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Evaluation of protective effects of gallic acid on cisplatin induced haematological alterations in rats

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Abstract
The study was aimed to investigate the protective effect of phytochemical gallic acid on haematological alterations induced by cisplatin (CP) in Wistar albino rats. One hundred and eight Wistar albino rats were equally divided into six groups. Group I served as control group, Group II received single dose of intraperitoneal injection of CP at 7.5mg/kg bw, Group III received gallic acid at 75 mg/kg bw for 45 days, Group IV was treated with gallic acid daily for 15 days prior to CP injection and discontinued post cisplatin injection, Group V received CP injection and concurrently received gallic acid for 45 days post cisplatin injection and Group VI was treated with gallic acid for 15 days prior to CP injection and continued for 45 days post cisplatin injection. CP administration caused significant (p<0.05) decrease in TEC, haemoglobin, TLC and platelet count as compared to normal control group. Gallic acid supplementation to CP treated rats significantly improved the haematological parameters. It was concluded that, gallic acid supplementation could reduce the haematotoxicity and protect against cisplatin induced toxicity.

Keywords: Gallic acid, cisplatin, haematotoxicity, nephroprotection

Introduction
Cisplatin (CP) is a widely used popular chemotherapeutic drug used in human and veterinary medicine in the treatment of variety of malignancies (Barabas *et al*., 2008) [7]. In humans, cisplatin is effectively used against bladder cancer, cervical cancer, ovarian cancer, testicular cancer, non-small cell lung cancer, mesothelioma, endometrial cancer, squamous cell carcinoma of the head and neck, malignant melanoma, adrenocortical carcinoma *etc*., (Purena *et al*., 2018) [28]. Cisplatin exerts cytotoxicity upon cancer cells through the formation of DNA adducts that includes inter and intrastrand cisplatin DNA cross links that arrest the cell cycle at S, G1 and G2-M phase thus induces cell death (Aldossary, 2019) [1]. The therapeutic efficacy of cisplatin enhances with dose acceleration. However, high dose cisplatin therapy has limitation due to its associated toxic effects such as nephrotoxicity, hepatotoxicity, cardio toxicity, testicular toxicity, bone marrow toxicity and ototoxicity resulting in worsened quality of life and shortened survival. Despite cisplatin's effectiveness in treating cancer, organ damage and emergence of chemo resistance are its major drawbacks (Dasari and Tchounwou, 2014) [12]. Mitochondrial oxidative stress, DNA damage, inflammation and apoptosis of normal tissues are some of the side effects of cisplatin in tissues (Ozkok *et al.*, 2014 and Almaghrabi *et al.*, 2015) [25, 5]. Hence to ameliorate the toxic effects of CP and to get its utmost benefits, supplementation with antioxidant rich natural phytochemicals is being widely explored.

Gallic acid (3,4,5-trihydroxybenzoic acid, GA) is one such phytochemical found ubiquitously in plant kingdom has attracted the attention of investigators due to its high antioxidant, anti-inflammatory and anticancerous activity. It is naturally found in many plants, fruits and vegetables such as strawberries, grapes, pomegranates, pineapples, bananas, lemons, gallnuts, sumac, witch hazel, tea leaves, oak bark, and apple peels (Manach *et al*., 2005). Gallic acid is abundant in processed beverages such as red wine and green tea. Gallic acid has wide range of biological and therapeutic properties. It is a strong chelating agent that protects cells and tissues against oxidative stress through its anti-inflammatory and antioxidant properties (Asci *et al*., 2017) [6]. The protective effect of gallic acid is due to its very potent free-radical scavenging activity and is attributed to the number of hydroxyl moieties attached to the aromatic ring of the benzoic molecules (Mamat *et al.*, 2020) [19]. In view of its beneficial effects from the existing literature, the present study was designed to explore the possibility of

usage of GA as a measure of long-time prophylactic therapy in cisplatin toxicity against haematological alterations.

Materials and Methods

Cisplatin (Cisplat®), was procured from Zydus Celexa, India and gallic acid was procured from Sigma Aldrich Company, China.

Animals and experimental protocol

Normal adult male Wistar albino rats weighing approximately 160-180 g were procured from commercial animal facility, Bengaluru. Rats were maintained under standard laboratory settings and fed with *ad-libitum* standard commercial rat pelleted feed and clean drinking water. The rats were allowed to acclimatize for a period of 15 days in experimental animal facility. The duration of experiment was for a period of 45 days and prior permission was obtained from the Institutional Animal Ethics Committee (IAEC) for the conduct of experiment. The rats were divided, based on the body weight into six groups with eighteen rats in each group and treated as follow:

Group I (Negative control): Rats injected with 0.5ml sterile normal saline intraperitoneally on Day 1 and gavaged distilled water daily for 45 days.

Group II (Positive control): Rats administered with cisplatin at 7.5 mg/kg bw intraperitoneally as a single dose on Day 1.

Group III (GA control group): Rats supplemented with gallic acid alone at the dose rate of 75 mg/kg bw daily for 45 days.

Group IV (Pre-treatment group): Rats supplemented with gallic acid for a period of 15 days prior to inducing toxicity by cisplatin on Day 1.

Group V (Concurrent group): Rats administered with cisplatin injection on Day 1 and concurrently treated with gallic acid for 45 days post cisplatin injection.

Group VI (Pre +concurrent group): Rats treated with gallic acid for 15 days prior to inducing toxicity by cisplatin on Day 1 and continued gallic acid supplementation for 45 days post cisplatin injection.

Haematological parameters evaluation

Few drops of blood were collected from the retro-orbital plexus of the rats under light ether anaesthesia at different time intervals of experiment (7^{th}, 14^{th}, 28^{th} and 45^{th} day post induction of toxicity) using ethylene diamine tetra acetic acid (EDTA) as an anticoagulant for analysis of various haematological parameters such as total erythrocyte count (TEC), haemoglobin (Hb), total leukocyte count (TLC) and total platelet count. For the haematological evaluation automated haematology analyzer (BC-2800 VET, Mindray) was used.

Statistical analysis

Statistical analysis was performed using the statistical software Graph Pad Prism, version 8.4.3 for windows. Mean values and standard error were calculated and all values were expressed as Mean (± SE). The data were analysed by two-way analysis of variance (ANOVA). $p<0.05$ was considered as significant compared to control.

Results and Discussion

Tables 1, 2, 3 and 4 and figures 1, 2, 3 and 4 represent the details regarding the toxic effects of CP and ameliorating effects of GA on haematological parameters in adult male Wistar rats. Single dose of cisplatin injection resulted in significant ($p<0.05$) decrease in the mean values of TEC, Hb, TLC and total platelet count in cisplatin control group (Group II) compared to those of control groups (Groups I and III) at all the intervals of observation. Significant reduction was observed in first two weeks of cisplatin injection and on subsequent intervals the values showed a meagre gradual improvement.

The mean values of TEC, Hb, TLC and total platelet count in gallic acid treatment groups (Group IV, V and VI) showed a significant improvement in comparison with cisplatin control group on all the days of observation. However, the mean values were significantly ($p<0.05$) lesser compared to the normal control group (Group I). Among the gallic acid treatment groups, Group IV showed lesser improvement however, showed better mean values of haematological parameters at first interval of study. The pre+ concurrent gallic acid treatment group (Group VI) showed a significant ($p<0.05$) higher progressive improvement compared to Group IV and Group V on all the intervals of investigation.

Blood parameter estimation acts as a pathological and physiological indicator of animal health. Cisplatin being a cytotoxic drug, is reported to cause several side effects such as acute renal failure, hepatotoxicity, cardio toxicity and intestinal toxicity including bone marrow suppression. Bone marrow is particularly sensitive to direct toxic effect of chemotherapeutic drugs due to presence of large number of proliferative cells under DNA synthesis (Das *et al*., 2008; Basu *et al*., 2017 and Cheki *et al*., 2021) [9, 8, 10]. Cisplatin induced myelosuppression has been reported to result in hypoplasia of myeloid and erythroid series and megakaryocyte hypoplasia (Shaymaa *et al.,* 2017) [31]. The mechanisms associated with cisplatin induced myelosuppression and other side effects include binding of cisplatin to DNA to form intra- and interstrand DNA adducts, which interfere with DNA transcription and replication and ultimately resulting in cell cycle arrest and cell death, glutathione depletion and increased oxidative stress (Chuang *et al*., 2022) [11]. Cisplatin-induced bone marrow damage is also accompanied by sensory and autonomic neuropathy of bone marrow which may cause the impairment of hematopoietic stem cells and bone marrow regeneration (Park *et al*., 2017) [27]. Thus, the reduction in the haematological parameters observed in the present investigation might be due to toxic effect of cisplatin on highly proliferative bone marrow cells as indicated above.

Anaemia observed in the present study in Cisplatin control group (Group II) with decreased TEC and Hb values could be attributed to the suppression of the activity of haematopoietic tissue, impaired erythropoiesis and accelerated erythrocyte destruction due to altered erythrocyte membrane permeability following cisplatin therapy (Hassan *et al*., 2010 Nasr, 2014 and Rajendrakumar *et al*., 2020) [17, 21, 29]. The significant reduction in TEC and Hb observed in the present study also could be attributed to cisplatin effect on kidneys. Nephrotoxicity is the foremost important side effect of cisplatin therapy and the severity of anaemia depends on the dose of cisplatin administered, cisplatin induced renal tubular damage and resultant erythropoietin depletion. The meagre improvement observed in the cisplatin control group (Group II) during 28^{th} and 45^{th} day of the study in the TEC and Hb could be related to the cessation of cisplatin effect with its elimination from the body with restoration of renal tubular

function. Wood and Hrushesky, (1995) [35] and Hartmann and Lipp (2014) [40] also observed recovery from anaemia and erythropoietin levels initiated after cessation of cisplatin therapy with restoration of renal tubular function which amply supports the findings of present study.

In the present study, a significant leukopenia and thrombocytopenia was observed in first two intervals which gradually and progressively improved in the subsequent intervals in cisplatin control group. Cisplatin induces transient decline in TLC levels in rats and could be attributed to direct toxic effect of cisplatin on bone marrow cells [Wood and Hrushesky (1995) [35] and Hartmann and Lipp (2014)] [40]. CP therapy is associated with severe myelosuppressive effects and the toxicity is correlated with peak levels of the drug in the first 2 weeks of treatment (Zahra *et al.,* 2008) [37]. Decreased number of platelets and lymphocytes in cisplatin therapy also due to cisplatin induced oxidative stress and apoptotic effect of cisplatin on these cells (Olas *et al*., 2005 and Shaymaa *et al.*, 2017) [24, 31]. Cisplatin induces apoptosis of platelets through activation of extracellular signal-regulated kinase (ERK) signalling pathway and also impairs platelet function by increasing ROS generation in platelets (Zhang *et al*., 2012) [38]. In the non-tumor-bearing host, cisplatin treatment might induce acute haematotoxicity that leads to stimulation of G-CSF, the major regulator of neutrophilic granulocytes and resultant rebound leukocytosis (Panopoulos and Watowich, 2008 and Lin *et al.,* 2020) [26, 18].

In the current study, gallic acid supplemented groups (Groups IV, V, and VI) showed a significant improvement in all the haematological values. The pre + concurrent treatment (Group VI) was observed to be better compared to only pre-treatment (Group IV) or only concurrent treatment (Group V). Gallic acid is a plant-derived polyphenolic compound with high antioxidant potential. Its powerful antioxidant property is attributed to its inherent hydrogen-donating capability to free radicals and getting itself oxidized to a stable quinine moiety (Singh *et al.*, 2014) [33]. The protective effect of gallic acid could be due to its free radical scavenging property, inhibition of lipid peroxidation, through increase in antioxidant defence system and sparing effect on glutathione. Many studies have demonstrated antioxidant effect of gallic acid is through upregulation of Nrf2 (Nuclear factor erythroid 2-related factor 2) (Feng *et al.* (2018) [15]; Zhou *et al.* (2019) [39] and Sanjay *et al.* (2021) [34]. Gallic acid significantly upregulated gene expression of GCLC (Glutamate-Cysteine Ligase Catalytic subunit), Prdx6 (Peroxiredoxin 6), Superoxide dismutase (SOD), Catalase (CAT) and Glutathione peroxidase (GPx) by increasing Nrf2-p (activated Nrf2) levels and gene expression levels with an improvement in antioxidant activity of SOD, CAT, GPx and GSH, and subsequent reduction in total oxidant levels (Sanjay *et al.* (2021) [34]. Protective effect of GA in improvement of haematopoietic function has been reported earlier in cyclophosphamide-and cisplatin-induced immune-suppression in Swiss albino mice (Shruthi *et al.*, 2018) [32]; sodium fluoride induced nephrotoxicity in the Wistar rats (Ola-Davies and Azeez, 2018) [23]; diazinon-induced cardiovascular and renal dysfunction in rats (Ajibade *et al.*, 2016); toxicity induced by lead in blood, liver and kidney of rats (Reckziegel *et al.*, 2016) [30] and haematotoxicity, cardiotoxicity, and hepatotoxicity induced by liquefied petroleum gas in rats (Akinmoladun *et al.*, 2021) [3]. Gallic acid and its esters are reported to exhibit antihemolytic property against 2,2' –Azobis (2-amidinopropane) hydrochloride (AAPH)-induced hemolysis of erythrocytes through their free radical scavenging activity (Ximenes *et al.*, 2008) [36]. These findings suggest that gallic acid can alleviate cisplatin induced oxidative stress and can protect blood cells, bone marrow and other organs against cisplatin induced oxidative stress injury. The preventive effect on haematotoxicity could be also due to nephroprotection exerted by gallic acid there by restoring erythropoietin levels. The nephroprotection property of gallic acid against cisplatin induced renal injury was reported in various studies by earlier workers Asci *et al.* (2017) [6]; Eslamifar *et al*. (2021) [14]; Akomolafe *et al.* (2014) [4]; Dogan *et al*. (2022) [13] and against paraquat toxicity by Nouri *et al.* (2021) [22]. Progressive improvement in TEC and Hb value with improvement in renal damage microscopically, in creatinine and BUN (blood urea nitrogen) values and renal antioxidant status (data not shown) was also observed in the present study.

Table 1: The mean (±SE) values of total erythrocyte count (TEC) (x10^6/µl) of experimental groups at different time intervals

Experimental groups	TEC) (x10^6/µl)			
	Days of post treatment			
	7th	14th	28th	45th
Group-I Negative control	8.38±0.079^{ax}	8.31±0.091^{ax}	8.43±0.060^{ax}	8.46±0.056^{ax}
Group-II Cisplatin control	5.3±0.054^{bx}	4.82±0.072^{by}	5.2±0.097^{bxy}	6.11±0.055^{bw}
Group-III Gallic acid control	8.54±0.057^{ax}	8.41±0.074^{ax}	8.49±0.045^{ax}	8.53±0.072^{ax}
Group-IV Pre-treatment only	6.2±0.038^{cxz}	5.85±0.027^{cy}	6.03±0.084^{cxy}	6.66±0.063^{cz}
Group-V Concurrent	5.81±0.069^{dx}	6.06±0.021^{dy}	6.77±0.088^{dz}	7.33±0.055^{dw}
Group-VI Pre + Concurrent	6.57±0.065^{ex}	6.69±0.086^{ex}	7.33±0.014^{ey}	7.85±0.076^{ez}

Values with different superscripts within a row and within a column vary significantly at $p<0.05$

Table 2: The mean (±SE) values of haemoglobin (g/dl) of experimental groups at different time intervals

Experimental groups	Haemoglobin (g/dl)			
	Days of post treatment			
	7th	14th	28th	45th
Group-I Negative control	15.43±0.13^{ax}	15.40±0.08^{ax}	15.58±0.16^{ax}	15.65±0.06^{ax}
Group-II Cisplatin control	10.05±0.18^{bx}	9.80±0.04^{bx}	10.52±0.17^{bx}	12.18±0.12^{by}
Group-III Gallic acid control	15.70 ±0.13^{ax}	15.63±0.14^{ax}	15.60±0.07^{ax}	15.73±0.09^{ax}
Group-IV Pre-treatment only	11.65±0.10^{cx}	11.55±0.09^{cx}	12.45±0.06^{cy}	12.95±0.08^{cy}
Group-V concurrent	11.33±0.15^{cx}	12.03±0.07^{dx}	13.30±0.09^{dy}	14.08 ±0.10^{dz}

Group-VI Pre + Concurrent	12.78±0.07^{dx}	12.83±0.15^{ex}	14.03±0.11^{ey}	14.75±0.06^{ez}

Values with different superscripts within a row and within a column vary significantly at $p<0.05$

Table 3: The mean (±SE) values of total leukocyte count (TLC) (x10^3/µl) of experimental groups at different time intervals

Experimental Groups	TLC (x10^3/µl)			
	Days of post treatment			
	7th	14th	28th	45th
Group-I Negative control	9.38±0.19^{ax}	9.35±0.21^{ax}	9.43±0.17^{ax}	9.40±0.15^{ax}
Group-II Cisplatin control	5.63±0.20^{bx}	5.9±0.29^{bxy}	7.38±0.16^{by}	8.65±0.09^{bz}
Group-III Gallic acid control	9.50±0.19^{ax}	9.40±0.09^{ax}	9.63±0.16^{ax}	9.53±0.13^{ax}
Group-IV Pre-treatment only	6.83±0.04^{bx}	6.40±0.17^{bx}	7.78±0.07^{by}	8.90±0.19^{aby}
Group-V Concurrent	6.50±0.04^{cx}	7.38±0.05^{cy}	8.15±0.07^{bcz}	9.13±0.16^{abz}
Group-VI Pre + Concurrent	7.88±0.13^{dx}	8.25±0.11^{dx}	8.43±0.05^{cx}	9.30±0.09^{ay}

Values with different superscripts within a row and within a column vary significantly at $p<0.05$

Table 4: The mean (±SE) values of platelets count(x10^3/µl) of experimental groups at different time intervals

Experimental groups	Platelets count(x10^3/µl)			
	Days of post treatment			
	7th	14th	28th	45th
Group-I Negative control	614.75±7.08^{ax}	652.00±7.71^{ax}	632.75±7.95^{ax}	654.5±4.09^{ax}
Group-II Cisplatin control	204.00±8.83^{bx}	260.00±7.07^{cx}	359.00±7.76^{cy}	462.75±3.53^{bz}
Group-III Gallic acid control	617.00±8.66^{ax}	620.75±5.65^{ax}	645.75±7.16^{ax}	655.25±3.12^{ax}
Group-IV Pre-treatment only	342.00±4.08^{cx}	327.50±6.78^{bx}	420.25±2.78^{by}	517.75±4.76^{cz}
Group-V Concurrent	268.75±6.79^{dx}	347.33±4.34^{by}	449.25±7.18^{bz}	565.25±4.11^{dw}
Group-VI Pre + Concurrent	474.75±8.47^{ex}	539.00±5.95^{dxy}	582.75±5.76^{dyz}	635.00±8.37^{az}

Values with different superscripts within a row and within a column vary significantly at $p<0.05$

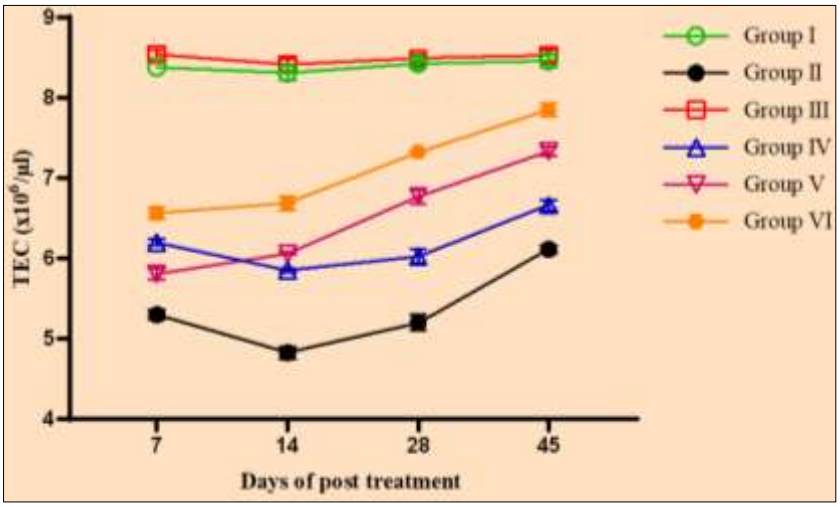

Fig 1: The mean (±SE) values of total erythrocyte count (TEC) (x10^6/µl) of experimental groups at different time intervals

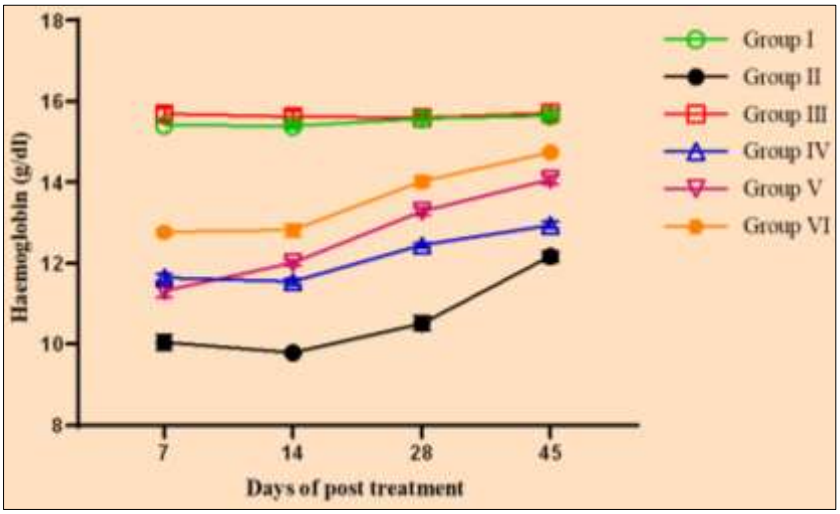

Fig 2: The mean (±SE) values of haemoglobin (g/dl) of experimental groups at different time intervals

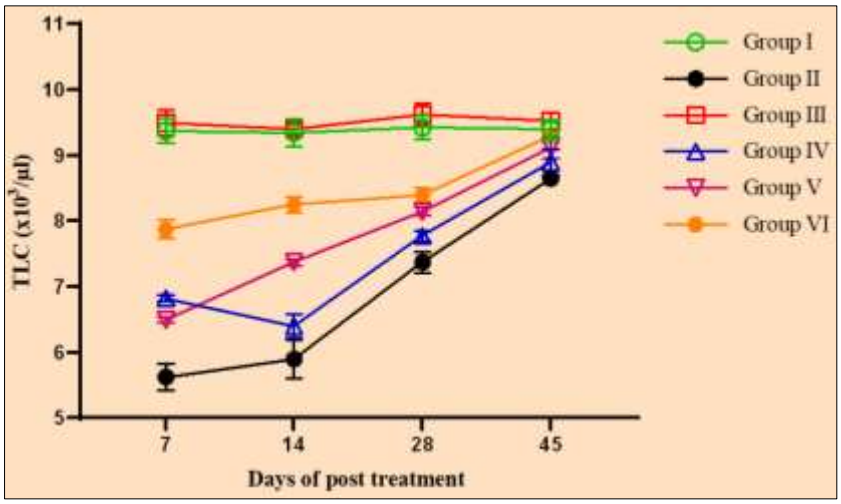

Fig 3: The mean (±SE) values of total leukocyte count (TLC) (x10^3/µl) of experimental groups at different time intervals

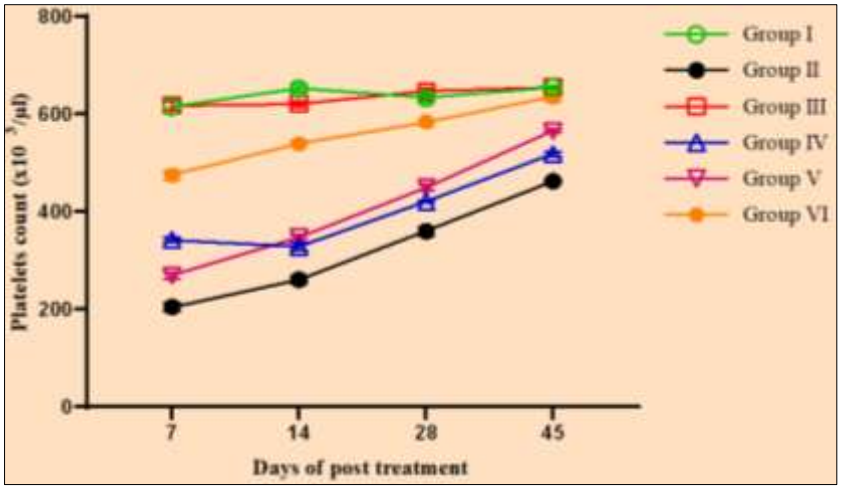

Fig 4: The mean (±SE) values of platelets count(x10^3/µl) of experimental groups at different time intervals

Conclusion

The study highlighted the beneficial effects of gallic acid supplementation at 75 mg/kg bw in ameliorating the CP induced haematological alterations in Wistar albino rats and possible preventive role of GA against CP induced toxicity.

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