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PROTECTIVE EFFECTS OF RUTIN AGAINST SODIUM ARSENITE-INDUCED HEMATOLOGICAL ALTERATIONS AND OXIDATIVE STRESS IN WISTAR RATS

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ABSTRACT

Sodium arsenite ($NaAsO_2$) is a pervasive environmental toxicant known to induce severe hematological alterations and systemic oxidative stress. Rutin, a natural bioflavonoid, possesses strong antioxidant and anti-inflammatory properties and may protect against such toxicity. This study investigated the effects of rutin on sodium arsenite-induced hematological changes and oxidative stress in Wistar rats. Thirty-five rats were divided into five groups (n=7): Group A (Control), Group B (Rutin alone, 50 mg/kg), Group C (Sodium arsenite alone), Group D (Sodium arsenite + Rutin 25 mg/kg), and Group E (Sodium arsenite + Rutin 50 mg/kg). After 14 days of treatment, hematological indices (RBC, Hb, WBC, differential counts, and neutrophil-lymphocyte ratio, NLR) and oxidative stress markers (lipid peroxidation/LPO, glutathione/GSH, glutathione S-transferase/GST, glutathione peroxidase/GPx, catalase/CAT, and superoxide dismutase/SOD) were evaluated. Sodium arsenite exposure produced significant ($p < 0.05$) hematological toxicity, indicated by reduced RBC and Hb levels and increased WBC count, neutrophilia, lymphocytopenia, and elevated NLR. It also caused oxidative stress by increasing LPO and reducing GSH, GST, CAT, and SOD activities. GPx activity increased significantly in the arsenite-only group, suggesting a compensatory response to oxidative insult. Co-treatment with rutin, particularly at 50 mg/kg, produced a dose-dependent improvement. Rutin restored RBC and Hb levels, normalized WBC counts and differentials, and improved the NLR. It also significantly ($p<0.05$) reduced lipid peroxidation, replenished depleted antioxidants, and moderated elevated GPx activity toward control levels. These findings indicate that rutin exerts a protective effect against sodium arsenite-induced hematological dysregulation and oxidative stress in Wistar rats.

Keywords: Sodium arsenite; Rutin; Oxidative stress; Hematological alterations; Wistar rats; Neutrophil-to-lymphocyte ratio; Antioxidant enzymes; Lipid peroxidation

INTRODUCTION

The pervasive contamination of groundwater with arsenic, particularly in its inorganic form as sodium arsenite ($NaAsO_2$), represents a critical global environmental health crisis affecting millions worldwide (Ratnaike, 2003). Chronic exposure to this potent toxicant is linked to a multitude of pathological conditions, including cancer, cardiovascular diseases, and profound systemic toxicity (Hughes *et al*., 2011). A primary mechanism underpinning arsenic-induced pathogenesis is the disruption of the body's delicate pro-oxidant/antioxidant balance. Sodium arsenite is a well-characterized inducer of oxidative stress, catalyzing the generation of reactive oxygen species (ROS) that overwhelm endogenous antioxidant defenses (Jomova *et al*., 2011). This oxidative assault leads to widespread cellular damage, including lipid peroxidation (LPO) and the depletion of crucial antioxidant reservoirs such as glutathione (GSH) and the enzymes glutathione S-transferase (GST), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) (Flora, 2011). Recent studies have further demonstrated that antioxidant compounds can significantly mitigate chemical-induced oxidative damage in experimental models (Omodamiro, 2025).

Concurrently, the hematopoietic system exhibits pronounced vulnerability to arsenic toxicity (Mazumder, 2005). Sodium arsenite exposure induces severe hematological dysregulation, manifesting as significant declines in red blood cell (RBC) count and hemoglobin (Hb) concentration hallmarks of anemia. Furthermore, it provokes marked leukocytosis with a distorted differential count characterized by severe neutrophilia, profound lymphocytopenia, and a disrupted neutrophil-to-lymphocyte ratio (NLR). The NLR has emerged as a clinically relevant integrative biomarker of systemic inflammation and physiological stress, with elevated values correlating with poor outcomes in various inflammatory and toxicological conditions (Zahorec, 2021). These hematological alterations signify not only bone marrow suppression and hemolytic damage but also a systemic inflammatory response, collectively compromising oxygen transport, immune competence, and overall physiological homeostasis.

In the search for safe and effective therapeutic agents to counteract these effects, natural flavonoids have attracted considerable scientific interest (Ganeshpurkar and Saluja, 2017). Rutin (quercetin-3-rutinoside), a ubiquitous bioactive glycoside found in numerous fruits, vegetables, and grains, is renowned for its potent antioxidant, anti-inflammatory, and cytoprotective properties (Enogieru *et al*., 2018; Omodamiro, 2025). Its ability to directly scavenge free radicals, chelate metal ions, and upregulate endogenous antioxidant enzyme activity positions it as a promising candidate for mitigating chemical toxicities (Al-Dhabi *et* al., 2020). The selection of doses in the present study was informed by established literature: the sodium arsenite dose of 10 mg/kg body weight is commonly employed in subacute oral rat studies to induce consistent hematotoxicity and oxidative stress over 10–28-day experimental periods (Flora, 2011). Similarly, rutin doses of 25 and 50 mg/kg body weight were chosen based on previous reports demonstrating significant protective effects against various toxicants in rodent models without overt

toxicity (Ganeshpurkar and Saluja, 2017; Enogieru *et al*., 2018). Investigations utilizing similar experimental models have reinforced the therapeutic potential of bioactive compounds in ameliorating chemical-induced oxidative injury (Omodamiro, 2025).

Therefore, this study was designed to systematically evaluate the potential of Rutin to ameliorate sodium arsenite-induced toxicity in a Wistar rat model. We specifically aimed to assess its protective effects on two interlinked fronts: (1) the restoration of hematological indices (RBC, Hb, WBC, differential counts, and NLR) towards normal physiological ranges, and (2) the mitigation of oxidative stress by modulating key biomarkers, including LPO, GSH, GST, GPx, CAT, and SOD levels.

MATERIALS AND METHODS

Chemicals and Reagents

Sodium arsenite ($NaAsO_2$) and Rutin (quercetin-3-rutinoside, CAS No. 153-18-4) were procured from Sigma-Aldrich Co. (USA). All other chemicals and solvents used were of analytical grade. Corn oil was obtained locally and used as the vehicle.

Animals and Ethical Approval

Thirty-five (35) healthy adult male Wistar rats (weighing 180–220 g) were used for the study. The sample size (n=7 per group) was determined based on previous toxicological studies with similar experimental designs, which demonstrated that this group size is sufficient to detect statistically significant differences between treatments while minimizing animal usage in accordance with the 3Rs (Replacement, Reduction, Refinement) principle (Flora, 2011; Ganeshpurkar and Saluja, 2017). The animals were obtained from the institutional animal house and housed in standard polypropylene cages under controlled environmental conditions (temperature: 25 ± 2°C; relative humidity: 55 ± 5%; and a 12-hour light/dark cycle). They were provided with a standard pellet diet and water ad libitum. All experimental procedures were conducted following the regulations governing the care and use of experimental animals (NIH, 1985). The Faculty of Life Sciences' Ethics Committee approved the animal research with approval number LS21046.

Experimental Design

After acclimatization, the rats were weighed and randomly assigned into five groups (n=7 per group). The treatment regimen, administered orally via gavage for a period of 14 consecutive days, was as follows:

Group A (Control): Received 2 ml/kg body weight of corn oil (vehicle).

Group B (Rutin Control): Received Rutin (50 mg/kg body weight, dissolved in corn oil).

Group C (Sodium Arsenite - SA): Received Sodium Arsenite (10 mg/kg body weight, dissolved in distilled water).

Group D (SA + Rutin 25): Received co-administration of Sodium Arsenite (10 mg/kg in distilled water) and Rutin (25 mg/kg, dissolved in corn oil).

Group E (SA + Rutin 50): Received co-administration of Sodium Arsenite (10 mg/kg) in distilled water and Rutin (50 mg/kg dissolved in corn oil).

The doses and duration were selected based on preliminary studies and relevant literature. All solutions were prepared fresh daily.

Sample Collection and Preparation

Twenty-four hours after the last administration, animals were fasted overnight and humanely sacrificed by cervical dislocation under mild anesthesia. Blood was collected directly from the heart into ethylenediaminetetraacetic acid (EDTA) tubes for immediate hematological analysis. The liver was rapidly excised, washed in ice-cold 1.15% potassium chloride (KCl) solution, blotted dry, and weighed. A portion of the harvested liver tissue (approximately 500 mg) was weighed and homogenized in ice-cold phosphate buffer (0.1 M, pH 7.4) using a motor-driven Teflon-glass homogenizer to produce a 10% (w/v) homogenate. The homogenate was centrifuged at 10,000 × g for 15 min at 4°C using a refrigerated centrifuge. The resulting post-mitochondrial supernatant (PMS) was carefully collected and used for the following spectrophotometric assays. All assays were performed within 24 hours of homogenate preparation, with samples kept on ice throughout to preserve enzyme activity.

Analytical Procedures

Hematological Analysis

A complete blood count (CBC) was performed on whole blood using an automated hematology analyzer. Parameters assessed included Red Blood Cell count (RBC), Hemoglobin concentration (Hb), White Blood Cell count (WBC), and Differential Leukocyte Count (Neutrophils, Lymphocytes, Monocytes).

Oxidative Stress Markers

Lipid peroxidation (LPO) was evaluated by measuring malondialdehyde (MDA) formation using the thiobarbituric acid reactive substances (TBARS) assay, following the method described by Ohkawa *et al.* (1979). The concentration of MDA was expressed as nmol MDA per mg protein.

Reduced glutathione (GSH) levels were determined using Ellman's reagent (5,5′-dithiobis-2-nitrobenzoic acid; DTNB) according to the method of Beutler *et al*. (1963). The absorbance of the yellow-colored chromophore was measured spectrophotometrically, and results were expressed as µg GSH per mg protein.

Glutathione S-transferase (GST) activity was assayed using 1-chloro-2,4-dinitrobenzene (CDNB) as substrate as described by Habig *et al*. (1974). Enzyme activity was expressed as µmol CDNB conjugate formed per minute per mg protein.

Glutathione peroxidase (GPx) activity was determined by monitoring the rate of NADPH oxidation at 340 nm in the presence of hydrogen peroxide, following the method of Paglia and Valentine (1967). GPx activity was expressed as nmol NADPH oxidized per minute per mg protein.

Catalase (CAT) activity was measured by assessing the rate of hydrogen peroxide decomposition at 240 nm according to the method described by Aebi (1984). Results were expressed as µmol H_2O_2 decomposed per minute per mg protein.

Superoxide dismutase (SOD) activity was assayed based on its ability to inhibit the auto-oxidation of pyrogallol, as described by Marklund and Marklund (1974). One unit of SOD activity was defined as the amount of enzyme required to produce 50% inhibition of pyrogallol auto-oxidation and was expressed as units per mg protein.

Protein concentration in the liver homogenates was determined using the Bradford method with bovine serum albumin as the standard, as described by Bradford (1976), to normalize enzyme activities.

Data Analysis

All data are presented as Mean ± Standard Deviation (SD) for seven animals per group (n=7). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. The statistical significance level was set at $p < 0.05$. Analyses were conducted using GraphPad Prism software (Version 8.0, GraphPad Software Inc., USA).

RESULTS AND DISCUSSION

Effect of Rutin on Hematological Indices in Sodium Arsenite-Exposed Rats

The hematological profile of the experimental animals is presented in Table 1. Administration of sodium arsenite (Group C) induced significant ($p < 0.05$) alterations in all measured blood parameters compared with the control group (Group A).

Sodium arsenite exposure resulted in a marked reduction in red blood cell (RBC) count and hemoglobin (Hb) concentration, indicating the development of anemia. Concurrently, a pronounced leukocytosis was observed, characterized by a significant increase in total white blood cell (WBC) count. The differential leukocyte count was also markedly distorted, showing significant neutrophilia and a drastic reduction in lymphocyte percentage, which consequently led to a sharp increase in the neutrophil-to-lymphocyte ratio (NLR). A reduction in monocyte percentage was also observed.

Administration of rutin alone (Group B) did not produce any significant difference compared with the control group, indicating that rutin at the administered dose did not adversely affect hematological parameters.

Co-administration of rutin with sodium arsenite produced significant dose-dependent improvement in hematological indices. Rats treated with rutin (25 mg/kg and 50 mg/kg) showed significantly higher ($p < 0.05$) RBC counts, hemoglobin levels, and lymphocyte percentages compared with the sodium arsenite-only group. Likewise, WBC count, neutrophil percentage, and NLR were significantly reduced relative to the arsenite group. Although these parameters did not return completely to control levels, rutin treatment markedly improved the hematological disturbances toward normal physiological ranges, with the 50 mg/kg dose producing the most pronounced protective effect.

Table 1: Effect of Rutin on Hematological Indices in Sodium Arsenite-Exposed Rats

Parameter	Control	Rutin	Sodium arsenite	Sodium arsenite + rutin (25 mg/kg)	Sodium arsenite + rutin (50 mg/kg)
RBC (10^6/µl)	6.20 ± 1.10	6.15 ± 1.20	4.04 ± 1.30*	4.88 ± 1.10[a]	5.47 ± 1.20[b]
Hb (g/dl)	14.84 ± 2.30	14.90 ± 2.00	6.90 ± 1.10*	10.10 ± 1.20[a]	12.00 ± 1.10[b]
WBC (10^3/µl)	10.04 ± 2.00	10.50 ± 2.20	21.90 ± 1.30*	16.00 ± 2.20[a]	12.72 ± 1.40[b]
Neutrophils (%)	40.10 ± 3.20	38.25 ± 3.10	84.09 ± 3.10*	74.88 ± 3.20[a]	51.19 ± 3.70[b]
Lymphocytes (%)	60.22 ± 3.30	60.04 ± 2.90	12.18 ± 1.30*	32.20 ± 2.70[a]	40.28 ± 1.60[b]
NLR	0.90 ± 0.10	0.84 ± 0.11	8.89 ± 0.61*	5.01 ± 0.12[a]	3.06 ± 0.11[b]
Monocytes (%)	3.70 ± 0.20	3.30 ± 0.10	1.50 ± 0.20*	2.00 ± 0.20[a]	2.20 ± 0.30[b]

Values are expressed as mean ± standard deviation; n = 7 *Significant as compared with control; $p < 0.05$; [a,b] Significant as compared with Sodium Arsenite; $p < 0.05$

Effect of Rutin on Sodium Arsenite-Induced Oxidative Stress

As presented in Figure 1, exposure to sodium arsenite produced significant disturbances in hepatic oxidative stress markers.

Lipid peroxidation (LPO) levels were significantly elevated in the sodium arsenite–treated group compared with the control group ($p < 0.05$), indicating enhanced membrane lipid damage. In addition, significant reductions were observed in reduced glutathione (GSH) levels and antioxidant enzyme activities, including glutathione S-transferase (GST), catalase (CAT), and superoxide dismutase (SOD).

In contrast, glutathione peroxidase (GPx) activity was significantly increased in the sodium arsenite group relative to the control, suggesting a compensatory response to excessive reactive oxygen species and hydrogen peroxide generation.

Co-administration of rutin significantly ameliorated sodium arsenite-induced oxidative stress in a dose-dependent manner. Treatment with rutin (25 mg/kg and 50 mg/kg) significantly reduced LPO levels while increasing GSH concentration and the activities of GST, CAT, and SOD compared with the sodium arsenite group ($p < 0.05$). Rutin treatment also moderated the elevated GPx activity toward control values. Although most parameters did not completely return to control levels, the higher dose of rutin (50 mg/kg) produced substantial improvement toward normal antioxidant status, demonstrating its protective effect against arsenite-induced oxidative damage.

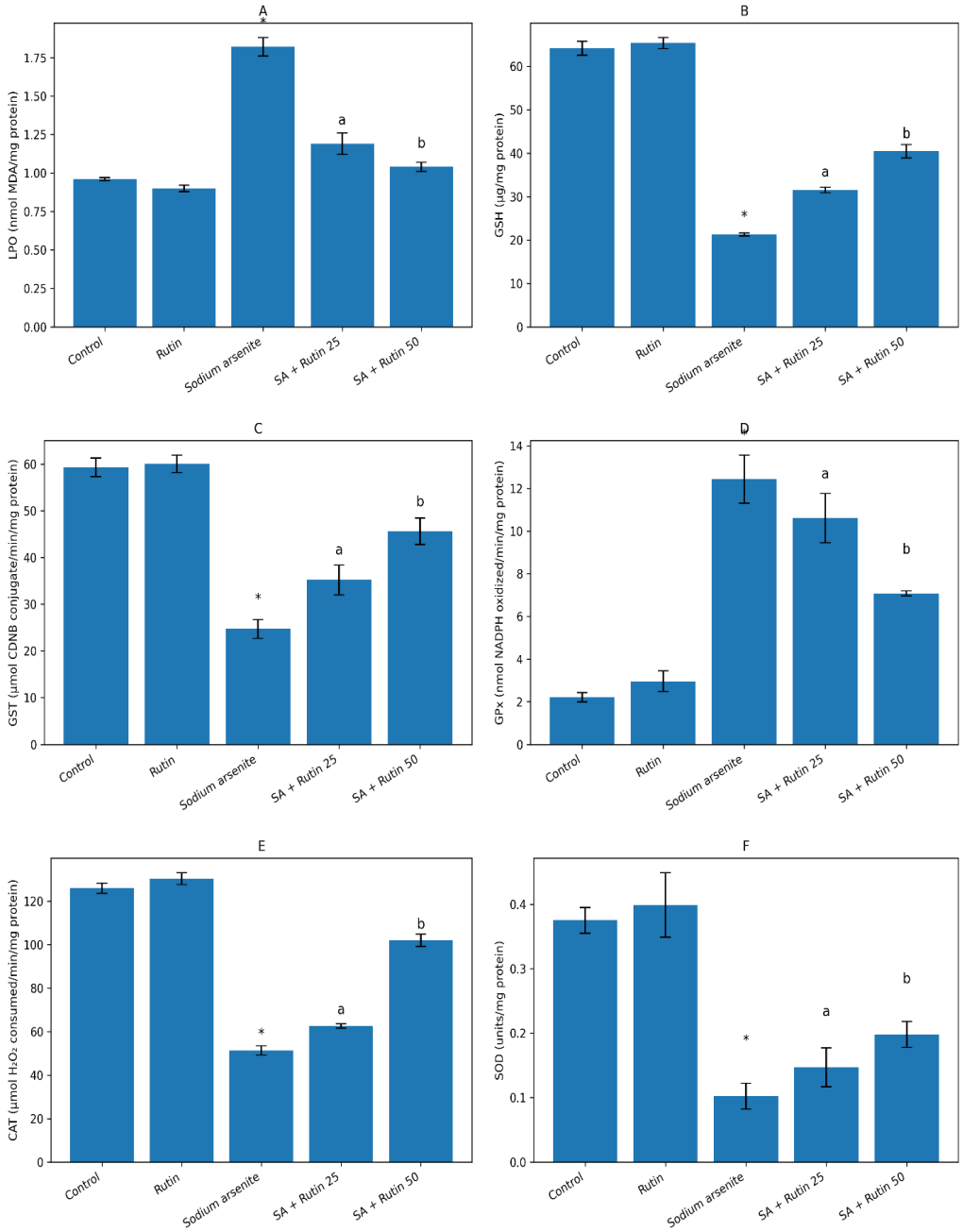

Figure 1: Effect of Rutin on Oxidative Stress Biomarkers in Sodium Arsenite-Exposed Rats. (A) Lipid Peroxidation (LPO); (B) Reduced Glutathione (GSH); (C) Glutathione S-transferase (GST); (D) Glutathione peroxidase (GPx); (E) Catalase (CAT); and (F) Superoxide Dismutase (SOD). Bars Represent mean ± SD (n = 7). *Significant Compared with the Control Group ($p < 0.05$); [a,b] Significant Compared with the Sodium Arsenite Group ($p < 0.05$). LPO: nmol MDA/mg Protein; GSH: µg/mg Protein; GST: µmol CDNB Conjugate/min/mg Protein; GPx: nmol NADPH oxidized/min/mg Protein; CAT: µmol H_2O_2 Consumed/min/mg Protein; SOD: units/mg Protein

Discussion

The present study provides evidence that rutin exerts protective effects against sodium arsenite–induced hematological disturbances and oxidative stress in Wistar rats. Sodium arsenite exposure produced marked alterations in both hematological indices and antioxidant defense parameters, while co-administration of rutin significantly ameliorated these toxic effects in a dose-dependent manner.

The severe anemia observed in the sodium arsenite–treated group, characterized by significant reductions in RBC count and hemoglobin concentration, is consistent with previous reports describing arsenic-induced hematotoxicity (Mazumder, 2005). Arsenic toxicity has been associated with oxidative damage to erythrocyte membranes, suppression of erythropoiesis, and shortened erythrocyte lifespan (Flora, 2011). In addition, sodium arsenite produced pronounced leukocytosis, neutrophilia, and lymphocytopenia, leading to a substantial elevation in the neutrophil-to-lymphocyte ratio (NLR). Elevated NLR has been widely recognized as an integrative marker of systemic inflammation and physiological stress (Zahorec, 2021). These alterations

suggest that arsenite exposure induces both inflammatory responses and impairment of normal hematopoietic processes. Rutin co-administration significantly improved these hematological alterations. The observed increase in RBC count and hemoglobin concentration following rutin treatment suggests a protective effect on erythrocyte integrity and possibly improved erythropoietic activity. Likewise, rutin treatment significantly reduced leukocytosis and neutrophilia while improving lymphocyte percentages and reducing the NLR. Importantly, although the hematological parameters improved significantly relative to the arsenite group, many values did not fully return to control levels. For example, lymphocyte percentages in the high-dose rutin group showed substantial recovery compared with arsenite exposure but remained lower than control values. This indicates that rutin provided significant but partial restoration toward physiological ranges, which is consistent with the short duration of exposure and treatment in the present study.

The hematological improvements observed with rutin treatment are closely associated with its antioxidant properties. Sodium arsenite exposure produced marked oxidative stress, as demonstrated by increased lipid peroxidation and significant depletion of endogenous antioxidants such as reduced glutathione (GSH) and antioxidant enzymes including GST, CAT, and SOD. These findings are consistent with previous studies indicating that arsenic toxicity is mediated largely through the generation of reactive oxygen species and disruption of cellular redox balance (Jomova *et al*., 2011; Flora, 2011). Arsenic toxicity is largely mediated through excessive production of reactive oxygen species that disrupt cellular redox balance and induce lipid peroxidation, mitochondrial dysfunction, and inflammatory signaling pathways (Concessao and Prakash, 2025).

Interestingly, glutathione peroxidase (GPx) activity was markedly elevated in the arsenite-treated group compared with controls. This increase may represent a compensatory adaptive response to increased oxidative stress and hydrogen peroxide accumulation. Similar increases in GPx activity during early stages of toxicant-induced oxidative stress have been reported in experimental models as a protective cellular response aimed at limiting oxidative damage. Rutin co-treatment moderated this elevated GPx activity toward normal levels, likely reflecting a reduction in oxidative burden due to its free radical scavenging properties.

Rutin treatment also significantly reduced lipid peroxidation while restoring depleted antioxidant defenses, including GSH, GST, CAT, and SOD activities. These findings support previous reports demonstrating that rutin acts as a potent antioxidant capable of scavenging reactive oxygen species, chelating metal ions, and enhancing endogenous antioxidant enzyme activity (Ganeshpurkar and Saluja, 2017; Enogieru *et al*., 2018). Experimental evidence has increasingly demonstrated the protective role of rutin against arsenic-induced toxicity in animal models. Recent studies have shown that rutin supplementation significantly reduces oxidative stress, inflammation, and apoptotic signaling in tissues exposed to sodium arsenite. For instance, rutin treatment was reported to attenuate arsenic-induced testicular toxicity in rats by restoring antioxidant enzyme activities and reducing lipid peroxidation and inflammatory mediators (Rahmani *et al*., 2022). The protective effects observed in the present study are therefore consistent with the established pharmacological profile of rutin as a cytoprotective flavonoid.

The superior protective effect observed at the higher dose of rutin (50 mg/kg) compared with the lower dose further supports a dose-dependent protective mechanism. Importantly, the rutin-only group did not exhibit significant alterations in any measured parameters, indicating that rutin at the tested dose is well tolerated and does not adversely affect hematological or oxidative stress markers.

Despite the promising findings, some limitations should be acknowledged. First, the experimental duration was relatively short (14 days), which may not fully represent chronic arsenic exposure scenarios. Finally, the study utilized only male rats, and therefore potential sex-related differences in response to arsenic toxicity or rutin treatment were not evaluated.

Overall, the findings of this study demonstrate that rutin significantly attenuates sodium arsenite-induced hematological alterations and oxidative stress in Wistar rats. The protective effects appear to involve both direct antioxidant activity and enhancement of endogenous antioxidant defense mechanisms. These results suggest that rutin may serve as a promising natural therapeutic agent for mitigating arsenic-induced systemic toxicity. However, further studies incorporating longer exposure durations, histopathological evaluation, and molecular investigations of antioxidant signaling pathways are necessary to fully elucidate the mechanisms underlying its protective effects.

CONCLUSION

Sodium arsenite exposure induced significant hematological disturbances and oxidative stress in Wistar rats, evidenced by anemia, leukocytosis, altered leukocyte differentials, and depletion of antioxidant defenses. Co-administration of rutin significantly ameliorated these toxic effects in a dose-dependent manner, with rutin at 50 mg/kg showing superior protective effects on both hematological and oxidative stress parameters. These findings suggest that rutin may serve as a promising natural antioxidant agent for mitigating arsenic-induced systemic toxicity.

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