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Modulatory Role of Saroglitazar on Novel Hematological Inflammatory Ratios and Metabolic Parameters in Animal Model of 5-Fluorouracil Toxicity

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Abstract

Background: 5-Fluorouracil (5-FU), a widely used chemotherapeutic agent, causes oxidative stress, inflammation, and multi-organ damage, particularly cardiotoxicity. Saroglitazar, a dual peroxisome proliferator-activated receptor α/γ agonist with lipid-lowering, insulin-sensitizing, and anti-inflammatory effects, may ameliorate these adverse outcomes. ***Objective***: To evaluate how saroglitazar influences hematological inflammatory ratios and metabolic parameters in a rat model of 5-fluorouracil-induced toxicity. ***Methods***: 35 adult males Wistar rats were categorized into five groups: Control (NC), 5-FU-treated positive control (PC), N-acetylcysteine (NAC) (100mg/kg) + 5-FU, SAR low (0.5mg/kg)+5-FU, and SAR high (5.0mg/kg)+5-FU. 150mg/kg 5-FU was given intraperitoneally on the 10th day of treatment. Biochemical markers were evaluated, including cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose, and HbA1c; inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR); and hematological markers such as hemoglobin concentration (Hb), red blood cell count (RBC), and white blood cell count (WBC). ***Results***: 5-FU treatment caused significant metabolic alteration, including dyslipidemia, hyperglycemia, systemic inflammation, and hematological suppression. Saroglitazar, on the other hand, improved lipid profiles by reducing cholesterol, triglycerides, and LDL and showed a glucose-lowering effect. It also reduced NLR and MLR, demonstrating their superior anti-inflammatory activity. Saroglitazar also improved RBC count and Hb levels, indicating its influence on erythropoiesis and bone marrow function. ***Conclusion***: Saroglitazar mitigates 5-fluorouracil-induced metabolic, inflammatory, and hematological disturbances, supporting its potential as an adjunct to chemotherapy. Assessing its long-term effectiveness and practical use is recommended.

Keywords: Chemotherapy-induced toxicity; 5-FU; Hematological inflammatory ratios; Saroglitazar.

الدور المعدل لساروغليتزار على نسب الالتهابات الدموية الجديدة والمعلمات الأيضية في نموذج سمية 5-فلوروراسيل في الجرذان

الخلاصة

الخلفية: 5-فلوروراسيل (5-FU) علاج كيميائي واسع الاستخدام، يسبب الإجهاد التأكسدي والالتهاب وتلف الأعضاء المتعددة، خاصة السمية القلبية. قد يخفف ساروغليتازار، وهو مستقبلات نشطة مزدوجة من البيروكسسوم النشط α/γ مع تأثيرات تخفيض للدهون، وتحسس للأنسولين، ومضادة للالتهابات، من هذه النتائج السلبية. **الهدف**: تقييم تأثير الساروغليتازار على نسب الالتهابات والمعايير الأيضية في نموذج الجرذان للسمية الناتجة عن 5-فلوروراسيل. **الطرائق**: تم تصنيف 35 ذكرا بالغا من جرذ ويستار إلى خمس مجموعات: ضابط (NC)، ضابط إيجابي معالج ب-5-FU (PC)، N-أسيتيل سيستين SAR ،5-FU+ (100mg/kg) (NAC) منخفض (0.5mg/kg)+5-FU، وSAR مرتفع (5.0mg/kg)+5-FU. تم إعطاء 150mg 5-FU داخل الصفاق في اليوم العاشر من العلاج. تم تقييم العلامات الكيميائية الحيوية، بما في ذلك الكوليسترول، والثلاثي الجليسريد، وبروتين الدهون منخفض الكثافة، وبروتين الدهون عالي الكثافة، والجلوكوز، وHbA1c؛ العلامات الالتهابية مثل نسبة العدلات إلى الخلايا اللمفاوية، ونسبة الخلايا الأحادية إلى الخلايا اللمفاوية، ونسبة الصفائح الدموية إلى الخلايا اللمفاوية ؛ والعلامات الدموية مثل تركيز الهيموغلوبين، وعدد كريات الدم الحمراء، وعدد خلايا الدم البيضاء. **النتائج**: أدى علاج 5-FU إلى تغيرات أيضية كبيرة، بما في ذلك خلل الدهون، وارتفاع سكر الدم، والالتهاب الجهازي، والقمع الدموي. أما ساروغليتازار، فقد حسن ملفات الدهون من خلال تقليل الكوليسترول والدهون الثلاثية وLDL وأظهر تأثيرا في خفض الجلوكوز. كما قلل من NLR وMLR، مما أظهر نشاطهما المضاد للالتهابات الأفضل. كما حسن ساروغليتزار عدد كريات الدم الحمراء ومستويات الهيدروبين، مما يشير إلى تأثيره على تتكون الحمراء ووظيفة نخاع العظم. **الخلاصة**: يخفف ساروغليتزار من الاضطرابات الأيضية والالتهابية والدموية الناتجة عن 5-فلوروراسيل، مما يدعم إمكانياته كمكمل للعلاج الكيميائي. يوصى بتقييم فعاليته طويلة الأمد واستخدامه العملي.

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INTRODUCTION

Chemotherapy is an essential treatment for numerous cancers, yet its non-selective cytotoxic effects sometimes result in significant adverse effects on healthy tissues [1]. 5-Fluorouracil (5-FU), an analog of uracil nucleotide, is a cytotoxic agent utilized in treating numerous malignancies, including gastric, colorectal, pancreatic, cervical, and breast cancers, as well as head and neck [2]. However, it is linked to multi-organ toxicity impacting the liver, kidneys, lungs [2,3], heart, and brain [4]. The mechanism of 5-FU-induced toxicity principally entails the inhibition of thymidylate synthase (TS), resulting in compromised DNA synthesis, cell cycle arrest, and death [5]. Furthermore, 5-FU produces reactive oxygen species (ROS), resulting in oxidative stress, mitochondrial impairment, and extensive tissue damage [6]. The liver is particularly vulnerable among

the damaged organs because it metabolizes 5-FU through dihydropyrimidine dehydrogenase (DPD). Excessive reactive oxygen species (ROS) production in hepatic cells leads to inflammation, apoptosis, and fibrosis, as indicated by increased ALT, AST, and bilirubin levels, with lipid peroxidation indicators such as lipid hydroperoxides (LOOH) [7]. Renal damage similarly results from the accumulation of fluoro-β-alanine (FBAL), a toxic metabolite of 5-FU that disrupts renal filtration and electrolyte equilibrium [6]. Histopathological findings include tubular degeneration, glomerular atrophy, and renal corpuscle shrinkage, corroborated by elevated levels of creatinine, urea, and uric acid [2]. The lungs are another significant target of 5-FU damage, with research indicating alveolar thickening, pulmonary edema, and heightened perivascular inflammation [3]. The observed effects are ascribed to diminished activity of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione-S-transferase (GST), in conjunction with increased levels of lipid peroxidation [8]. Moreover, neurotoxicity is a critical issue, as 5-FU has demonstrated the ability to compromise the blood-brain barrier (BBB), facilitating the accumulation of oxidative stress and resulting in neuronal apoptosis [1]. The resultant changes in neurotransmitter levels, specifically serotonin and dopamine, are associated with cognitive impairments, anxiety, and depression generated by chemotherapy [4]. Cardiotoxicity is one of the most serious effects of 5-FU therapy since it ranks as the second most commonly associated chemotherapeutic drug with cardiovascular toxicity, after anthracyclines [9]. The clinical manifestation of fluoropyrimidine cardiotoxicity encompasses a diverse array of symptoms, including angina pectoris, myocardial infarction, cardiogenic shock, arrhythmias (including atrial fibrillation, ventricular arrhythmias, and atrioventricular block), coronary vasospasm, and heart failure [10–12]. Several pharmacological agents, such as dexrazoxane, glutathione, N-acetylcysteine, and simvastatin [13–15], have been extensively studied for their potential in mitigating chemotherapy-induced toxicity. Among the glitazars, saroglitazar is the only glitazar currently undergoing clinical development. It is a dual PPARα/γ agonist that significantly reduces serum lipids and glucose levels [16]. A recent study demonstrated that saroglitazar reduces hypertriglyceridemia and enhances insulin sensitivity and β-pancreatic cell function by mitigating glucolipotoxicity, potentially via direct PPARγ activation in individuals with type 2 diabetes (T2DM) and elevated blood triglyceride levels [17]. However, the impact of saroglitazar on hematological biomarkers and CBC-derived inflammatory ratios has not been studied yet; accordingly, this study was designed to assess the protective effects of saroglitazar against 5-FU-induced toxicity in rats through evaluation of its effects on inflammatory ratios and metabolic biomarkers.

METHODS

Chemicals, reagents, and experimental animals

Saroglitazar powder and N-acetylcysteine (NAC) powder were obtained from MACKLIN, Biochemical Co., Ltd., Shanghai, China. 5-Fluorouracil (5-FU) 500 mg/10 mL vial from Accord Healthcare Ltd, U.K. Thirty-five male Wistar rats, weighing 250 and 300 grams, were acquired from the animal house of the University of Sulaimani. They were housed in well-ventilated plastic cages at an ambient temperature of 25 ± 2°C and a humidity level of 55 ± 5%, maintained under a 12-hour dark-light cycle for two weeks prior to the experiment, and the rats were provided with conventional laboratory chow with water ad libitum. Experimental protocols adhered to the Guidelines for Animal Experimentation and received approval from the Ethical Committee of the University of Sulaimani (Certificate number 2, dated 28th November 2024), and the study was conducted in accordance with ARRIVE guidelines [18].

Study design and setting

The rats were randomly allocated into five groups, 7 animals each, as follows: Group I, the negative control group, received 1.0 ml of distilled water (D.W.) orally by gavage tube daily for 10 days from the start of the study; group II, the positive control group, was treated with 1.0 ml D.W. orally by gavage tube daily for 10 days and on the 10th day was treated with a single intraperitoneal (I.P.) injection of 5-fluorouracil (5-FU) (150 mg/kg); group III, the N-acetylcysteine-treated group, was treated with 100 mg/kg of N-acetylcysteine orally by gavage tube daily for 10 days and on the 10th day was treated with 5-FU (150 mg/kg) by I.P. injection; group IV, the SAR low-treated group, received 0.5 mg/kg of saroglitazar orally by gavage tube daily for 10 days and then on the 10th day was treated with 5-FU (150 mg/kg) by I.P. injection; and group V, the SAR high-treated group, was treated with 5 mg/kg of saroglitazar orally by gavage tube daily for 10 days and then on the 10th day the rats were treated with 5-FU (150 mg/kg) by I.P. injection. All institutional and national protocols for the care and utilization of laboratory animals have been complied with. The doses of saroglitazar [19], 5-FU [2], and N-acetylcysteine [20] were chosen depending on previous studies.

Outcome measurements

The rats employed in the experiment were weighed prior to the initiation of treatment and on scarification day, utilizing a weighing scale. Delta total body weight = Total body weight at day 11 - Total body weight at day 1. The heart was removed carefully, debrided of any

extraneous tissue, and weighed. The relative organ weight was quantified utilizing the subsequent equation: Relative organ weight = Organ weight (g) x [100/Body weight (g)]. On the 11th day of the experimental protocol, all animals were anesthetized using ketamine and xylazine to ensure humane handling, and approximately 5 mL of whole blood was collected from each rat via cardiac puncture. The blood samples were promptly transferred to sterile collection tubes and permitted to clot naturally at room temperature. After clot formation, the samples were subjected to centrifugation at 5000 revolutions per minute (rpm) for 5 minutes to separate the serum from the cellular components. The sera were extracted and stored under appropriate conditions for subsequent biochemical analysis. The serum samples were used to assess the lipid profile, comprising total serum cholesterol, serum triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). The assessments utilized commercially available kits designed for the Cobas c 311 fully automated analyzer (Roche Diagnostics, USA), adhering to the standardized protocols provided by the manufacturer. A comprehensive hematological analysis was conducted alongside the lipid profile to assess systemic blood parameters. The blood tests performed comprised a complete blood count (CBC) and fasting blood glucose measurements to evaluate short-term glucose homeostasis. Additionally, derived hematological indices, including the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), were computed as indicators of inflammatory status. To improve accuracy and reduce physiological variability, all blood samples were collected from rats in a fasting state, specifically to ensure precise evaluation of glucose-related parameters. Biochemical and hematological analyses were performed using validated laboratory techniques under standardized conditions to ensure data accuracy, reproducibility, and reliability.

Statistical analysis

The statistical analysis was conducted utilizing GraphPad Prism 8. The values of the measured parameters were presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was conducted for group comparisons, followed by Tukey's multiple comparisons test. The results were deemed statistically significant when the *p*-value was below 0.05.

RESULTS

In the 5-FU treated group (PC), 5-FU did not affect the delta total body weight (TBW) compared to the control group. Whereas the NAC-received group produced a non-significant reduction in ΔTBW ($p > 0.05$) compared to the positive control group. Meanwhile, saroglitazar in the SAR low-dose group (SAR low) achieved a significant decrease in ΔTBW ($p < 0.05$) in comparison to the positive control group (PC). Furthermore, for saroglitazar in the SAR high-dose (SAR high) group, a non-significant reduction was observed in ΔTBW ($p > 0.05$) as compared to the positive control group (Figure 1A).

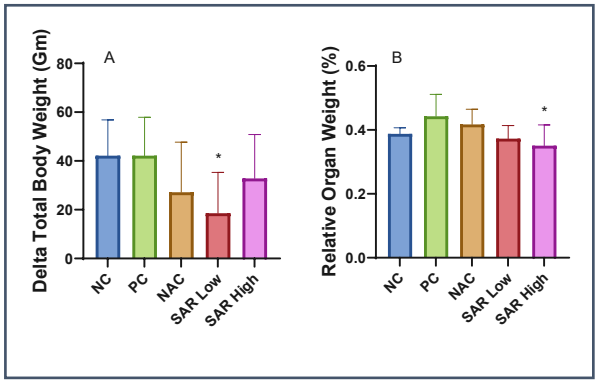

Figure 1: Effect of saroglitazar on (A) The change in weight, (B) Relative organ weight. Values are presented as mean ± S.D (n= 7). * Statistically significant compared to the positive control using ANOVA and unpaired t-test ($p < 0.05$).

Regarding the relative organ (heart) weight, 5-FU achieved a non-significant increase in relative body weight ($p > 0.05$) compared to the control group (NC). Furthermore, a non-significant decrease was observed in the NAC group ($p > 0.05$) in comparison to the positive control group. Whereas in the SAR low-dose treated group, saroglitazar resulted in a non-significant decrease in relative organ weight ($p > 0.05$) compared with the positive control group. However, in the SAR high-dose group, saroglitazar produced a significant reduction in relative organ weight in comparison with the positive control group ($p < 0.05$) (Figure 1B). The administration of 5-FU alone did not produce significant changes in serum lipid profile parameters, including total cholesterol, triglycerides, low-density lipoprotein (LDL), or high-density lipoprotein (HDL), relative to the negative control group. Similarly, treatment with N-acetylcysteine (NAC) did not result in significant changes in lipid biomarkers compared to the 5-FU group (PC), suggesting that NAC alone does not influence lipid metabolism in the context of this study. In contrast, the group receiving low-dose saroglitazar (SAR low) demonstrated a statistically significant decrease in serum triglyceride levels ($p < 0.001$) and LDL concentrations ($p < 0.01$) relative to the rats treated only with 5-FU (PC), indicating a lipid-lowering effect at this dosage. Notably, the high-dose saroglitazar-treated group (SAR high) exhibited a significant effect, markedly reducing serum total cholesterol levels ($p < 0.05$), triglycerides ($p < 0.0001$), and LDL ($p < 0.01$) in comparison to the 5-FU group (PC). Across all experimental groups, including those administered NAC or dose of saroglitazar, no significant changes in HDL levels were observed, which remained consistent with baseline values (Figure 2A–D).

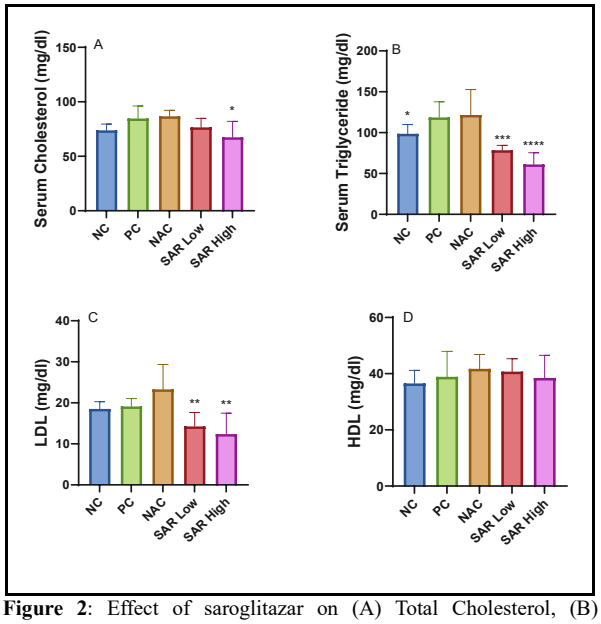

Figure 2: Effect of saroglitazar on (A) Total Cholesterol, (B) Triglycerides (TG), (C) LDL, and (D) HDL. Values are presented as mean ± S.D (n= 7). * Significant difference compared to the positive control using ANOVA and unpaired t-test (* $p< 0.05$), (** $p< 0.01$), (*** $p< 0.001$), and (**** $p< 0.0001$).

Conversely, fasting blood glucose levels demonstrated more significant variations among the treatment groups. A significant increase in blood glucose levels was observed in the 5-FU-treated group (PC) relative to the control group (NC) ($p< 0.001$), suggesting that 5-FU acutely disrupts glucose homeostasis. Treatment with low-dose saroglitazar (SAR low) led to a decrease in blood glucose levels relative to the 5-FU group (PC); nonetheless, this decrease was not statistically significant ($p> 0.05$). Administration of high-dose saroglitazar (SAR high) resulted in a significant reduction in blood glucose levels compared to the 5-FU group (PC) ($p< 0.0001$), indicating a dose-dependent effect on glycemic control (Figure 3).

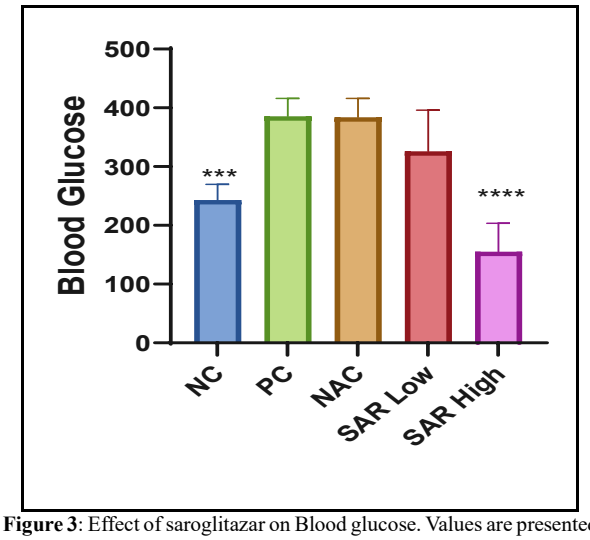

Figure 3: Effect of saroglitazar on Blood glucose. Values are presented as mean ± S.D (n= 7). * Significant difference compared with the positive control using ANOVA and unpaired t-test (*** $p< 0.001$), and (**** $p< 0.0001$).

5-FU resulted in a significant decrease ($p< 0.01$) in the level of Hb compared to the control group (NC), while in the NAC-treated group, NAC produced a non-significant increase ($p> 0.05$) in the level of Hb as compared to the 5-FU group (PC). Furthermore, a non-significant increase ($p> 0.05$) in Hb was observed in the SAR low-dose treated group (SAR low) in comparison to the 5-FU group. However, in the SAR high-dose received group (SAR high), the saroglitazar produced a significant increase ($p< 0.01$) in the level of Hb compared to the 5-FU group (PC) (Figure 4A). Regarding the WBC level, 5-FU resulted in a significant ($p< 0.05$) decrease compared to the control group (NC), whereas a non-significant increase ($p> 0.05$) in WBC was observed in the NAC-treated group as compared to the 5-FU group (PC). Meanwhile, the saroglitazar in the SAR low-dose treated group (SAR low) achieved a non-significant increase ($p> 0.05$) in the level of WBC compared to the 5-FU group (PC). Moreover, in the SAR high-dose received group (SAR high), the saroglitazar resulted in a non-significant increase in the level of WBC in comparison to the 5-FU group (PC) (Figure 4B). Concerning the RBC level, 5-FU produced a significant decrease ($p< 0.01$) compared to the control group (NC), whereas NAC resulted in a significant increase ($p< 0.01$) in the level of RBC compared to the 5-FU group (PC). However, in the SAR low-dose-treated group (SAR low), the saroglitazar produced a significant increase ($p< 0.01$) in comparison to the 5-FU group (PC). Furthermore, the saroglitazar in the SAR high dose group (SAR high) resulted in a significant increase ($p< 0.001$) in the level of RBC as compared to the 5-FU group (PC) (Figure 4C).

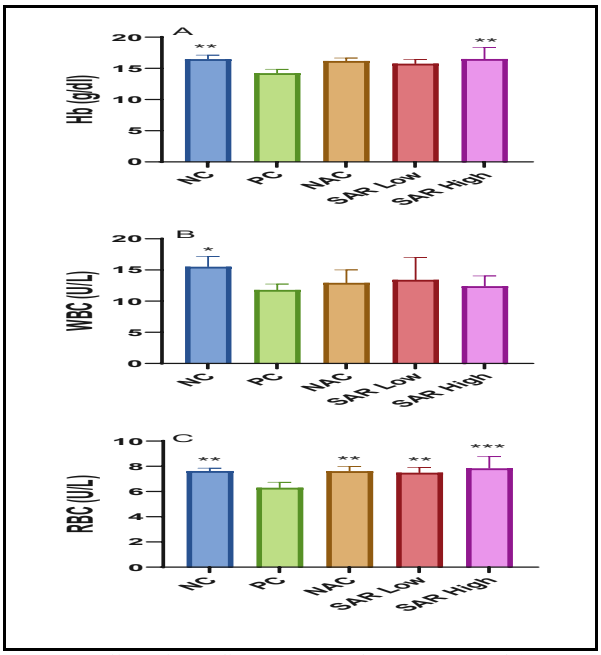

Figure 4: Effect of saroglitazar on (A) Hb, (B) WBC, and (C) RBC. Values are presented as mean ± S.D (n= 7). * Significant difference compared to the positive control using ANOVA and unpaired t-test, (* $p< 0.05$), (** $p< 0.01$), and (*** $p< 0.001$).

Compared to the control group (NC), administration of 5-FU led to a pronounced elevation in inflammatory hematological indices, particularly the neutrophil-to-lymphocyte ratio (NLR), which increased significantly ($p< 0.0001$), and the monocyte-to-lymphocyte ratio (MLR), which also showed a notable rise ($p< 0.001$). However, 5-FU treatment did not produce any statistically significant changes in the platelet-to-lymphocyte ratio (PLR), indicating a more selective impact on leukocyte subsets rather than on platelet counts or distribution. Co-administration of NAC was found to significantly attenuate the 5-FU-induced elevation in both NLR and MLR ($p< 0.01$ for both), reflecting its anti-inflammatory potential and immunomodulatory effect in mitigating chemotherapy-associated systemic inflammation. In the group treated with a low dose of saroglitazar, a statistically significant reduction was observed only in the MLR ($p< 0.0001$), while NLR and PLR remained unaffected. Conversely, high-dose saroglitazar produced a broader anti-inflammatory response, significantly lowering both NLR and MLR values ($p< 0.01$) when compared with the 5-FU group (PC). Despite these changes in leukocyte ratios, PLR remained stable and unaltered across all experimental groups, including NAC and saroglitazar-treated animals, suggesting that platelet-associated inflammatory changes were minimal under the experimental conditions (Figure 5A–C).

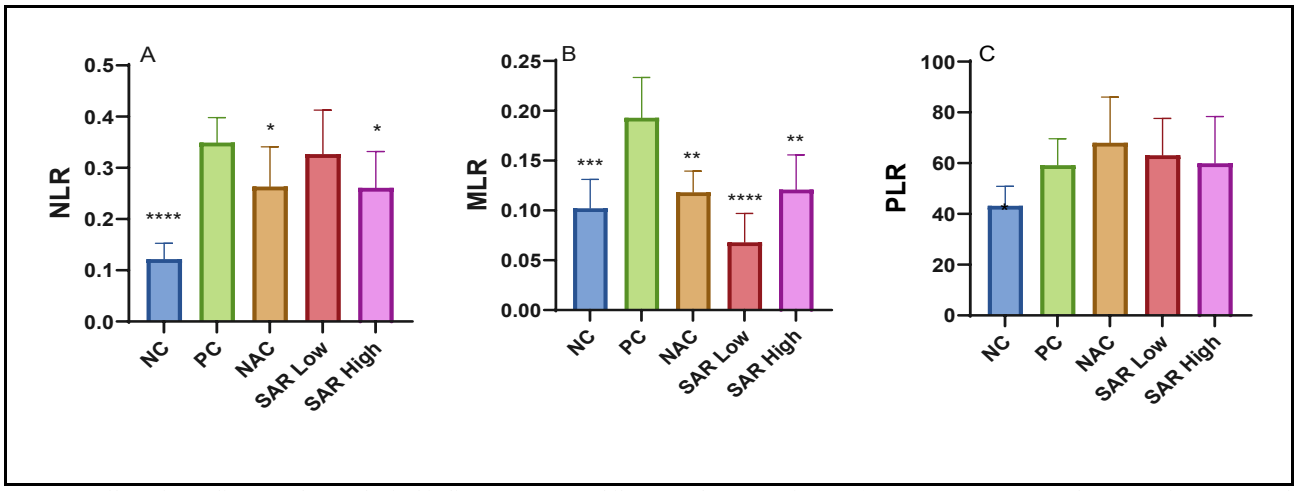

Figure 5: Effect of saroglitazar on hematological indices: (A) Neutrophil to Lymphocyte Ratio (NLR), (B) Monocyte to Lymphocyte Ratio (MLR), and Platelets to Lymphocyte Ratio (PLR). Values are presented as mean ± S.D (n= 7). * Significant difference compared to the positive control using ANOVA and unpaired t-test, (* $p< 0.05$), (** $p< 0.01$), (*** $p< 0.001$), and (**** $p< 0.0001$).

DISCUSSION

Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors that modulate lipid metabolism, glucose homeostasis, and inflammatory responses. Their activation produces pleiotropic effects, rendering them potential therapeutic targets for metabolic disorders, cardiovascular illnesses, and inflammatory conditions [21]. Dual PPAR agonists, particularly PPARα/γ agonists, confer additional benefits beyond the modulation of glucose and lipid metabolism. They affect multiple physiological processes, including anti-inflammatory, antioxidant, and immune-modulatory systems. Activation of PPARα augments lipid catabolism, diminishes triglyceride concentrations, and facilitates fatty acid oxidation; hence, it mitigates against metabolic disorders [22]. PPARγ activation enhances insulin sensitivity, promotes glucose absorption, and is essential for antioxidant defense. It additionally modulates immune function by fostering an anti-inflammatory macrophage phenotype [23]. PPAR agonists have been investigated for their ability to alleviate chemotherapy-induced toxicity, which is marked by oxidative damage, systemic inflammation, and metabolic abnormalities [24]. To the best of our knowledge, this work is the first study investigating the protective effect of different doses of saroglitazar in 5-FU-induced toxicity. Saroglitazar, a dual PPARα/γ agonist, exhibits lipid-lowering, anti-inflammatory, and antioxidant actions, positioning it as a possible candidate for mitigating chemotherapy-induced side effects. 5-FU, a commonly utilized chemotherapeutic drug, is recognized for inducing metabolic dysregulation, systemic inflammation, and organ damage associated with oxidative stress [25]. Concerning alterations in body weight, 5-FU did not cause a substantial decrease in TBW, and NAC similarly caused no remarkable variation. Nonetheless, a low dose of saroglitazar markedly diminished ΔTBW, but the high dose exhibited no meaningful impact. This study corroborates prior observations that PPARγ activation affects adipogenesis and energy metabolism, potentially contributing to weight control [26]. The high-dose saroglitazar cohort had a substantial decrease in relative heart weight in comparison to the 5-FU cohort, a finding not seen in the NAC-treated cohort. The decrease in heart weight may be ascribed to saroglitazar's established lipid-lowering and anti-inflammatory properties, which protect against myocardial stress and hypertrophy [27]. Regarding lipid profile modifications, 5-FU caused a non-significant elevation in cholesterol,

triglycerides, and LDL levels, presumably attributable to oxidative stress-induced dyslipidemia [28]. NAC did not significantly affect lipid markers; however, saroglitazar, especially at high doses, markedly decreased LDL and triglyceride levels. These results align with the recognized lipid-modulating actions of PPARα agonists, which improve lipid clearance and diminish problems associated with hyperlipidemia [23]. Saroglitazar demonstrated enhanced lipid-lowering effectiveness compared to NAC, underscoring its metabolic advantages over other antioxidants. Relating to glycemic parameters, 5-FU significantly elevated blood glucose levels, likely attributable to its effects on insulin resistance and pancreatic stress [29]. NAC had no significant effect on glucose regulation, but high-dose saroglitazar significantly lowered blood glucose levels, showing that it works by activating PPARγ to make insulin more effective [30]. The glucose-lowering capability highlights saroglitazar's superiority over NAC in alleviating chemotherapy-induced metabolic disturbances. 5-FU significantly influenced the hematological parameters, including (Hb), (WBC), and (RBC). The chemotherapeutic agent markedly diminished hemoglobin and red blood cell counts, a well-established consequence of its myelosuppressive properties [31]. NAC did not significantly restore Hb or RBC levels, while high-dose saroglitazar significantly increased Hb and RBC levels, suggesting its potential role in hematopoietic support. This enhancement is likely ascribed to its anti-inflammatory properties, which support bone marrow function and erythropoiesis [32,33]. Saroglitazar, in contrast to NAC, offered significant hematological protection against the toxicity of 5-FU. Inflammatory parameters, including NLR, MLR, and PLR, serve as novel and critical indicators of systemic inflammation. 5-FU significantly elevated NLR and MLR, indicative of heightened inflammatory responses [2]. NAC produced a significant reduction in both NLR and MLR, reflecting its moderate anti-inflammatory effects [34]. Nevertheless, saroglitazar, especially at high doses, exhibited a remarkable anti-inflammatory effect by reducing NLR and MLR significantly, surpassing NAC in magnitude [35]. This indicates that saroglitazar, via PPARγ-mediated mechanisms, demonstrates superior immunomodulatory effects compared to NAC in the context of chemotherapy-induced inflammation.

Study Limitations

Although our data indicate that saroglitazar alleviates 5-FU-induced metabolic, inflammatory, and hematological abnormalities in an acute rat model, some limitations must be acknowledged. The limited group size (n= 7) may constrain statistical power. The 10-day treatment and single high-dose 5-FU regimen represent acute toxicity but may not reflect the chronic or cumulative effects observed in clinical oncology. Third, the physiology of rodents and their medication metabolism diverge from that of humans, necessitating careful extrapolation for dose and efficacy translation. Ultimately, we did not evaluate potential off-target effects or long-term safety concerns associated with saroglitazar. Subsequent research should incorporate larger cohorts, prolonged follow-up durations, and supplementary clinical data to corroborate these findings and ascertain the therapeutic importance of saroglitazar in cancer patients.

Conclusion

Saroglitazar demonstrates a protective effect against 5-FU-induced toxicity in rats, revealed as improvements in lipid and glucose metabolism, inflammation, and hematological parameters. It significantly reduced dyslipidemia, lowered inflammatory markers (NLR, MLR), and improved red blood cell counts and hemoglobin levels. These results suggest saroglitazar as a promising adjunct to 5-FU chemotherapy. Further research is needed to explore its long-term efficacy, mechanisms of action, optimal dosing, and clinical applicability.

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Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Available from the corresponding author based on a reasonable request.

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