Received: 12 September 2023, Accepted: 12 October 2023

Original Research

Journal of Advanced Veterinary Research
(2023) Volume 13, Issue 9, 1815-1820

Protective Role of Curcumin against Hematological Alterations and Hepatic Damage Induced by Gentamicin in Rats

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Abstract

Gentamicin (GEN) is considered an aminoglycoside antibiotic which is widely used to treat numerous bacterial infections. It has toxic effect on liver tissue. Curcumin (CMN) is a natural polyphenolic compound with antioxidant as well as anti-inflammatory potentials. The current study sought to investigate the effect of CMN in protecting against GEN-induced hematological alterations and hepatotoxicity. Rats were randomly assigned into 4 equal groups: Control, gentamicin group (100 mg/kg b.wt, i.p, daily for seven days), curcumin group (200 mg/kg b.wt, orally for 21 days) and curcumin plus gentamicin group. After 21 days, some hematological and serum biochemical parameters were measured. GEN-intoxicated group showed a marked decline in RBCs count, Hb concentration as well as PCV% with insignificant difference in MCV, MCH and MCHC. Moreover, there were leukopenia, lymphopenia and neutrophilia in GEN group. Concerning to the serum biochemical examination, a substantial increase in the serum activities of ALT, AST and ALP with a marked decline in the total protein, albumin and globulin serum levels were recorded following GEN injection. In addition, there was a marked increase in the cholesterol, triglycerides and glucose serum levels. Improvement in all tested parameters were noticed following concurrent CMN administration with GEN. Based on these results, CMN could be recommended as a treatment strategy for protection against GEN-induced hematological alterations and hepatic injury.

KEYWORDS
Gentamicin, Curcumin, Hepatotoxicity, Oxidative stress, Hematological alterations.

INTRODUCTION

Gentamicin (GEN) is known as a common aminoglycoside antibiotic, applied in treating Gram-negative bacterial infections. Its major serious side effects are nephrotoxicity, ototoxicity, hepatotoxicity (Ahmadvand *et al*., 2020) as well as hematotoxicity with documented leukopenia (Bustos *et al*., 2016). Although its harmful effects, it still a drug of choice for treatment of a range of clinical cases due to its chemical stability, rapid onset of bactericidal action and broad-spectrum activity (Aboubakr and Abdelazem, 2016). The body's hematopoietic system is the primary target to be intoxicated by some drugs and antibiotics as the hematological system is sustained by highly perfused tissues (Mumtaz *et al*., 2014). The hematological parameters may be changed due to the GEN harmful effects of on hematopoietic organs, particularly the kidney and liver as well as renal tubular injury and increased destruction of RBCs (Dahdouh *et al*., 2019). The mechanism of GEN-induced hepatotoxicity is multi-factorial and not fully comprehended (Arjinajarn *et al*., 2017). Since, hepatotoxicity is regarded as one of the most serious toxic effects caused by oxidative stress and inflammation which trigger and progress hepatic fibrosis, resulting in hepatic failure (Bulboacă *et al*., 2022). GEN increases oxidative stress, lipid peroxidation, reactive oxygen species stimulation like superoxide anion, hydrogen peroxide and hydroxyl radical, resulting in mitochondrial dysfunction and lowers the activity of several antioxidant enzymes such as superoxide dismutase and catalase (Yarijani *et al*., 2021).

One of the most promising polyphenolic hydrophobic natural compounds is curcumin (CMN) with a chemical structure [1,7-bis(4-hydroxy-3-methoxyphenyl)- 1,6 hepta- diene-3,5-dione] (Abdelhamid *et al*., 2020). It is considered the primary yellow pigment taken from turmeric which is a widely used spice extracted from the *Curcuma longa* Linn. rhizomes (Aboul-Fotouh *et al*., 2018). It is extensively used due to its therapeutic efficacy and sufficient safety requirements as it prevent oxidative damage, inflammation as well as apoptosis occurred in GEN-induced renal and hepatic toxicity in rats (Ali, 2022). It protects vital organs such as: kidney and liver from oxidative damage by maintaining antioxidant enzyme activity that lowers lipid peroxidation (AlBasher *et al*., 2020). CMN could do its antioxidative potentials either directly as a chemical antioxidant because it is able for scavenging reactive oxygen as well as nitrogen free radicals or indirectly via modulating cellular defenses that in turn have antioxidant effects (Azab *et al*., 2016). The present study was planned to evaluate the CMN protective effect against GEN induced alterations in blood picture and hepatotoxicity via evaluation of some hematological parameters as well as serum hepatic biomarkers.

MATERIALS AND METHODS

Chemicals

Curcumin ($C_{21}H_{20}O_6$) [Product No: C1386, purity ≥ 65%] was purchased from Sigma Aldrich CO. (St. Louis, MO, USA) and sus-

ISSN: 2090-6277/2090-6269/

pended in corn oil. Gentamicin, available commercially as Garamycin (Gentamicin sulfate 80 mg/2ml ampoules) was got by Memphis Pharmaceutical & Chemical Industries Company, Cairo, Egypt.

Animals, GEN and CMN administration

A total of 32 male albino rats weighting 170-190 g, were procured from Tanta laboratory animal house and housed in clean properly ventilated plastic cages and supplied with standard rodent food pellets and plan water ad-libitum under conventional environmental conditions (12 h light-dark cycle and constant temperature of 25±2°C). The procedures of our experiment were carried out under approval of the Animal Research Ethical Committee of Mansoura University's Faculty of Veterinary Medicine, Egypt, MU-ACUC (VM.MS.23.04.50).

After keeping the rats two weeks for adaptation, they were separated randomly into 4 equal groups (n=8 rats/ group):

Control group (Cont), rats received corn oil, orally via gastric gavage for 21 days and injected intraperitoneally (i.p) with physiological saline at the last 7 days, daily.

Gentamicin group (GEN), rats received corn oil, orally for 21 days and injected with GEN (100 mg/kg b.wt, i.p, once a day) at the last seven days (Farombi and Ekor, 2006).

Curcumin group (CMN), rats were treated daily with CMN which was dissolved in corn oil at a dose of 200 mg/kg b.wt, orally via gastric gavage for 21 days (Ahmida, 2012), and injected intraperitoneally (i.p) with physiological saline at the last 7 days, daily.

Curcumin plus gentamicin group (CMN+GEN), rats were treated daily with CMN (200 mg/kg b.wt, orally for 21 days) plus GEN (100 mg/kg b.wt, i.p) at the last 7 days. All treatments were given to rats daily.

Sample collection and preparation

After 21 days, rats were anesthetized (mixture of ketamine and xylazine at dose 50 and 10 mg/kg, respectively by i.p injection) then, blood samples were drawn from the medial canthus of the eye. Two types of blood samples were collected. The first sample was collected into a tube containing anti-coagulant (dipotassium salt of EDTA) for hematological examination. The second sample was collected into a plain tube, left to promote clotting. The serum samples were collected by centrifugation for 10 minutes and stored at −20°C until performing serum biochemical examination.

Hematological analysis

Erythrocyte count (RBCs $\times 10^6$/µl), hemoglobin concentration (Hb g/dl) and packed cell volume (PCV%), as well as blood indices; mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were estimated. Also, total leukocyte count (TLC) was counted manually and Giemsa stained blood smears were examined for differential leukocyte count (DLC) (Feldman *et al*., 2000).

Assessment of serum biochemical parameters

Human (Wiesbaden, Germany) kits were used to measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, and albumin, while commercial colorimetric assay kits from Spinreact (Sant Esteve de Bas, Spain) were used to measure alkaline phosphatase (ALP), triglycerides, total cholesterol and glucose. All these biochemical tests were assayed spectrophotometrically (spectrophotometer, BM, Germany, 5010), according to manufacturer's instructions and protocols.

Statistical analyses

The quantitative data were expressed as mean ± standard error of the mean (SEM). The statistical analysis was carried out by usage of SPSS (version 20, USA). The statistical comparison between the studied groups was conducted via One-way ANOVA followed by Duncan test. Statistical significance was fixed at P-value < 0.05.

RESULTS

Influence of CMN and GEN on the hematological results

The erythrogram results as presented in Figure 1; showed that RBCs, Hb and PCV were decreased significantly in GEN group with respect to the control one. Meanwhile, there were a marked increase in these parameters in GEN-intoxicated rats protectively treated with curcumin (CMN+GEN) compared with GEN group but not return to their normal values except RBCs still insignificantly differed compared either with GEN or control group. The above mentioned erythrogram results insignificantly differed in the CMN-treated group compared to the control one. Moreover, there was no significant statistical difference in MCV, MCH and MCHC in all tested groups.

There was a marked reduction in the TLCs count, lymphocytes and monocytes counts with a significant increase in the neutrophils count in GEN-injected rats compared to the control rats. CMN co-treatment with GEN improved these parameters except neutrophils and monocytes still insignificantly differed from GEN-intoxicated group. Insignificant differences were recorded in eosinophils between all experimental groups. Leukogram picture were observed in Figure 2.

Influence of CMN and GEN on the serum biochemical parameters

Liver function biomarkers

As presented in Figure 3, our results showed a marked elevation in the ALT, AST and ALP serum activities in the GEN-injected rats compared to the control one. In contrast, their activities significantly declined in the CMN+GEN group in comparison with the GEN non treated rats but remained markedly elevated compared with the control one.

GEN-injected rats exhibited a marked decline in the serum levels of total protein, albumin and globulin in comparison with the control rats. The CMN+GEN-treated group had higher serum levels of total protein, albumin and globulin than GEN one and still comparable with the control rats. Concerning A/G ratio, it was changed insignificantly in all tested groups. All above forementioned parameters differed insignificantly in the CMN group compared to the control one (Figure 4).

Serum cholesterol, triglycerides and glucose levels

Figure 5 shows that GEN injection resulted in a marked elevation in the cholesterol, triglycerides and glucose serum levels. Meanwhile, their levels were significantly reduced in CMN+-GEN-treated group compared with the GEN non-treated one but not return to their normal values. In CMN group, these parameters were insignificantly changed when compared to the control one.

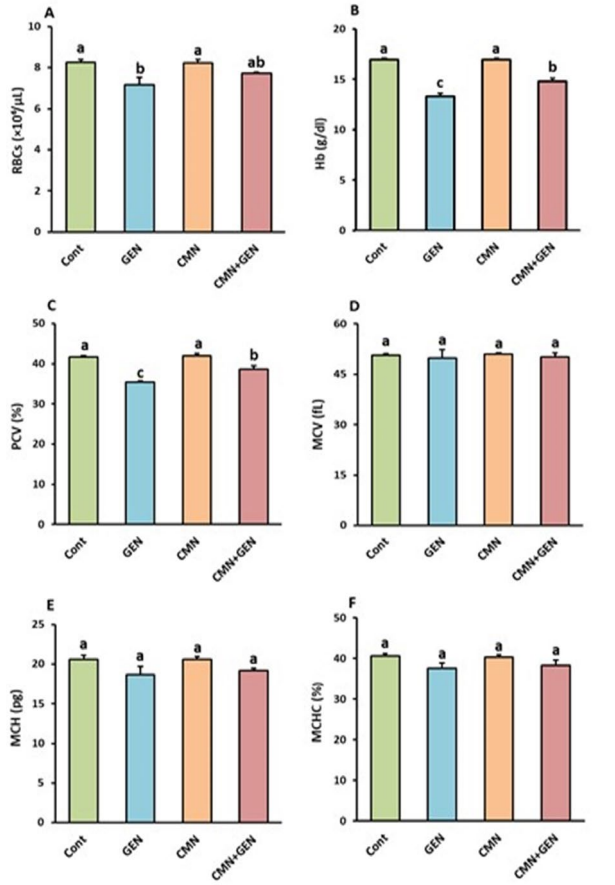

Figure 1. Erythrogram following treatment with curcumin in gentamicin-intoxicated rats (Mean± SE):Values with different superscript letters consider significance at p< 0.05.A; RBCs (Red blood cells count), B; Hb (Hemoglobin), C; PCV (Packed cell volume), D; MCV (Mean corpuscular volume), E; MCH (Mean corpuscular hemoglobin), F; MCHC (Mean corpuscular hemoglobin concentration).

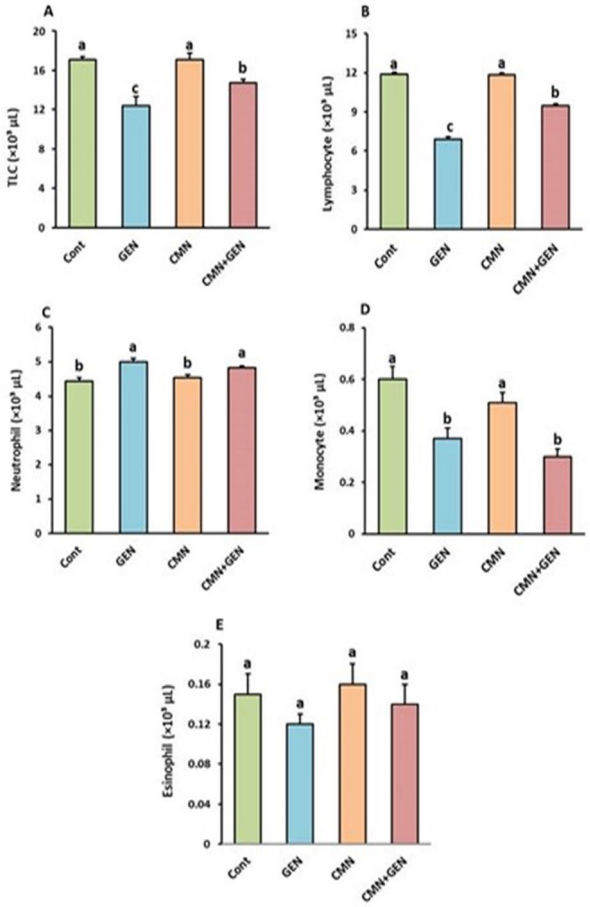

Figure 2. Leukogram following treatment with curcumin in gentamicin-intoxicated rats (Mean± SE):Values with different superscript letters consider significance at p< 0.05.A; TLC (total leukocytes count), B; lymphocyte, C; neutrophil , D; monocyte, E: eosinophil.

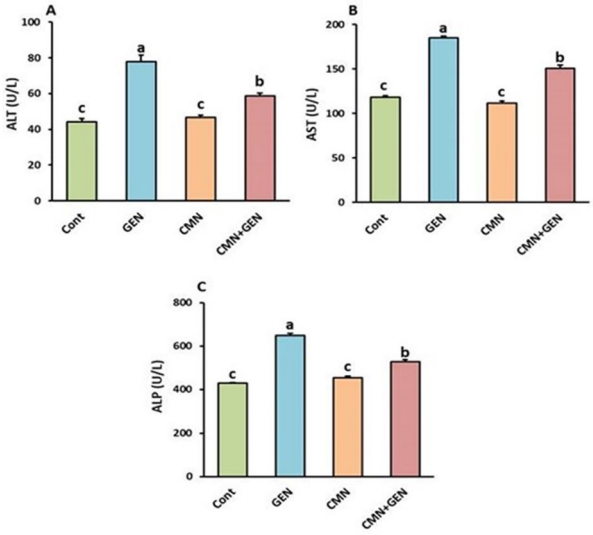

Figure 3. Liver enzymes following treatment with curcumin in gentamicin-intoxicated rats (Mean± SE):Values with different superscript letters consider significance at p< 0.05.A; ALT (Alanine Aminotransferase), B; AST (Aspartate Aminotransferase), C; ALP (Alkaline phosphatase).

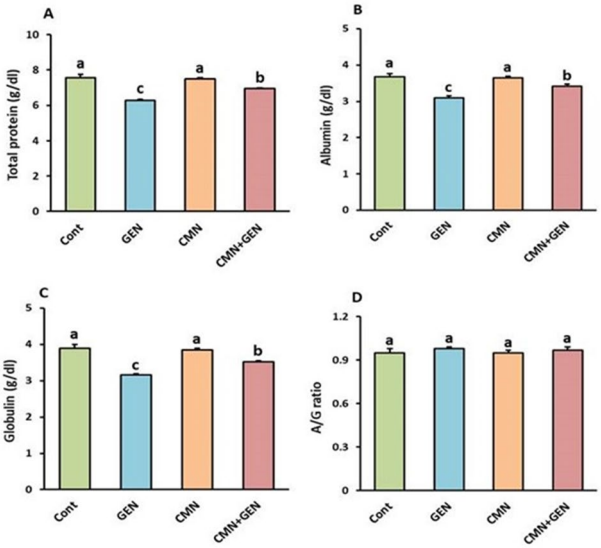

Figure 4. Proteinogram following treatment with curcumin in gentamicin-intoxicated rats (Mean± SE):Values with different superscript letters consider significance at p< 0.05.A; T.P (Total protein), B; Albumin, C; Globulin, D; A/G ratio (Albumin/Globulin ratio).

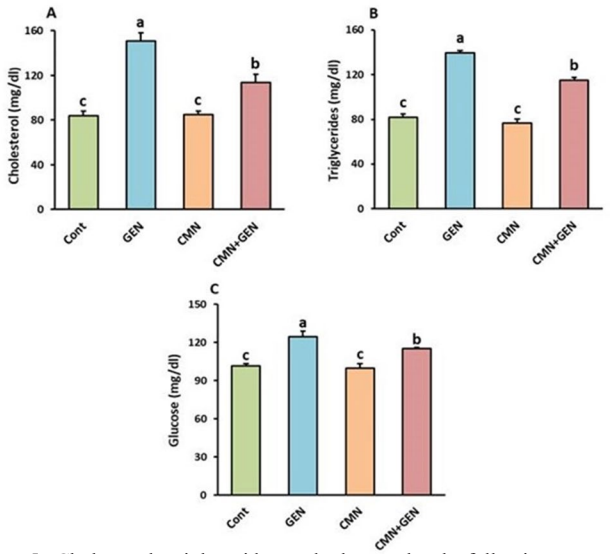

Figure 5. Cholesterol, triglycerides and glucose levels following treatment with curcumin in gentamicin-intoxicated rats (Mean± SE):Values with different superscript letters consider significance at p< 0.05.A; Cholesterol, B; Triglycerides, C; Glucose.

DISCUSSION

The mechanism of GEN-induced toxicity on the body's tissues includes oxidative reactions, cellular damage, apoptosis and generation of free radicals which have harmful effects on some organs such as kidney and liver (Mirazi *et al*., 2021). It produces reactive oxygen species, that are able for induction of apoptosis in liver cells of rats resulting in hepatic failure (Mishra and Shrivastava, 2019). Our current study explained the toxic effects of GEN on some hematological and serum hepatic biomarkers.

Hematological profile in the animals is considered an important indicator for the body's physiological or pathophysiological condition (Elsayed *et al*., 2014). The red blood cell and its indices are important markers for evaluating circulatory RBCs as well as diagnosis of anemia and can be used to measure the capacity of mammalian bone marrow to produce RBCs (Sabastine *et al*., 2021). Our data showed a marked decrease in RBCs count, Hb concentration and PCV accompanied by insignificant difference in MCV, MCH and MCHC in GEN-intoxicated group comparing with the control one, indicating normocytic normochromic anemia. GEN-induced kidney disease is considered as a model for inflammatory renal anemia (Gheith and El-Mahmoudy, 2019) and its etiology is multifactorial, including erythropoietin deficiency (the most predominant and specific cause), shortened half-life of RBCs, blood loss, abnormal iron metabolism, chronic inflammation, infection and oxidative stress (Li *et al*., 2020). The primary site of production of erythropoietin hormone (the major physiological regulator of erythropoiesis) is the renal cortex peritubular cells so, the major cause of GEN induced anemia is erythropoietin deficiency following renal injury caused by GEN (Meky *et al*., 2015). As inflamed kidney had a reduced ability for the production of adequate erythropoietin hormone (Gheith and El-Mahmoudy, 2019). Additionally, the decrease in RBCs count, Hb concentration and PCV% were a result of the inhibition of erythropoiesis a long side with the increase in the erythrocyte destruction rate in hemopoietic organs (Mumtaz *et al*., 2014).

Our data revealed leukopenia, lymphopenia, neutrophilia and monocytopenia in GEN group. The decrease in the blood cells number in GEN-intoxicated rats might be explained by inhibition of protein synthesis that is essential for cell mitosis (El Dakroury and Elseify, 2014). Also, leukopenia could be justified by the occurrence of cardiovascular depression due to GEN injection which caused deficiency in the immune system (Hussain and Kadhem, 2020). Lymphopenia might be attributed to a weakened immune response (Suljević *et al*., 2023). Moreover, neutrophilia observed following GEN injection may explained by its role as a first defense line against tissue damage, bacteria, infectious agents and toxic compounds via phagocytosis (Hussain and Kadhem, 2020). In addition, the decline in the number of blood monocytes could be attributed to GEN-induced renal injury which promoted inflammatory cascade and subsequently migration of monocytes from the blood circulation to the damaged tissues (Sahu *et al*., 2014).

The liver plays an important function in both drug detoxification and organism homeostasis. The liver possesses a leading role in the organism homeostasis as well as drug detoxification (Khaksari *et al*., 2021). The most important adverse effects of GEN in liver are hepatic tissue inflammation accompanied by hepatocyte apoptosis (Arjinajarn *et al*., 2017). In our experiment, a substantial elevation in the serum ALT, AST and ALP activities were recorded following GEN injection, indicating hepatic dysfunction. These enzymes are useful indicators for hepatocellular damage and are normally present in large amounts in the cytoplasm of hepatic cells (Mishra and Shrivastava, 2019). GEN induced hepatocellular damage and alteration of the cellular membrane permeability resulting in leakage of these enzymes into circulation (Ahmadvand *et al*., 2020).

Albumin and globulin are considered two key constituents of serum proteins. Albumin is primarily produced in the liver so, it is used for monitoring the liver function (Hozayen *et al*., 2011). The serum levels of total protein, albumin, and globulin were significantly decreased in GEN group, indicating hepatocyte destruction besides liver injury (Galaly *et al*., 2014). The decline in total protein content might be attributed to proteolysis and decreased protein synthesis (Atsamo *et al*., 2021) caused by the breakdown of protein synthesizing subcellular structures (Hozayen *et al*., 2011).

Our study exhibited a marked increment in the serum levels of cholesterol and triglycerides which may be attributed to impairment of hepatic cells to metabolize lipids or lipid peroxidation. Moreover, the elevation in serum lipids might be resulted from their increased synthesis in the liver and / or reduced of lipoprotein lipase enzyme (Aboubakr and Abdelazem, 2016). Also, the renal injury induced by GEN resulted in secondary hyperlipidemia which might be ascribed to increased cholesterol biosynthesis in the liver due to increased bioavailability of cholesterol precursor mevalonate as a result of diminished mevalonate catabolism in the injured kidney (Ataman *et al*., 2018). In addition, hypercholesterolemia might be resulted from cholestasis which reflected by increased ALP activity or protein loss due to nephropathy (Babaeenezhad *et al*., 2021). Moreover, hypertriglyceridemia might be attributed to reduction of lipoprotein lipase activity (responsible for the triglyceride degradation in the VLDL) resulting in delayed removal of the circulating triglyceride-rich lipoproteins (Ataman *et al*., 2018).

Our data showed a significant increase in the serum glucose level in GEN-intoxicated rats since GEN reduced the release of insulin from pancreas islets leading to increase the glucose level. Moreover, GEN could decrease the glomerular filtration a long side with alteration of the activities of several enzymes responsible for carbohydrate metabolism (Abdel-Azeem *et al*., 2017).

CMN possesses a wide range of pharmacological effects such as anti-inflammatory, antioxidant, anti-apoptotic and immunomodulatory properties (Farkhondeh and Samarghandian, 2016). CMN might exert its antioxidative activity either directly as a chemical antioxidant because it could neutralize reactive oxygen as well as nitrogen free radicals or indirectly by modifying cellular defenses, which in turn have antioxidant potentials (Otuechere *et al*., 2014). In our study, CMN alone had no side effects on all of the tested parameters as it is safe and this is previously proved in many researches (Galaly *et al*., 2014; Abdelhamid *et al*., 2020).

The apparent hepatic and hemato-protective effect of CMN might be attributed to its ability to neutralize the increased free radicals (Yousef *et al*., 2010). CMN prophylactive treatment with GEN resulted in improvement of the alteration in blood picture as previously proved (El-Maddawy and El-Sayed, 2018). CMN is able for enhancement of erythropoiesis, stabilization of cell membranes and inhibiting cellular damage (Emam *et al*., 2023) result-

ed from reactive oxygen species leading to restoring the blood volume, therefore CMN could minimize the negative changes occurred in hemogram (Uluişik *et al*., 2020).

The CMN protective effect against the reduction in leukocyte count could be explained by its antioxidant as well as anti-inflammatory properties (Abd-El Megid *et al*., 2021). It increased the total WBCs count due to its immune-stimulating activity (Sharma *et al*., 2011). Also, the increment in lymphocytes count might be justified by CMN ability for the immune system activation, resulting in stimulation of lymphopoiesis (Emam *et al*., 2023).

Several researches have recommended the CMN protective effects versus hepatotoxicity caused due to various toxic agents (Saber *et al*., 2019). The CMN hepatoprotective efficacy could be ascribed directly to its chelating as well as antioxidant properties (Alhusaini *et al*., 2019). CMN successfully mitigated the toxic effects of GEN on hepatic function by enhancing anti-oxidant defense system, lowering the oxidative stress, apoptosis and inflammation (Galaly *et al*., 2014). Our results revealed that CMN co-treatment with GEN improved the increment in the serum levels of ALT, AST and ALP activities as CMN can protect hepatocytes against induced hepatotoxicity due to its ability to inhibit the cellular outflow as well as loss of the functional integrity of cell membrane (Ali, 2022). CMN is able for cell membrane stabilization and tissue protection from oxidative damage caused by free radicals or promote damaged cells regeneration leading to decrease release of transaminases (AST and ALT) and ALP from the cell cytoplasm (Abdelhamid *et al*., 2020).

Our current study agreed with Galaly *et al*. (2014) who recorded that the oral protective treatment with CMN in GEN-intoxicated rats significantly elevated the decreased total protein and albumin serum levels. CMN provided hepatoprotection via protecting the integrity of the hepatic cell membrane through lipid peroxidation decrease (Saber *et al*., 2019).

In our experiment, protective treatment with CMN in GEN-intoxicated rats resulted in a significant improvement in the elevated serum levels of cholesterol, triglycerides and glucose, indicating the CMN's positive effect on the lipid profile. In addition, CMN's hypoglycemic effect may be linked to its ability to stimulate the polyol pathway, which involves the conversion of glucose to sorbitol with the help of aldose reductase When NADPH is present (El-Bahr, 2013). The antioxidant activity as well as the blood glucose lowering effect of CMN could be responsible for this favorable metabolic effect (Belhan *et al*., 2020).

CONCLUSION

The current experiment figured out the protective and ameliorative effects of curcumin against gentamicin induced alterations in blood picture and liver function. These results proved the beneficial effects of CMN as it has antioxidant and anti-inflammatory properties.

ACKNOWLEDGMENTS

The authors are deeply grateful to all members of the Department of Clinical Pathology of for their help and encouragement.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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