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Research Article

Dose-Dependent Effects of Caffeine-Coated Silver Nanoparticles on Radioprotection and Antioxidant Activity in the Liver of Swiss Albino Mice

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Abstract

Background: Ionizing radiation, commonly used in radiotherapy and industrial applications, is known to cause significant oxidative damage by generating reactive oxygen species (ROS). This damage affects cellular macromolecules, leading to DNA breaks, lipid peroxidation, and depletion of antioxidant defenses. Nanotechnology, particularly the use of bioactive silver nanoparticles (AgNPs), has emerged as a promising strategy for mitigating radiation-induced toxicity. This study investigates the radioprotective effects of caffeine-coated silver nanoparticles in Swiss albino mice exposed to gamma radiation.

Methodology: Male Swiss albino mice were pre-treated with caffeine-coated AgNPs at doses of 25, 50, 100, 150, and 200 mg/kg for 15 days, followed by 5 Gy whole-body gamma irradiation. Body weight, liver weight, lipid peroxidation (LPO), and reduced glutathione (GSH) levels were assessed up to 30 days post-irradiation.

Results: Moderate doses (50 and 100 mg/kg) improved body and liver weights, reduced LPO, and preserved GSH levels. Low (25 mg/kg) and high doses (150–200 mg/kg) were less effective or showed signs of toxicity.

Conclusion: Caffeine-coated AgNPs offer dose-dependent radioprotection against gamma radiation-induced oxidative damage, with 50–100 mg/kg showing optimal effects.

Keywords: Caffeine-coated silver nanoparticles, radioprotection, gamma radiation, oxidative stress, GSH, LPO, Swiss albino mice, ROS, nanomedicine, antioxidant therapy

INTRODUCTION

Ionizing radiation is employed in many industrial, therapeutic, and other nuclear energy applications, as well as in the development of new crop types with high yields and in extending the shelf life of food products[1]. Furthermore, gamma radiation is linked to the production of reactive oxygen species (ROS), which destroy DNA and cellular membranes and cause oxidative damage, especially to different tissues[2]. When tested for radioprotective effectiveness, several medicinal plants have demonstrated protective benefits against the harmful effects of ionizing radiation. Numerous substances, such as antioxidants, immunostimulants, cell proliferation stimulators, anti-inflammatory, and antimicrobials, are present in plant extracts that exhibit radioprotective effectiveness[3,4]. Numerous medical applications and biological research topics at the cellular and molecular level are made possible by the biomedical sciences and nanotechnology[5]. Utilizing and creating materials with nanoscale dimensions is the focus of nanotechnology. Nanoparticles with nanoscale dimensions have a very high surface area to volume ratio and, as a result, very precise characteristics[6].

Numerous advantages of drug delivery with nanoparticles have been identified over the course of several decades, including improving the drugs' serum solubility, prolonging the duration of systemic circulation, releasing the drugs in a controlled and sustained manner, directing the drugs to the appropriate tissues and cells, and concurrently delivering multiple drugs to the same cells for combination therapy[7]. Numerous industries, including the food, feed, space, health, chemical, and consumer cosmetics sectors, have adopted nanoparticles, necessitating the development of an environmentally benign synthesis process. Silver attracted a lot of attention among the different nanomaterials because of its exceptional conductivity, stability, catalytic, and antibacterial qualities[8-10]. Products containing silver have demonstrated antibacterial action against a variety of microorganisms, including bacteria, fungi, and protozoa. Long before antibiotics were employed in contemporary medicine, silver was used to treat infected wounds. Researchers are interested in silver

nanoparticles (AgNPs) because of their potential use as antibacterial agents[11-13]. Additionally, silver nanoparticles have radioprotective properties. Because chemical and physical methods have a number of drawbacks, including the use of hazardous solvents, the creation of hazardous byproducts, and high energy consumption, biologically produced metallic nanoparticles are chosen. According to recent reports, green produced silver nanoparticles have outstanding antibacterial, anti-inflammatory, and free radical scavenging properties[14-15].

Coffea arabica belongs to the Rubiaceae family. Because of their high levels of caffeine and phenolic chemicals, the seeds of some species known as coffee beans have been referred to as a functional beverage that contributes significantly to antioxidants in human nutrition[16].

Phenolic chemicals and their derivatives, such as chlorogenic acids, alkaloids, including caffeine, diterpenoid alcohols, such as cafestol and kahweol, carbohydrates, lipids, and volatile and heterocyclic compounds, are among the chemical components of *Coffea arabica*[17-18]. Numerous noteworthy biological actions, including antibacterial, antiviral, anti-inflammatory, and inhibition of oxidative macromolecular damage, have been reported in studies involving *C. arabica* extracts. Caffeine has anti-inflammatory and antioxidant properties[19-20]. Caffeine in the mice liver exhibits radioprotection against gamma irradiation damage[21]. Interestingly, due to its neuroprotective properties, regular caffeine usage has been linked to a decreased risk of neurodegenerative diseases like Parkinson's and Alzheimer's[22].

MATERIALS AND METHODS

Animal Care and Handling: With the Institutional Animal Ethic Committee (IAEC) prior approval of the proposal No. UDZ/IAEC/2021/24, Swiss albino mice (*Mus musculus*),male sex and weighing 30±5 g, 6–8 weeks old, were selected for the current investigation. The animals were kept with a controlled temperature of 25 ± 2 ºC and light (light: dark, 12 hours, 12 hours, respectively) at the Animal House Facility in the Department of Zoology, University of Rajasthan, Jaipur, Rajasthan, India. The animals were fed a regular mouse diet and given unlimited access to water. All protocols and procedures were carried out in compliance with the Committee for Control and Supervision of Experiments on Animals(CCSEA), New Delhi.

Source of irradiation: Using a Cobalt teletherapy equipment (ACT-C9) supplied by the Atomic Energy Agency, Canada, animals were exposed to gamma rays at the Cancer Treatment Centre's Radiotherapy Department at SMS Medical & Hospital in Jaipur, Rajasthan, India. For the current investigation, 5 Gy was selected based on prior research. The mice were kept in well-ventilated Perspex boxes with 0.5mm Perspex plates separating them into 7x7x10cm mini-chambers, with one mouse per mini-chamber. A dosage rate of 83 cGy per minute is obtained by exposing the entire body to gamma radiation with a source surface distance (SSD) of 80 cm. Throughout the experiment, the dose rate was adjusted in compliance with the Co^{60} decay table.

Drug: Caffeine coated silver nanoparticles were bought and analyzed from Nano Bio Lab, Udaipur. The average mean particle size of nanoparticles was up to 40 nm.

Experiment design: Animals were divided into six groups (Groups I-VI) of five animals each. Group I was served as control, and the nanoparticles were given orally to Groups II-VI at different doses of 25, 50, 100, 150, and 200 mg/kg.BW, respectively, for 15 days to determine the optimum dose of caffeine-coated silver nanoparticles against 5 Gy gamma radiation. These animals were given 5 Gy of whole-body gamma radiation on the fifteenth day, thirty minutes after the last injection of caffeine-coated silver nanoparticles in different groups. For 30 days, these animals were kept under close observation for any signs of disease, changes in body weight, morbidity, mortality, or behaviour. After 1, 3, 7, 15 and 30 days, the surviving animals were sacrificed for investigation of various parameters as per standard procedures, and the liver was isolated carefully for biochemical investigations.

Behavioural Study: Over the course of the 30-day experiment, all groups were closely monitored regularly to check for clinical symptoms of illness, morbidity (such as lethargy, ruffled fur, diarrhoea, or abnormal posture), and mortality. Documentation was also made of any obvious physical abnormalities, general behavioural changes (like adjustments to activity levels, social interactions, or grooming habits), and gait. Each animal in each group was weighed once a week.

Biochemical Study: The Moron *et al.* (1979)[23] method was used to quantify glutathione (GSH) in the liver. After treating tissue homogenate with 0.1 ml of 25% trichloroacetic acid (TCA), the resulting precipitate was centrifuged for 10 minutes at 3900 rpm. Two milliliter of 0.5 mM of 5, 5'-dithio-bis (-2-nitro benzoic acid) (DTNB) produced in 0.2 M phosphate buffer pH 8 were added to one milliliter of supernatant to assess the amount of free endogenous sulfhydryl in a total volume of three milliliter. An orange-colored complex will be created when GSH and DTNB react. The absorbance was measured using a UV-VIS spectrophotometer at 412 nm. Ohkawa *et al.* (1979)[24] used thiobarbituric acid reactive substance (TBARS) to quantify the amount of lipid peroxidation (LPO) in the liver. The concentration of TBARS was determined using 1,1,3,3-tetramethoxypropane (TMP) as a reference, and expressed as n moles of malondialdehyde per mg of tissue. At 532 nm, absorbance was measured.

Statistical analysis: mean ± SE was used to express the results. ANOVA was used to statistically compare the groups.

RESULTS

Behavioural Study: Treatment of mice with different concentrations of caffeine-coated silver nanoparticles prior to exposure to 5 Gy, delayed or alleviated the manifestations of radiation sickness, such as a decrease in food and water consumption, irritability, epilation,

weight loss, lethargy, diarrhoea, facial edema, etc. Some of the animals developed facial edema from 1 to 2 weeks following exposure. During the second week following exposure, there were limited animals that exhibited extra activity in group VI.

Body weight: With a slight decline of 3.98%, the control group exhibits negligible changes in the absence of intervention. A significant drop of 24.89% is seen with the 25 mg dose, indicating a strong and gradual effect. A moderate drop of 13.89% is seen in the 50 mg group, suggesting a less noticeable but consistent effect. A drop of 9.70% is seen with the 100 mg dose, indicating a moderately long-lasting effect. A reduction of 14.47% is shown with the 150 mg dose, suggesting a more potent and long-lasting effect. Over the course of the trial, the 200 mg dose showed the greatest significant decrease (25.25%), indicating a potent or potentially harmful effect, as shown in Figure 1.

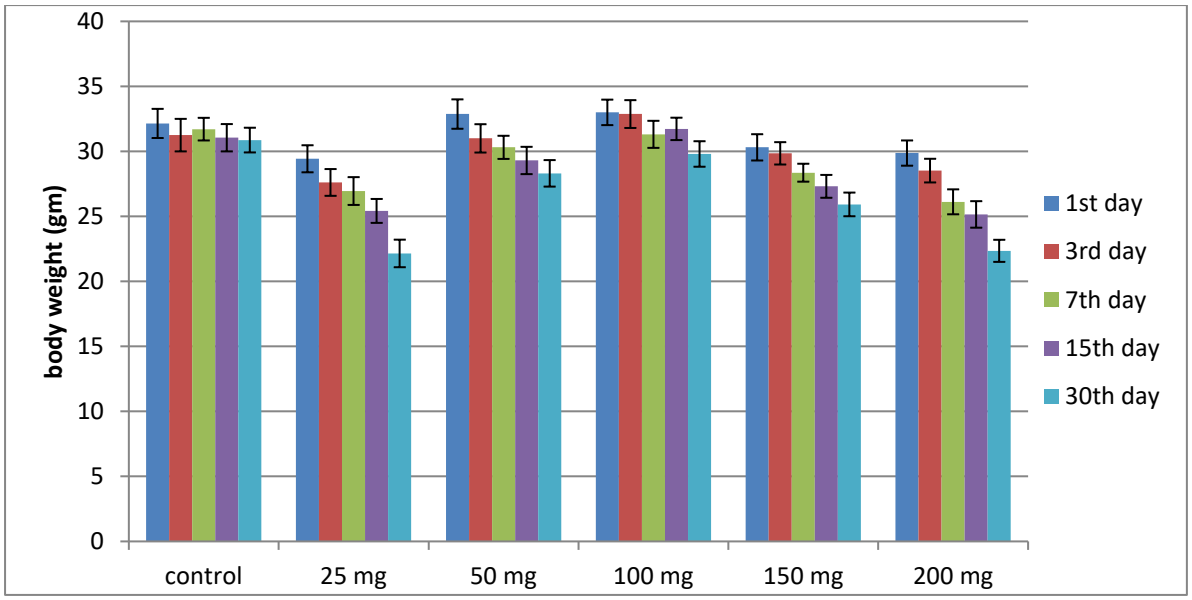

Figure 1: Body Weight of Animals

Liver weight: The varying impacts of the different doses over time are shown by the percentage changes. Since there is no intervention, a minor 8.49% drop in the control group is to be expected. The 25 mg group, on the other hand, shows an 18.97% drop, suggesting that this dose has a moderate but steady effect. While the 100 mg group grows by 3.00%, indicating a temporary or balanced effect at this dose level, the 50 mg group exhibits a modest increase of 11.21%, showing a mild positive or neutral effect. However, the 150 mg group exhibits a significant 21.37% drop, indicating a more potent and long-lasting effect. Last but not least, the 200 mg group exhibits the most striking drop of 52.75%, indicating that this dosage may have toxic or extremely suppressive effects, resulting in a significant and protracted influence on the measured parameter, as shown in Figure 2.

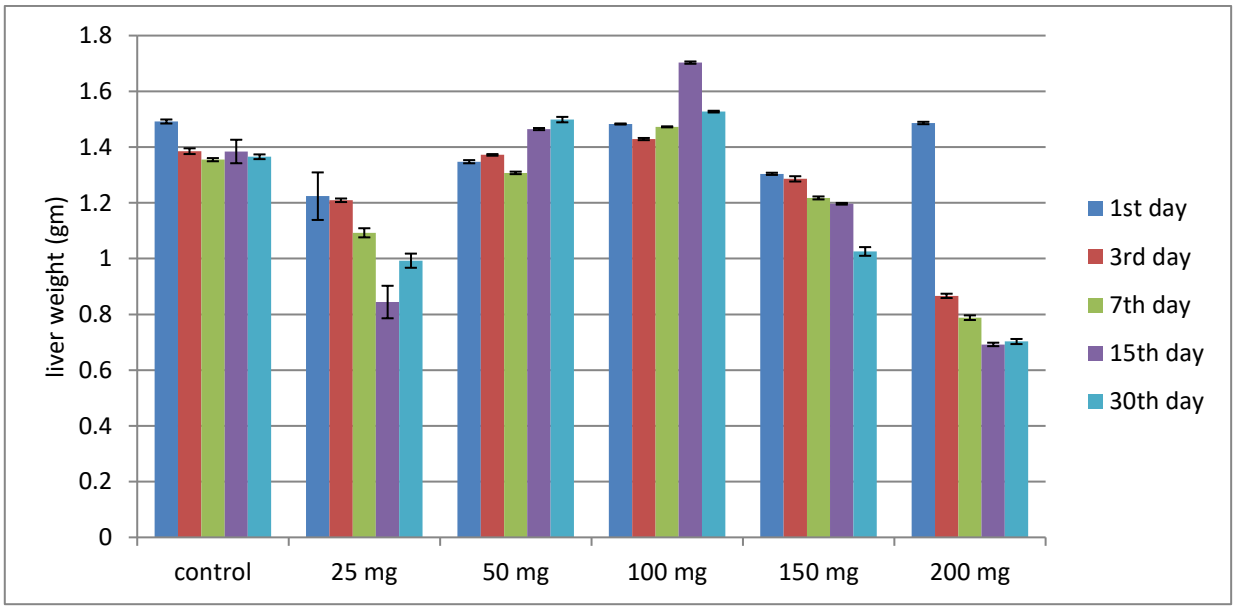

Figure 2: Liver Weight of Animals

LPO: The control group shows a modest decrease of 9.47%, indicating minimal changes without intervention. The 25 mg dose exhibits a decrease of 13.21%, suggesting a consistent but moderate effect. The 50 mg group shows a larger reduction of 23.88%, indicating a stronger effect compared to the lower doses. The 100 mg group shows the most significant decrease of 30.34%, reflecting a more potent effect on the measured parameter. The 150 mg and 200 mg doses demonstrate more stable values, with decreases of 6.33% and 6.76%, respectively. Both 50mg and 100 mg doses show an initial increase followed by a slight reduction, suggesting that these moderate doses may lead to a stabilization of the parameter at levels higher than the control or higher doses, as shown in Figure 3.

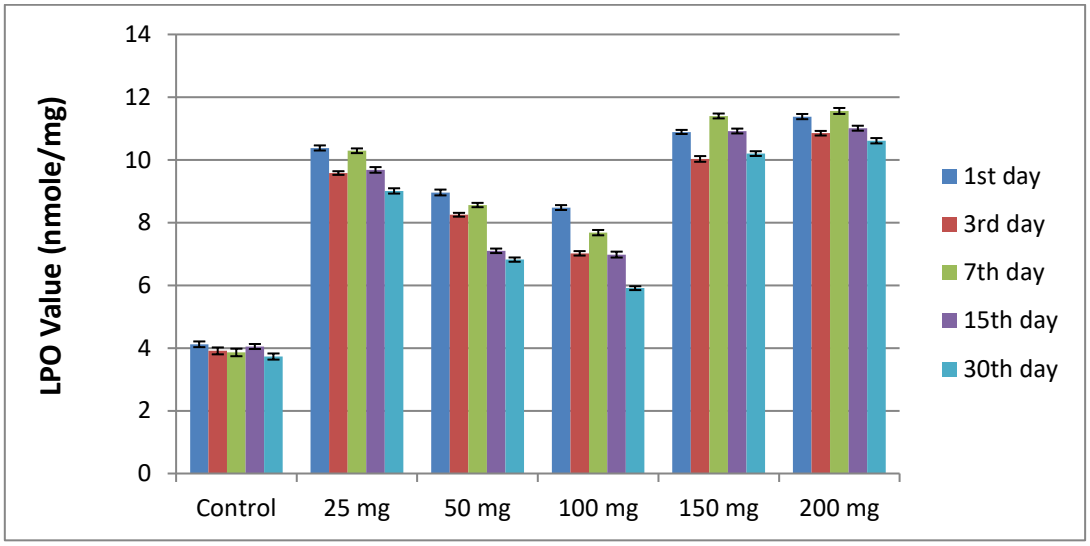

Figure 3: LPO measurement of Animals

GSH: The results demonstrate that the control group showed minimal fluctuation over time, with a slight decrease of 1.30% from day 1 to day 30, indicating stability in the absence of any intervention. The 25 mg dose initially decreased but showed a positive trend, increasing by 12.21% by day 30, suggesting that it initially reduced the parameter but later led to a recovery. The 50 mg dose exhibited a steady increase, with a 12.62% rise by day 30, indicating a consistent enhancement in the measured parameter over time. Similarly, the 100 mg dose showed a 10.39% increase, reflecting a sustained positive effect throughout the study period. In contrast, the 150 mg and 200 mg doses showed minimal or negative changes, with decreases of 0.64% and 2.26%, respectively, as shown in Figure 4.

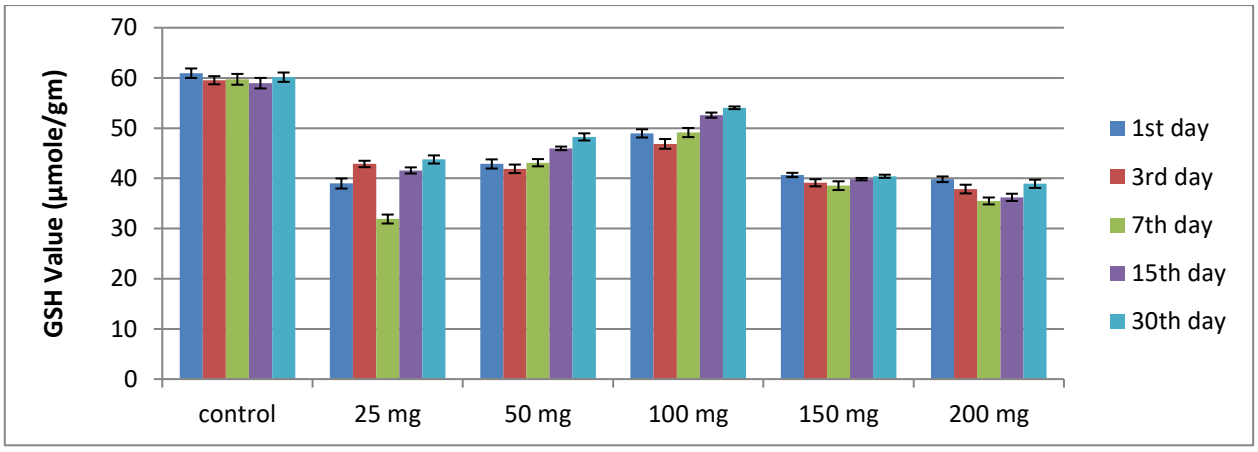

Figure 4: GSH measurement of Animals

DISCUSSION

Radiation therapy, particularly gamma radiation, is widely used in oncology but is known to cause significant damage to healthy tissues, especially the liver, due to its central role in metabolism and detoxification[25]. In this study, we observed a clear dose-dependent variation in the protective effects of caffeine-coated silver nanoparticles against gamma radiation-induced physiological and biochemical changes in Swiss albino mice. The results indicate that moderate doses were associated with a recovery in body weight and liver weight by day 30, suggesting a reversal of radiation-induced tissue damage.[26]

Caffeine is recognized for its ability to neutralize free radicals and support DNA repair, which plays a vital role in mitigating radiation damage[27]. Silver nanoparticles

further enhance this radioprotective potential through their potent reactive oxygen species (ROS)-scavenging abilities, effectively reducing lipid peroxidation and cellular damage[28]. In our study, lower doses (e.g., 25 mg/kg) resulted in significant reductions in body and liver weight, possibly due to inadequate ROS scavenging and potential nanoparticle-induced stress, consistent with prior findings where sub-therapeutic nanoparticle levels exacerbated tissue damage [29-30].

Oxidative stress markers such as LPO showed significant increases with higher doses, while GSH levels declined, highlighting the cellular oxidative burden imposed by radiation and the varying efficacy of nanoparticle-based interventions. The intermediate doses exhibited a relative stabilization of LPO and GSH values over time, implying an adaptive antioxidant response supported by the caffeine-silver synergy. High doses, although reducing LPO slightly, led to sustained reductions in GSH, possibly due to the overaccumulation of nanoparticles and resultant cytotoxicity [31-33].

The variations in body and liver weights parallel findings in other studies where radiation-induced weight loss was reversed through antioxidant interventions[34]. Caffeine's ability to modulate the hypothalamic-pituitary-adrenal (HPA) axis and reduce systemic inflammation may also contribute to weight normalization post-radiation[35]. Meanwhile, silver nanoparticles can enhance mitochondrial activity and reduce apoptotic signalling, promoting cellular survival[36].

Overall, our findings support the growing consensus that nanotechnology-based antioxidant strategies, particularly those combining bioactive molecules like caffeine with metal-based carriers, offer a powerful means of mitigating radiation-induced oxidative damage. However, it is essential to consider dose optimization to maximise therapeutic benefits while minimising potential nanoparticle toxicity. Further research is needed to elucidate the exact molecular pathways through which caffeine-coated silver nanoparticles confer radioprotection and to assess their long-term safety in clinical settings.

CONCLUSION

The data reveal significant dose-dependent variations in the effects of treatment on body weight, liver weight, and oxidative stress markers in Swiss albino mice. The control group showed minimal fluctuation in body weight and liver weight over time, suggesting no significant intervention-induced changes. In contrast, the 25 mg dose resulted in a notable decrease in both body weight and liver weight, with values continuing to decline over the study period. This suggests that the 25 mg dose has a pronounced effect on the animals, possibly leading to weight loss and liver shrinkage, potentially due to toxic effects. The 50 mg dose exhibited a moderate reduction in both body weight and liver weight, indicating that this dose leads to some physiological changes but is less detrimental than the 25 mg dose. The 100 mg dose showed an initial decrease in both parameters, followed by stabilization, suggesting an initial negative effect, followed by recovery or adaptation. The 150 mg group displayed a consistent decline in both body weight and liver weight, indicating that this dose has a sustained impact on the animals, likely causing cumulative damage. The 200 mg dose caused the sharpest decrease in both body and liver weights, with values reaching their lowest at day 30. This suggests that the 200 mg dose may be highly detrimental, overwhelming the physiological capacity of the mice and leading to severe weight and organ reductions.

Regarding oxidative stress markers, LPO levels increased with higher doses, reflecting the extent of lipid peroxidation and cellular damage. The control group showed stable LPO levels, indicating minimal oxidative stress. However, the 25 mg dose resulted in a significant rise in LPO values, suggesting that this dose induces notable oxidative stress in the liver. This increase in LPO was accompanied by a decrease in GSH levels, indicating that the liver's antioxidant defenses were compromised. The 50 mg dose also led to a moderate increase in LPO, although not as drastic as the 25 mg dose, suggesting that it induces oxidative stress, but to a lesser extent. Similarly, GSH levels in the 50 mg group showed some depletion, although the liver's antioxidant capacity was less overloaded than in the 25 mg group. The 100 mg dose caused a significant increase in LPO levels, indicating a substantial elevation in oxidative stress, with a corresponding reduction in GSH levels, suggesting that the higher dose leads to a marked depletion of antioxidant reserves in the liver. The 150 mg dose displayed the highest LPO levels, indicating severe oxidative damage. In line with this, GSH levels were significantly reduced, indicating that the liver's antioxidant defense was nearly exhausted. The 200 mg dose showed the highest overall LPO levels, reflecting extensive oxidative damage and significant depletion of GSH levels, suggesting a profound disruption in the liver's ability to manage oxidative stress.

Overall, the results indicate a clear dose-dependent impact on body weight, liver weight, and oxidative stress markers. Lower doses (25 mg and 50 mg) lead to moderate reductions in body and liver weight and a mild increase in oxidative stress, while higher doses (100 mg, 150 mg, and 200 mg) result in more severe reductions in body and liver weights, with significant increases in LPO levels and a marked decrease in GSH levels. These findings suggest that while lower doses may lead to mild physiological changes, higher doses, particularly 150 mg and 200 mg, induce substantial damage to both the liver and the overall organism. The increasing oxidative stress and depletion of antioxidants at higher doses suggest a toxic or detrimental effect on liver function, highlighting the need for careful consideration of dose levels to avoid severe organ damage and dysfunction.

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