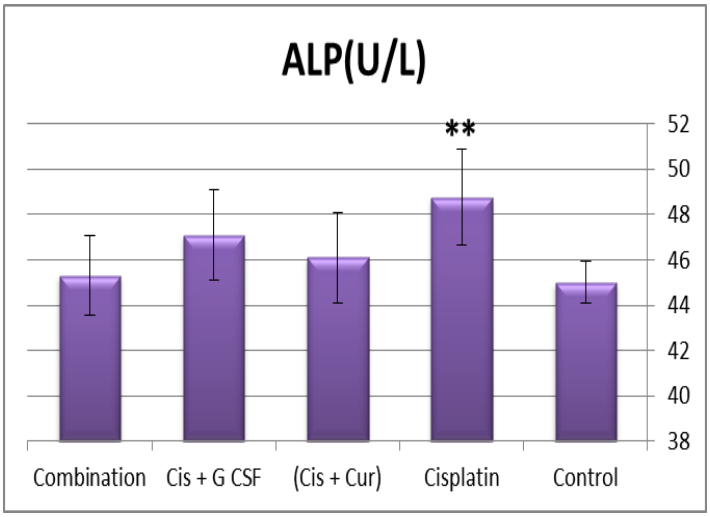

Figure (3): Fluctuations in Serum Alkaline Phosphatase (ALP) levels among the various experimental cohorts. The symbol ** denotes a statistically significant variance ($p \leq 0.01$) when comparing the Cisplatin-intoxicated mice against the baseline Normal Control.

Oxidative Stress Biomarkers and Antioxidant Defense:

Biochemical analysis of hepatic tissue homogenates demonstrated that Cisplatin significantly intensified lipid peroxidation, as evidenced by elevated MDA concentration (12.84±1.15 nmol/mg protein; $p<0.001$). Simultaneously, endogenous antioxidant defenses were markedly depleted, with clear reductions in SOD activity (74.2±8.9 U/mg protein) and GSH level (2.15±0.34 µmol/mg protein). Although each single-agent treatment ameliorated these changes to some extent, the Combined therapy group exhibited the greatest correction of oxidative imbalance, restoring antioxidant parameters to values closest to those of the control group. The detailed oxidative stress profile is shown in Table 2.

Table (2): Hepatic oxidative stress biomarkers and antioxidant enzyme status.

Parameter	Group I (Normal Control)	Group II (Cisplatin)	Group III (Cis+ Curcumin)	Group IV (Cis + G-CSF)	Group V (Combined)
MDA (nmol/mg protein)	3.15±0.42	12.84±1.15***	8.62±0.74**	7.14±0.65**	4.38±0.51
SOD (U/mg protein)	185.4±12.6	74.2±8.9***	112.5±10.3**	138.7±11.4*	168.3±14.2
GSH (µmol/mg protein)	6.24±0.58	2.15±0.34***	3.82±0.41**	4.56±0.39*	5.72±0.48

Data are presented as mean ± standard deviation for ten animals in each experimental group. Abbreviations: Cis, cisplatin; MDA, malondialdehyde; SOD, superoxide dismutase; GSH, reduced glutathione. Statistical significance compared with the normal control group (Group I) is denoted as *$p \leq 0.05$, **$p \leq 0.01$, and ***$p \leq 0.001$.

Discussion:

The present findings further substantiate the well-recognized dual toxicity profile of Cisplatin, which simultaneously compromises hepatic integrity and hematopoietic function[13]. The marked increase in hepatic MDA, together with the pronounced depletion of SOD and GSH, confirms that Cisplatin exposure generated a state of substantial oxidative stress within liver tissue. These observations are in agreement with previous reports indicating that platinum accumulation in hepatocytes promotes mitochondrial dysfunction and excessive ROS generation, thereby driving oxidative cellular injury (19).

A profound leukopenic response was also documented following Cisplatin administration. This hematological deficit can be interpreted in light of the known ability of Cisplatin to form DNA cross-links in rapidly proliferating hematopoietic stem cell populations, thereby triggering apoptosis and reducing the production of circulating white blood cells. From a clinical perspective, such myelosuppression is highly relevant because it increases vulnerability to infection and frequently imposes chemotherapy delays or dose reduction, circumstances that may adversely affect treatment efficacy (5).

When administered alone, G-CSF effectively promoted hematological recovery but exerted little influence on liver function indices or oxidative stress markers. This outcome is consistent with its established receptor-mediated action on myeloid progenitor cells, a mechanism that supports hematopoietic regeneration without directly conferring antioxidant or hepatoprotective activity (7,8).

By contrast, Curcumin monotherapy produced clear hepatoprotective effects, as shown by the attenuation of hepatic enzyme leakage and the improvement of oxidative stress biomarkers. This protective action may be attributed to the β-diketone moiety within the Curcumin molecule, which facilitates direct ROS scavenging, Moreover, the cytoprotective potential of Curcumin is further amplified by its capacity to trigger the Nrf2/HO-1 signaling axis. This activation subsequently drives the transcriptional up-regulation of genes dependent on the Antioxidant Response Element (ARE), thereby reinforcing the cellular defense architecture against oxidative insults (10,20 and12).

Interestingly, Curcumin also afforded modest hematological protection, an effect that may be related to preservation of the bone marrow stromal niche and partial support of hematopoietic homeostasis (21).

The most notable outcome of the present work is the superior efficacy of the combined therapeutic regimen. Co-administration of Curcumin and G-CSF resulted in near-complete normalization of both hematological and hepatic parameters. A plausible explanation for this finding is a dual-mode synergistic mechanism in which Curcumin minimizes oxidative damage and preserves mitochondrial and tissue integrity, thereby creating a more favorable microenvironment for cellular survival, simultaneously, G-CSF exerts a mitogenic influence by promoting the expansion and lineage-specific maturation of surviving hematopoietic progenitor cells within the bone marrow microenvironment. It is also conceivable that Curcumin may enhance responsiveness to G-CSF by limiting apoptotic signaling and supporting the functional stability of the bone marrow niche. In this regard, the combined intervention appears to address both the oxidative basis of tissue damage and the regenerative requirements of immune reconstitution. The current observations align with earlier empirical data, which suggest that integrating potent antioxidants with hematopoietic growth factors provides a superior therapeutic strategy for ameliorating the systemic toxicities associated with chemotherapeutic agents (9).

Taken together, the current data provide strong experimental support for a combined therapeutic strategy that is mechanistically coherent and biologically effective. Rather than targeting a single toxic pathway, this regimen appears to provide broader cytoprotection by simultaneously mitigating hepatic oxidative injury and restoring hematopoietic competence, a combination that may be especially advantageous in the context of platinum-based chemotherapy.

Conclusion:

In summary, the combined administration of Curcumin and G-CSF provided comprehensive protection against the hematotoxic and hepatotoxic effects associated with Cisplatin treatment. The dual regimen was more effective than either monotherapy in preventing immune cell depletion and in preserving hepatic biochemical and oxidative balance. These findings establish a strong experimental basis for considering this combination as a supportive strategy in oncology settings. Future investigations should focus on clarifying the precise molecular mechanisms underlying this synergistic interaction and on evaluating its clinical relevance through well-designed randomized controlled trials.

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