International Journal of Biomedical Research Science (IJBRS)
An Open Access International Journal
Online ISSN: 3107-8745
Vol 02 No (1) Jan-Feb-Mar-Apr 2026

Effect of *Mussaenda glabrata* Leaf Extract on Cisplatin Induced Hematotoxicity, Nephrotoxicity And Neurotoxicity in Albino Wistar Rats

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ARTICLE INFO

Received Date: 23/01/2026

Accepted Date: 20/04/2026

Publication Date: 30th April 2026

Page Number:- 20-26

Available at: www.ijbrs.com

ABSTRACT:

This research was aimed to explore effect of *Mussaenda glabrata* extract of leaves against cisplatin induced hematotoxicity, neurotoxicity and nephrotoxicity in experimental rats. Toxicities were induced in healthy adult wistar rats by administering cisplatin, single dose of 8mg/kg, on 5th day through intraperitoneal route. After completion of nine days dosing with the test drug, on 10th day, various hematological, biomarkers, antioxidants and histopathological studies were performed. *Mussaenda glabrata* leaf extract had a significant beneficial role in cisplatin induced hematotoxicity by increasing the hematological parameters compared to cisplatin treated group. It also exhibited a significant protection against cisplatin induced nephrotoxicity and neurotoxicity by suppressing the biomarkers and by elevating the antioxidant parameters at different doses compared to cisplatin treated group. According to research findings, *Mussaenda glabrata* extract of leaves may be protective against the neurotoxicity, nephrotoxicity and hematotoxicity caused by the anti-cancer medication cisplatin. MGLE's antioxidant action may thus be directly linked to its protection. These results support the theory that antioxidant-rich medicinal herbs may have protective properties.

KEY WORDS: Cisplatin, *Mussaenda glabrata* leaf extract, Hematoprotective, Neuroprotective, Nephroprotective.

INTRODUCTION

Cisplatin is considered one of the key chemotherapy agents for cancer treatment that may be used to treat a variety of human cancers in various organs [1].

Nephrotoxicity can develop from cisplatin buildup in the tubules that are proximal inside the kidney once it is excreted by the kidneys. Subjects having a creatinine clearance more than 60 milliliters per minute are often the only ones who can use it; nonetheless, cisplatin-induced nephrotoxicity is frequent and can restrict dosage and/or dose intensity. When patients who have received a complete course of chemotherapy develop peripheral neuropathy, cisplatin neurotoxicity is medically obvious and may impact the treatment plan and the patient's quality of life [2].

One of the main causes of neurotoxicity is believed to be the build-up of cisplatin within dorsal root ganglia neurons as platinum-DNA adducts. There are currently no medications that can stop the development of cisplatin-induced neurotoxicity and the high frequency of neurotoxicity restricts the chemotherapeutic efficacy of cisplatin [3].

The development of synthetic medications has led to the necessity for alternative therapies and medical care due to their negative effects. From ancient times to the present, herbs and herbal treatments have been used extensively to heal illnesses [4].

Cisplatin's anticancer properties have been attributed to its capacity to bind DNA and generate covalent cross-links, which in turn block transcription and DNA replication. However, the host's development of numerous adverse effects and/or the cancer cells' acquisition of drug resistance limit the complete therapeutic efficacy of cisplatin [5].

Mussaenda glabrata syn. Mussaenda frondosa, also called "Vellaiilai" in Tamil, is a member of the Rubiaceae family and one of the medicinally significant plants. Jaundice, hyperacidity, ulcers, diuretic, wound, leprosy, swelling, asthma, antibacterial, hypolipidemic effect, hepatoprotective action, fever and cough are among the traditional ailments that leaves are used to cure [6].

Till now no study has been reported, regarding, protective effect of *Mussaenda glabrata* leaf extract [MGLE] against cisplatin induced hematotoxicity, nephrotoxicity and neurotoxicity. Hence the current study was designed to demonstrate the impact of extract of leaves from *Mussaenda glabrata* in different doses against cisplatin induced hematotoxicity, nephrotoxicity and neurotoxicity.

MATERIAL AND METHODS

Chemicals: Cisplatin was obtained from Cipla, Mumbai, India. Biochemical estimation kits were obtained from Precision Biomed Pvt. Ltd., Mumbai, India. All chemicals, solvents used for this study were of the analytical grade obtained from reputed suppliers from India.

Animals: Both sexes of experimental rats weighing between 175 and 250 grams were kept in an adequately conditioned animal housing with a 12:12 light-dark cycle at 25 ° ± 5 °C and 50± 5% relative humidity. Every rat was given a commercially accessible standard pellet diet and unlimited access to water. In accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals' (CPCSEA) recommendations, the animals were kept and research was carried out. Institutional Animal Ethics Committee [IAEC] approved the study bearing Reference No.: SDCP/IAEC/13/2020 dated 15/02/2020.

Preparation of *Mussaenda Glabrata* leaf extract [MGLE] [7] Kerala was the source of M.glabrata. The plant material was identified by the Department of Botany, University College, Mangalore, 575001. Leaves that had been shade-dried were ground into a reasonably coarse powder. The Soxhlet extractor was used to obtain petroleum ether, chloroform, alcohol, and aqueous extracts of leaves. Till the solvent in the thimble was clear, the extractions were carried out 12 times. The deep brown semisolid substance was stored for later use in an airtight container once the solvent had evaporated.

Phytochemical estimation of the extract [8]: The presence of several phytochemical elements, including alkaloids, proteins, carbohydrates, glycosides, phytosteroles, saponins, tannins and flavonoids were examined by qualitative analysis of the MGLE extract.

Experimental Protocol

Dose selection [9,10]: Cisplatin dosages for rats have been determined to be 200 mg/kg and 400 mg/kg by oral route based on earlier studies of the literature.

Cisplatin induced toxicity model [9,10]: The current study has nine-day duration. On the fifth day, a single intraperitoneal (i.p.) dosage of 8 mg per kg of cisplatin was given to healthy adult Wistar rats in order to cause hematotoxicity, nephrotoxicity, and neurotoxicity. The MGLE was given orally to each group for nine days.

Following nine days of test medication dosage, the rats being studied was put to sleep by ether inhalation on the tenth day (six days following cisplatin injection). From each rat, blood was taken and split into two samples. Also kidneys and brain were removed and one sample was used to estimate hematological parameters while the other was utilized to estimate biomarkers. The kidney's two sections were employed for histological research and antioxidant assessment, respectively. The animal's brain was removed, cleaned in cold saline, blotted and prepared for biochemical along with histological analysis in order to assess neurotoxicity.

Groupings: Good health mature wistar rats were split into four distinct groups of six rats each. Group I: Normal (saline 10 ml/kg oral) for 9 days. Group II: Cisplatin (8mg/kg intraperitoneal) on the 5th day of treatment. Group III: Low dose MGLE (200 mg/kg intraperitoneal) + CIS on the 5th day of treatment. Group IV: High dose MGLE (500 mg/kg intraperitoneal) + CIS on the 5th day of treatment.

RESULTS

Isolation of *Mussaenda Glabrata* Leaf Extract: The practical yield of MGLE from 100g of dried plant powder of M. glabrata by maceration process was found to be 35 g. The evidence of carbohydrates, steroids, triterpenoids, glycosides and flavonoids were confirmed by preliminary qualitative analysis of the MGLE extract.

Effect of MGLE on CIS induced hematotoxicity: MGLE showed high efficacy against CIS induced hematotoxicity. CIS treated rats explored extremely significant ($P<0.001$) decrease in RBC (red blood corpuscles) compared to normal group. The rats pretreated with MGLE (200 mg/kg) and MGLE (400 mg/kg) showed extremely significant ($P<0.001$) increase in RBC compared to CIS group. CIS treated rats showed

extremely significant (P<0.001) increase in WBC (white blood corpuscles) compared to normal group. The rats pretreated with MGLE (200 mg/kg) and MGLE (400 mg/kg) showed extremely significant (P<0.001) decrease in WBC compared to CIS group.CIS treated rats showed most significant (P < 0.01) decrease in Hb (haemoglobin) compared to normal group. The rats pretreated with MGLE (200 mg/kg) and MGLE (400 mg/kg) showed most significant (P<0.001) increase in Hb compared to CIS group.CIS treated rats showed extremely significant (P<0.001) decrease in platelets compared to normal group. The rats pretreated with MGLE (200 mg/kg) and MGLE (400 mg/kg) showed extremely significant (P<0.001) increase in platelets compared to CIS group. See table 1.

Table 1. Effect of MGLE on CIS induced hematotoxicity

TREATMENT	RBC (106 cell/µL)	WBC (103 cell/µL)	Hb (g/dL)	Platelets (10^5 cell/µL)
NORMAL	4.69±0.101	4.656±0.003	13.825±0.006	6.256±0.009
CIS	2.548±0.073###	7.305±0.067###	10.345±0.007###	2.915±0.001###
MGLE200+CIS	2.913±0.005**###	6.631±0.192**###	10.685±0.087**###	3.391±0.151*###
MGLE400+CIS	3.31±0.026***###	6.039±0.166***###	10.896±0.077***###	3.626±0.171**###

n=6; data are presented as MEAN ± SEM. Statistical significance was determined using one-way ANOVA then Tukey-Kramer multiple comparison test. **P<0.01 and ***P<0.001 indicate significant differences compared to the control group, while ##P<0.01 and ###P<0.001 denote significant differences compared to the normal group.

Effect of MGLE on CIS induced nephrotoxicity serum biomarkers: In this model of experimentation, the CIS induced rats showed an extremely significant (P<0.001) increase in creatinine level when compared with normal control. Prior treatment of MGLE (200 mg/kg) and MGLE (400 mg/kg) showed highly significant (P<0.001) decrease in serum creatinine level respectively when compared with the control group.In this experimental model, the CIS induced rats control showed an extremely significant (P<0.001) increase in urea level when compared with normal control. Prior treatment of MGLE (200 mg/kg) and MGLE (400 mg/kg) showed extremely significant (P<0.001) decrease in urea level respectively when compared with the control group. In this model of experimentation, the CIS induced rats revealed an extremely significant (P<0.001) increase in uric acid level when compared with normal control. Prior treatment of MGLE (200 mg/kg) and MGLE (400 mg/kg) showed more significant (P<0.001) decrease in uric acid level respectively when compared with the control group. See table 2.

Table 2. Effect of MGLE on CIS induced nephrotoxicity serum biomarkers

TREATMENT	CREATININE (mg/dl)	UREA (mg/ml)	URICACID (mg/ml)
NORMAL	0.963±0.009	37.858±0.032	1.587±0.021
CIS	4.457±0.019###	70.808±0.048###	6.312±0.029###
MGLE200+CIS	3.510±0.225**###	59.352±4.008*###	5.065±0.269*###
MGLE400+CIS	3.203±0.297***###	57.809±3.788*###	4.732±0.494**###

n=6; data are presented as MEAN ± SEM. Statistical significance was determined using one-way ANOVA then Tukey-Kramer multiple comparison test. **P<0.01 and ***P<0.001 indicate significant differences compared to the control group, while ##P<0.01 and ###P<0.001 denote significant differences compared to the normal group.

Effect of MGLE on CIS induced nephrotoxicity antioxidants: Investigation of antioxidants in homogenate kidney tissue showed an extremely significant (P<0.001) decrease in GSH compared to normal group. The rats pretreated with MGLE (200 mg/kg) and MGLE (400 mg/kg) showed more significant (P<0.001) increase in GSH compared to CIS group. Investigation of antioxidants in homogenate kidney tissue showed more significant (P<0.001) decrease in catalase compared to normal group. The rats pretreated with MGLE (200 mg/kg) and MGLE (400 mg/kg) showed extremely significant (P<0.001) increase in catalase compared to CIS group. Investigation of antioxidants in homogenate kidney

tissue showed more significant (P<0.001) decrease in SOD (super oxide dismutase) compared to normal group. The rats pretreated with MGLE (200 mg/kg) and MGLE (400 mg/kg) showed extremely significant (P<0.001) increase in SOD compared to CIS group. See Table 3.

Table 3. Effect of MGLE on antioxidants in CIS induced nephrotoxicity antioxidants

TREATMENT	GSH (ηM/g wet gland)	SOD (U/mg wet gland)	Catalase (U/mg wet gland)
NORMAL	17.509±0.058	96.262±0.007	22.75±0.012
CIS	8.737±0.006###	49.566±0.007###	12.08±0.017###
MGLE200+CIS	10.36±0.530*###	66.977±4.388*###	15.729±0.660**###
MGLE400+CIS	10.867±0.548**###	75.715±6.885**##	17.488±1.003***###

n=6; data are presented as MEAN ± SEM. Statistical significance was determined using one-way ANOVA then Tukey-Kramer multiple comparison test. **P<0.01 and ***P<0.001 indicate significant differences compared to the control group, while ##P<0.01 and ###P<0.001 denote significant differences compared to the normal group.

Effect of MGLE on CIS induce neurotoxicity antioxidants: Investigation of antioxidants in homogenate brain tissue showed an extremely significant (P<0.001) decrease in GSH of CIS treated group compared to normal. The rats pretreated with MGLE (200mg/kg) and MGLE (400mg/kg) showed extremely significant (P<0.001) increase in GSH compared to cisplatin control. Investigation of antioxidants in homogenate brain tissue showed an extremely significant (P<0.001) decrease in catalase of CIS treated group compared to normal. The rats pretreated with MGLE (200mg/kg) and MGLE (400mg/kg) showed extremely significant (P<0.001) increase in Catalase compared to cisplatin control. Investigation of antioxidants in homogenate brain tissue showed an extremely significant (P<0.001) decrease in SOD of CIS treated group compared to normal control. The rats pretreated with MGLE (200 mg/kg) and MGLE (400 mg/kg) showed extremely significant (P<0.001) increase in SOD compared to Cisplatin control. See Table 4.

Table 4. Effect of MGLE on CIS induced neurotoxicity antioxidants

TREATMENT	GSH (mmol/g tissue)	SOD (U/g tissue)	CAT (U/g tissue)
NORMAL	17.781±0.024	15.86±0.025	17.735±0.007
CIS	8.715±0.024###	8.558±0.019###	10.556±0.014###
MGLE200+CIS	9.853±0.270**###	10.655±0.489**###	11.648±0.286**###
MGLE400+CIS	10.253±0.360***###	11.490±0.508***###	12.597±0.318***###

n=6; data are presented as MEAN ± SEM. Statistical significance was determined using one-way ANOVA then Tukey-Kramer multiple comparison test. **P<0.01 and ***P<0.001 indicate significant differences compared to the control group, while ##P<0.01 and ###P<0.001 denote significant differences compared to the normal group.

DISCUSSION

This study aimed to determine if *Mussaenda glabrata* extract of leaves could prevent cisplatin-induced hematoxicity, nephrotoxicity, and neurotoxicity in albino wistar rats. The study found that *Mussaenda glabrata* leaf extract significantly reduced the effects of cisplatin. The Rubiaceae family includes the flowering plant species M. glabrata. The entire wild Mussaenda plant has anti-inflammatory properties and is used to treat pruritis, bronchitis, fever, wounds, ulcers, cough and jaundice [11].

One well-known chemotherapeutic medication is CIS. Numerous human malignancies, including as those of thelung, ovaries, bladder, head and testicles have been treated with it. Nephrotoxicity is the most prevalent of the roughly 40 distinct toxicities of cisplatin. Ototoxicity, haematological neurotoxicity, hepatotoxicity, gastrointestinal and cardiotoxicity are additional frequent adverse effects [12,13]. One of the most critical metrics for determining the toxicity of the anti-cancer medication cisplatin in both people and animals is the haematopoietic system. According to the current study, rats treated with CIS for five days experienced considerable toxic effects in their haematological

parameters, while animals pretreated with MGLE shown a strong defence against hematotoxicity. The substantial reduction in the number of erythrocytes, hemoglobin, and platelets validated the harmful effects of CIS on haematological parameters [14].

The CIS demonstrated a significant decrease in the RBC level in the current investigation, confirming the hematotoxicity. When compared to a normal control group, the observed decline was highly significant, and the magnitude of toxicity was quite high. Several factors could be responsible, including bone marrow cell deterioration or an increase in the osmotic brittleness of red blood cells. Therefore, CIS poisoning may result in a reduction of red blood cells due to either haematopoietic tissue activity suppression, erythropoiesis impairment, or both. Because of the increased permeability of the RBC membrane, cisplatin treatment accelerated the destruction of RBCs and decreased erythropoietin, which is a haemopoietic growth factor. This, in turn, caused changes in haematological parameters [14].

In platelets and lymphocytes, CIS induces oxidative stress that may impact their lifespan, trigger apoptosis, and ultimately decrease the quantity of these cells in the circulation. In addition to a drop in RBC count, a decrease in platelet count may result from cisplatin's inhibition of bone marrow function, reduced platelet generation or consumption, or enhanced platelet aggregation. Also results suggests that thrombocytopenia with leukopenia in the cisplatin-treated group may have been caused by the apoptotic impact of cisplatin on platelets and lymphocytes, which in turn decreased the quantity of these cells in the blood. Additionally, decreased haemoglobin and erythrocyte counts may be caused by bleeding from intestinal affections caused by cisplatin and red cell destruction caused by free radicals [14].

Animals treated with CIS in the current study had higher WBC levels. This may be the result of an inflammatory response or the infection brought on by the injection of CIS. Additionally, CIS may cause oxidative stress in lymphocytes and thrombocytes of human being, resulting in their necrosis 14. Due to haemoglobin's sensitivity to oxidative stress, we observed a decrease in platelets and haemoglobin levels following CIS administration. Extracellular signal-regulated protein kinase (ERK) in platelets is activated in a dose-dependent manner by cisplatin, resulting in platelet death and decreased platelet function, both of which are signs of haematological toxicity. RBC, Hb, and platelet counts are beneficially increased in response to MGLE dose-dependent prophylactic therapy against CIS-induced hematotoxicity indicators. An increase in these erythrocytes may be linked to either preventing bone marrow suppression or promoting erythropoiesis. However, the inhibition of ERK in platelets is the cause of the increase in platelet counts. A lower WBC count may be associated with reduced inflammation across the haemopoietic system [14].

The CIS-treated group exhibits a substantial increase in urea, creatinine and uric acid in nephrotoxicity. The two primary indicators of nephrotoxicity and hepatorenal development are serum creatinine and urea. The natural product of muscle digestion, serum creatinine is removed unaltered by renal system. An anomaly in the kidney's glomerular filtration mechanism might be the cause of the rise in blood creatinine levels. The waste product produced by the liver's urea cycle during protein metabolism is called urea. Serum urea levels rise as a result of GFR deficit and decreased blood volume. The enzyme uridase produces uric acid as a byproduct of purine biotransformation [15,16].

The elevated levels of creatinine, urea, and uric acid brought on by CIS are effectively corrected by the MGLE pretreatment. The pathophysiology of CIS and other cytotoxic drug-induced nephrotoxicity has been proposed to include oxidative stress damage and generation of reactive oxygen species (ROS). The disturbance of the dynamic balance between pro-oxidants and free radicals, which antioxidants scavenge, results in cellular damage [17]. The current investigation shows that CIS administration significantly lowers GSH levels. The poisonous molecule acrolein is the cause of the decrease in GSH content in renal tissues following CIS treatment. Acrolein causes the kidney's tubular cells to necrotise by binding GSH in the plasma membrane, interfering with the antioxidant defence mechanism, and raising ROS. Following CIS administration, a significant decrease in SOD and catalase levels was noted in the current study.

The essential antioxidant enzymes SOD and catalase transform molecules of oxygen into non-toxic byproducts. When ROS levels rise, SOD levels fall [18]. The inhibition of catalase function is the cause of the increase in H2O2 levels. Consequently, the SOD activity is likewise inhibited by catalase deficiency. Increased ROS and lipid peroxidation are the primary causes of the decrease in these antioxidant enzymes. Following CIS therapy, the MGLE pretreatment dramatically raises the levels of GSH, SOD, and catalase [18]. Histopathological analysis and the results of serum markers and antioxidant parameters were connected. Bowman's capsule shrinkage, congestion, blood vessel dilatation, inflammation, and infiltration are all symptoms of CIS treatment. By examining positive effects such no alteration in Bowman's capsule size, mild inflammation, and no blood capillary congestion, the MGLE pretreatment effectively increased the toxic consequences brought on by the CIS renal system [18].

Numerous research in the field of neuroprotection have shown that oxidative stress, LPO, and mitochondrial dysfunction are all involved in the neurotoxicity caused by CIS. CIS causes cytotoxicity by producing reactive oxygen species (ROS). In brain tissues, injection of CIS resulted in reduction in activity of antioxidant defense enzymes, increase in levels of LPO, NO and decrease in concentrations of non-enzymatic components of GSH that prevent/defend against LPO. It is acknowledged that both are associated with oxidative stress and lead to andiscrepancy between the antioxidant capacity of the body and the production of radicals obtained from oxygen [19-22].

The study's findings demonstrate that, in comparison to the normal group, the CIS-treated animals' neural SOD and GSH levels dramatically dropped. The reduction of brain antioxidants

is prevented by simultaneously administering MGLE (400 mg/kg, orally) and CIS therapy. The loss of both zinc and copper, which are necessary for enzyme function, may be the cause of the drop in SOD activity following CIS injection. The superoxide anion generated during the regular metabolic process cannot be scavenged by the reduced SOD activity. LPO can be initiated and progressed by the superoxide anion. Following CIS injection, there is also a reduction in GSH activity. As a result, the brain's capacity to scavenge harmful H2O2 and lipid peroxides was diminished [23-25].

The fact that MGLE restored neuronal SOD and GSH activity indicates that the extract can shield the enzymes. The toxicity of CIS can be significantly increased by GSH deficiency. The neurotoxicity caused by CIS is known to be significantly influenced by free radicals and MGLE clearly shows that the elevated GSH levels provide protection. Oxidative stress is brought on in the brain by ROS and free radicals. CIS becomes more harmful when GSH is depleted. GSH depletion, which seems to be the primary mechanism for LPO and reduced antioxidant enzyme activity, is another cause of LPO. These findings provide credence to the idea that antioxidant system depletion is a contributing factor in the neurotoxicity process observed in rats treated with CIS [23-25]. MGLE's antioxidant action may thus be directly linked to neuroprotection. These results support the theory that antioxidant-rich medicinal herbs may have neuroprotective properties.

CONCLUSION

The current study showed that MGLE (200 mg/kg and 400 mg/kg orally) exhibited hematoprotective, nephroprotective, and neuroprotective properties against cisplatin. Cisplatin caused experimental rats to become nephrotoxic, neurotoxic, and hematotoxic. The herb's possible antioxidant properties, free radical-fighting activity, regulation of serum indicators and safeguarding of histopathological characteristics may all contribute to its effectiveness as a preventative therapy. To prove the reality clinically, more study is needed.

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