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Original Article
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Comparative Evaluation of the Preventive Effects of Citral, Silymarin, Thymoquinone, and Curcumin on 5-Fluorouracil-Induced Cardiac and Pulmonary Toxicity in Rats

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Objectives: 5-fluorouracil chemotherapy is a highly recommended treatment for different types of solid tumors. However, this treatment can have severe side effects on the heart and lungs. In this study, we compared the protective effects of citral, silymarin, thymoquinone, and curcumin against 5-fluorouracil-induced toxicity in the heart and lungs of rats.
Methods: 56 healthy adult male rats were randomly assigned to seven experimental groups (n = 8), including healthy and carrier (dimethylsulfoxide) groups, 5-fluorouracil, citral group, silymarin group, thymoquinone group, and curcumin group. Blood samples and representative tissue specimens of the heart and lungs were immediately collected at the end of the experiment to measure the biochemical parameters, conduct histopathological studies, and analyze antioxidant activity, respectively.
Results: The intraperitoneal administration of 5-fluorouracil caused cardiotoxicity, as evidenced by elevated serum levels of creatine phosphokinase, creatine kinase-MB ($p < 0.05$), and lactate dehydrogenase ($p < 0.05$). Besides, 5-fluorouracil increased malondealdehyde levels, indicating a lipid peroxidation index and a decrease in the total antioxidant capacity index in the cardiac and pulmonary tissues ($p < 0.05$) of the animals. The preventive and therapeutic use of all the above compounds, in combination with 5-fluorouracil, led to a decrease in the mentioned cardiac serum biomarkers and malondealdehyde in the animals ($p < 0.05$). In addition, all the therapeutic compounds increased total antioxidant capacity in the heart and lungs ($p < 0.05$), indicating a high antioxidant capacity of these biological substances in ameliorating the resultant oxidative and histologic damages.
Conclusion: Our study indicated that the natural compounds citral, silymarin, thymoquinone, and curcumin, when combined with 5-fluorouracil, could minimize the histopathological and biochemical changes caused by 5-fluorouracil treatment in the heart and pulmonary tissues likely via antioxidant mechanisms. These products can be useful and effective in chemotherapy patients by reducing the potential adverse effects of 5-fluorouracil administration.

Keywords: cardiopulmonary toxicity, 5-fluorouracil, citral, silymarin, thymoquinone, curcumin

INTRODUCTION

5-fluorouracil (5-FU) chemotherapy is one of the most commonly prescribed and well-tolerated anti-cancer regimens for treating various types of solid tumors, including gastric and advanced colorectal cancers, as well as genitourinary, breast, skin, liver, head, and neck malignancies in adults [1-3]. However, the administration of 5-FU can lead to severe cardiovascular side effects and toxicities in numerous organs and tissues [4, 5]. Previous reports indicate that approximately 31%-34% of

patients treated with the 5-FU chemotherapy regimen exhibit severe dose-limiting toxicities associated with the drug [6]. It is well-documented that genetic defects or congenital deficiencies in the activity of the dihydropyrimidine dehydrogenase (DPD) enzyme can increase the risk of adverse drug reactions associated with 5-FU [3].

The clinical symptoms of 5-FU-related toxicities include fever; oral and gastrointestinal inflammation; nausea; vomiting; diarrhea; and abnormalities in hematology, digestive, cutaneous, and neurological systems [7, 8]. Scientific evidence suggests that oxidative stress, apoptosis, and the release of pro-inflammatory cytokines play important roles in the pathogenesis of 5-FU-induced gastrointestinal (oral) mucosal injury, as well as renal and cardiac toxicities [4, 5, 9]. However, chemotherapy regimens in combination with phytochemical agents containing natural antioxidants may promote the effectiveness of anticancer treatments while reducing adverse side effects, toxicities, and resistance [1].

The primary component of lemongrass (*Cymbopogon citratus*) essential oil, citral (3,7-dimethyl-2,6-octadienal), can help reduce reactive oxygen species (ROS) levels and manage oxidative stress [10]. This oil exhibits a wide range of pharmacological effects, including anti-inflammatory, antifungal, antibacterial, antiviral, anticancer, and antioxidant properties [11]. The flavonoid silymarin is the most well-known ingredient of *Silybum marianum*, a medicinal plant belonging to the Asteraceae family, which has many biological properties, including hepatoprotective, and cardioprotective effects, as well as antineoplastic, anti-inflammatory, and antioxidant activities [12]. Thymoquinone, a diterpenoid alkaloid found in *Nigella sativa* (black cumin), exhibits potent antioxidant and anti-inflammatory activities by reducing inflammatory cytokines such as IL1, TNFα, and cyclooxygenase [13]. Similarly, the main component of *Curcuma longa*, curcumin, is well-documented for its antioxidant, anti-neoplastic, antiviral, anti-rheumatic, and anti-inflammatory properties [14]. The phenolic groups found in curcumin's structure enhance its capacity to eliminate ROS and superoxide radicals [15].

Today, medicinal plants and their derivatives represent the main approach to treating debilitating illnesses and are increasingly used as alternatives to chemical drugs [16]. However, a review of the literature reveals a lack of scientific data or research articles on the comparative protective effects of these treatment regimens against 5-FU-induced toxicity in cardiac and pulmonary tissues. Given the severe potential complications that can occur in patients following the administration of 5-FU, this study was designed to investigate and compare the preventive effects of citral (CIT), silymarin (SYL), thymoquinone (TQ), and curcumin (CUR) on 5-FU-induced cardiopulmonary toxicity in rats, in terms of histopathology, clinical biochemistry, and antioxidant capacity assessments.

MATERIALS AND METHODS

1. Animals

A total of 56 male Sprague–Dawley rats weighing 220 ± 10 g were obtained from the Laboratory Animal and Research Center at Shiraz University of Medical Sciences. The animals were housed under standard temperature, humidity, and lighting conditions during the study and adaptation period. This included a temperature range of 22℃ ± 2℃, humidity levels of 40%-50%, and a 12-hour light/dark cycle. The rats had free access to a standard, hygienic pellet diet and fresh drinking water. All methods and experiments performed in this study adhered to the rules and guidelines of the Ethics Committee for Biomedical Research and Care of Laboratory Animals, established by Shiraz University (Approval No: IR.US.REC.1402.011).

The animals were anesthetized with ketamine (80 mg/kg, i.p, Alfasan, Netherlands) and xylazine (10 mg/kg, i.p, Alfasan, Netherlands) on the 14th day of the experiment. Blood samples were then collected to evaluate biochemical parameters before the rats were euthanized in a CO_2 chamber. Representative tissue samples from the heart and lungs were promptly collected for histopathological studies and antioxidant activity analysis.

2. Experimental design

After a one-week adaption period, the rats were randomly assigned to seven experimental groups (n = 8), as follows (Fig. 1):

Group I (control): injected with 1 mL of distilled water intraperitoneally for 14 days,

Group II (carrier control): received the carrier (DMSO) for 14 days, as well as 20 mg/kg/day of 5-FU injected intraperitoneally from the 9th day until the end of the study,

Group III (5-FU): received 20 mg/kg/day of 5-FU, administered intraperitoneally, starting from the 9th day until the end of the experiment,

Group IV (Citral + 5-FU): received 30 mg/kg/day of citral for 14 days, as well as 20 mg/kg/day of 5-FU administered intra-

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1st Day	9th Day	14th Day
Control	DW: i.p.	DW: i.p.
Carrier Control	DMSO+DW: i.p.	DMSO+DW: i.p. 5-FU: i.p.
5-fluorouracil (5-FU)	No Intervention	5-FU: 20mg/kg-i.p.
Citral (CIT)	CIT: 30mg/kg-i.p.	CIT: 30mg/kg-i.p. 5-FU: 20mg/kg-i.p.
Silymarin (SLY)	SLY: 50mg/kg-i.p.	SLY: 50mg/kg-i.p. 5-FU: 20mg/kg-i.p.
Thymoquinone (TQ)	TQ: 10mg/kg-i.p.	TQ: 10mg/kg-i.p. 5-FU: 20mg/kg-i.p.
Curcumin (CUR)	CUR: 200mg/kg-i.p.	CUR: 200mg/kg-i.p. 5-FU: 20mg/kg-i.p.

Figure 1. The overall schedule of the experiment. DW, Distilled Water; i.p., Intraperitoneal; DMSO: Dimethylsulfoxide.

peritoneally, starting from the 9th day until the end of the study,

Group V (Silymarin + 5-FU): received 50 mg/kg/day of silymarin for 14 days, as well as 20 mg/kg/day of 5-FU administered intraperitoneally, starting from the 9th day of the experiment to the end of the study,

Group VI (Thymoquinone + 5-FU): received 10 mg/kg/day of thymoquinone for 14 days, as well as 20 mg/kg/day of 5-FU administered intraperitoneally, starting from the 9th day until the end of the study, and

Group VII (Curcumin + 5-FU): received 200 mg/kg/day of curcumin for 14 days, as well as 20 mg/kg/day of 5-FU, administered intraperitoneally, starting from the 9th day until the end of the study.

3. Histopathological evaluations

Heart and lung tissue samples were promptly collected and placed in 10% neutral buffered formalin for histopathological evaluation. After 48 hours of fixation, the tissues underwent dehydration, clearing, and impregnation using a tissue processor (Autotechnicon). Subsequently, the tissue specimens were embedded in paraffin wax, and sections were cut into 5-μm-thick slices using a rotary microtome device. Finally, the prepared slides were stained with hematoxylin and eosin (H&E) and examined under a microscope (Olympus, CX21FS1, Japan).

4. Serum biochemical evaluations

Biochemical parameters of cardiac function were measured by separating the serum after centrifuging blood samples at 3,000 rpm for 15 min following blood clotting. Cardiac function markers, including creatine phosphokinase (CPK), creatine kinase-myocardial band (CK-MB), and lactate dehydrogenase (LDH) enzymes, were measured using the commercial kits from Pars Azmoun Company (Tehran, Iran) and analyzed with the autoanalyzer Alpha Classic from Sanjesh Company (Isfahan, Iran).

5. Antioxidant activity

To prepare tissue extracts, 1 g of semi-frozen tissue was first thawed at room temperature, and then crushed and transferred into a 10-mL glass test tube. Next, 5 mL of phosphate-buffered saline (PBS) was added to the tissue sample, and the mixture was homogenized using an ultrasonic homogenizer. After homogenization, the samples were transferred again into the microtube and centrifuged at 5,000 rpm for 20 min to remove and refine the tissue residues. The supernatant was collected and transferred into new microtubes to measure antioxidant activity. Finally, the total antioxidant capacity (TAC) and malondialdehyde (MDA) levels were measured using Naxifer™ and Nalondi™ commercial kits (Navand Salamat Co, Iran) respectively, following the manufacturer's instructions.

6. Statistical analysis

Data were analyzed using GraphPad Prism software version 10.0 (USA) and reported as mean ± standard error of the mean. Statistical comparisons were made using appropriate methods, including one-way ANOVA followed by Tukey's post-hoc test. A p-value of < 0.05 was considered statistically significant for all comparisons.

RESULTS

1. Serum biochemical factors of cardiac function

The results of the serum biochemical factors of cardiac function, including CPK, CK-MB, and LDH, are summarized in Fig. 2. Although the concentrations of CPK, CK-MB, and LDH were higher in the rats treated with 5-FU compared to the control group, the difference was only significant for the LDH value ($p < 0.05$). All investigated treatments reduced the activity of CPK, CK-MB, and LDH enzymes compared to the 5-FU group. However, only the administration of TQ significantly reduced the elevated CK-MB and LDH levels caused by 5-FU ($p < 0.05$).

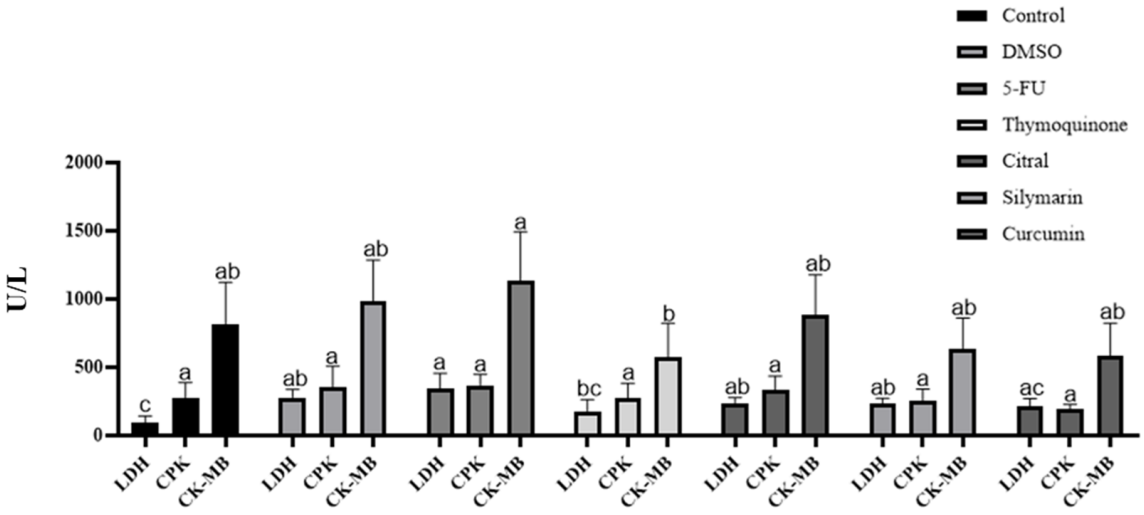

Figure 2. The effects of citral, silymarin, thymoquinone, and curcumin on serum cardiac parameters in the 5-FU-treated rats. The Values are Mean ± SEM (n = 6). Analyzed by ANOVA, followed by post-hoc Tukey's tests. Different letters show statistically significant differences in the column ($p < 0.05$). CPK, Creatine Phosphokinase; CK-MB, Creatine Kinase MB; LDH, Lactate Dehydrogenase.

Furthermore, no statistically significant differences were observed among the treatment groups ($p > 0.05$).

2. Tissue antioxidant parameters and histopathology

1) Heart

The results of cardiac antioxidant capacity, including MDA and TAC levels, of the treated rats are presented in Fig. 3. 5-FU administration reduced TAC levels of cardiac tissues compared to the control group, although this reduction was not statistically significant ($p > 0.05$). All treatment regimens increased TAC levels, with CIT, SLY, and CUR showing statistically significant improvements ($p < 0.05$, Fig. 3A). Similarly, 5-FU administration increased the cardiac concentration of MDA compared to the control group, but the differences were not statistically significant ($p > 0.05$). All treatment strategies reduced the elevated levels of MDA caused by 5-FU, although these reductions were also not statistically significant ($p > 0.05$, Fig. 3B).

Histopathological examination of H&E-stained heart sections revealed a normal structural architecture of cardiac muscle cells or fibers in the control group, without any abnormal changes such as cell swelling, vacuolar degeneration, necrosis, or inflammatory cell infiltration (Fig. 3Ca). In contrast, the FU-treated group showed severe vascular changes, such as the presence of interstitial edema fluid between the muscle fibers, congestion, and myocardial hemorrhage. In addition, vacuolar degeneration in the cytoplasm and swelling of cardiac muscle fibers were observed in this group (Fig. 3Cc). Similar to the 5-FU-treated group, the DMSO group exhibited severe congestion of cardiac vessels and myocardial hemorrhage (Fig. 3Cb). In all treatment groups, the cardiac histopathological lesions were less severe compared to the 5-FU group, and the findings were identical to those observed in the control group (Fig. 3Cf, g).

2) Lungs

5-FU injection significantly reduced the TAC activity in pulmonary tissues compared to the control rats ($p < 0.05$). All treatments increased the TAC levels in the lung, however, the increase was statistically significant only for the CIT treatment ($p < 0.05$, Fig. 4A). Administration of 5-FU increased pulmonary MDA levels compared to the control group, but the increase was not statistically significant ($p > 0.05$). All treatment regimens reduced the increase in MDA levels caused by 5-FU, with the reduction being statistically significant only for the SLY-treated group ($p < 0.05$, Fig. 4B).

Histopathological examination of the lung tissue parenchyma revealed a normal pulmonary architecture in the control group, including intact bronchi and bronchioles, alveolar spaces with thin interalveolar septa, and normal connective tissue. The overall epithelial lining of the bronchi, bronchioles, and alveoli was normal, without any necrotic or degenerative changes or hyaline membrane formation (Fig. 4Ca). The main histopathological changes observed in the lung tissue of rats treated with

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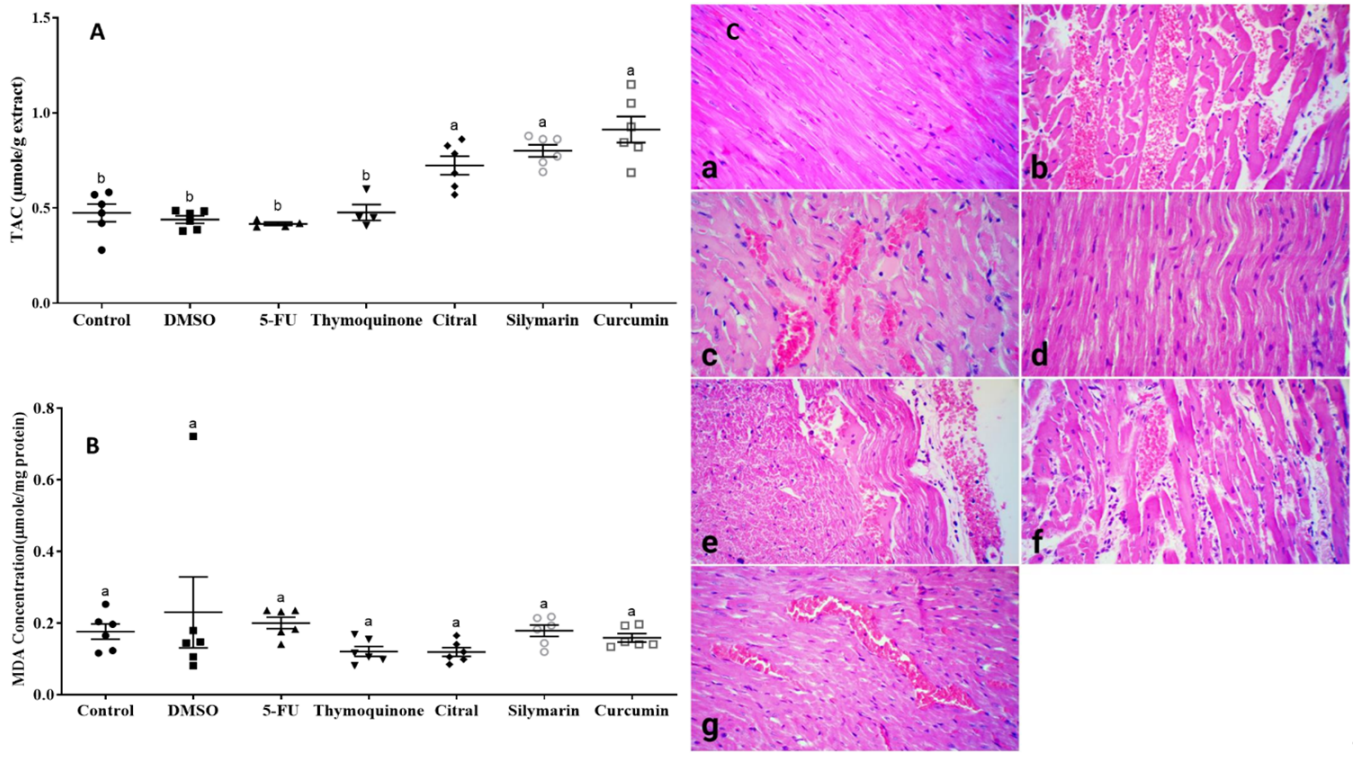

Figure 3. Quantitative analysis on the cardiac tissue's antioxidant capacity (TAC) and malondealdehyde (MDA) concentration after drug treatment. (A) Antioxidant capacity was assayed with Naxifer™ and Nalondi™ commercial kit. (B) Malondealdehyde concentration was measured with Naxifer™ and Nalondi™ commercial kits. (C) H&E images were prepared with cardiac histopathology of rats (n = 6). (a) Healthy control, (b) DMSO control, (c) 5-FU, (d) Citral, (e) Silymarin, (f) Thymoquinone, (g) Curcumin. The results of the statistical test (ANOVA) and Tukey's post hoc test are shown as mean ± SEM. Different letters on the columns in parts (A) and (B) indicate significant differences ($p < 0.05$).

5-FU included significant widening or thickening of the alveolar septal wall, infiltration of mononuclear inflammatory cells in the interstitial spaces, and severe hemorrhages within the alveoli and interstitium (Fig. 4Cc). Similarly, in the DMSO group, severe pulmonary congestion, mild emphysematous changes, and infiltration of a few intra-alveolar foamy macrophages were observed (Fig. 4Cb). Histopathological analysis of the lung tissue revealed that the treatment regimens ameliorated the pulmonary changes caused by 5-FU administration, in all the treated groups. Findings such as thickening of the intra-alveolar septa, lymphocyte infiltration, and vascular changes notably decreased in the treated groups compared to the 5-FU-treated group (Fig. 4Cf, g).

DISCUSSION

5-FU serves as a key component in anticancer treatment plans and is widely used to target various malignant tumors [17]. However, it is important to note that 5-FU can cause cardiotoxicity, which ranks as the second leading cause of cardiac complications in patients with cancer after anthracyclines [18]. Additionally, there have been reports of lung injury associated with 5-FU usage [19]. These side effects significantly restrict the clinical application of 5-FU.

Cardiotoxicity has been reported in rats following administration of 5-FU. A study by Safarpour et al. in 2022 found that 5-FU increased the levels of cardiac enzymes AST, LDH, and CK-MB. Histopathological examination revealed the presence of lesions such as necrosis and congestion [20]. Another study in 2022 showed that 5-FU administration led to increased levels of LDH, CK-MB, and troponin I, and microscopic examination revealed the presence of cardiac lesions [17]. In the present study, we investigated the cardiotoxic effects of 5-FU by measuring CPK, LDH, and CK-MB enzyme levels, all of which showed significant increases following 5-FU injection. Histopathological examination also confirmed the involvement of cardiac tissues. Previous studies have suggested that oxidative stress and inflammation may play a role in 5-FU-induced

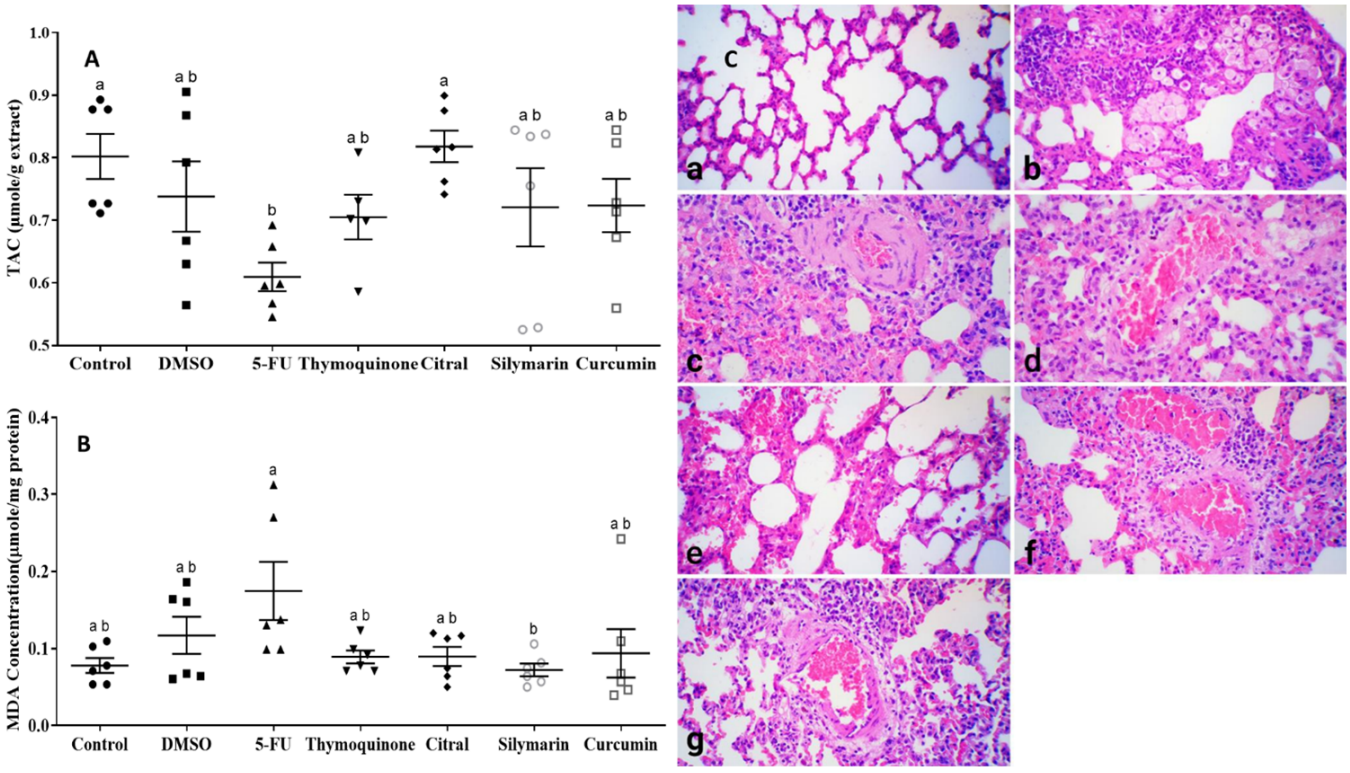

Figure 4. Quantitative analysis on the pulmonary tissue's antioxidant capacity (TAC) and malondealdehyde (MDA) concentration after drug treatment. (A) Antioxidant capacity was assayed with Naxifer™ and Nalondi™ commercial kit. (B) Malondealdehyde concentration was measured with Naxifer™ and Nalondi™ commercial kits. (C) H&E images were prepared with lung histopathology of rats (n = 6). (a) Healthy control, (b) DMSO control, (c) 5-FU, (d) Citral, (e) Silymarin, (f) Thymoquinone, (g) Curcumin. The statistical test (ANOVA) and Tukey's post hoc test results are shown as Mean ± SEM. Different letters on the columns in parts (A) and (B) indicate significant differences ($p < 0.05$).

cardiotoxicity. 5-FU can disrupt the balance of oxidants/antioxidants by reducing TAC and increasing MDA levels [20]. Another study found that 5-FU reduced the levels of antioxidant agents SOD, CAT, GPx, and GSH while increasing MDA levels [4]. This study also observed increased levels of inflammatory factors such as IL-1β, IL-6, and TNFα in cardiac tissue. Our study confirmed that TAC levels decreased and MDA levels increased under the influence of 5-FU, consistent with previous findings indicating the role of oxidative stress in 5-FU-induced cardiotoxicity. However, this study did not investigate the role of inflammation and apoptosis as important contributors to 5-FU-induced organ damage. Future research should address these aspects to provide a more comprehensive understanding of the toxic mechanisms of 5-FU.

As a primary site of 5-FU elimination, the lungs are highly vulnerable to ROS because of their direct exposure to high oxygen tensions and environmental pollutants from different sources, which can diminish the quality of life of a patient [21]. It is widely known that the formation of free radicals and subsequent inflammatory reactions can impair the function of lung tissue structures, leading to respiratory dysfunction, pulmonary edema, and the accumulation of inflammatory exudate [22, 23]. A study conducted in 2022 reported that 5-FU caused lung lesions in rats, such as interstitial fibrosis and congestion in the lung tissue. The interalveolar wall also thickened owing to the infiltration of inflammatory cells. In addition, TBARS and NO levels increased owing to oxidative stress, while the levels of antioxidants, such as GSH, decreased [24]. In a separate study in 2024, 5-FU was found to cause pulmonary edema, congestion, interstitial hemorrhage, and hepatization. Under the influence of 5-FU, the levels of pro-inflammatory factors such as IL-1β, IL-6, and TNFα increased, while that of IL-10, an anti-inflammatory cytokine, decreased. Additionally, oxidative stress markers such as TBARS were elevated, while antioxidant factors like GSH and SOD were significantly reduced [25]. Our present study aligns with these findings, as 5-FU caused various lesions in the lung tissue, including thickening of the interalveolar wall, infiltration of mononuclear inflammatory cells in the intersti-

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tial space, and bleeding in the interstitial and alveolar spaces. Furthermore, our study revealed that TAC levels decreased and MDA levels increased owing to 5-FU-induced oxidative stress. However, the current study did not investigate the role of inflammation in the organ toxicity caused by 5-FU. Inhibition of oxidative stress by natural antioxidants can alleviate organ toxicity caused by 5-FU [26]. Phytochemicals, known for their diverse biological activities, such as antioxidant and anti-inflammatory properties, are thought to be effective in protecting organ systems, especially the heart and lungs, thereby improving individuals' quality of life [27].

For the above reasons, and considering the severe potential complications and adverse reactions of 5-FU in other organs, we evaluated the protective effects of CIT, SLY, TQ, and CUR against the toxicity caused by 5-FU administration in the cardiac and pulmonary tissues of rats. According to the literature, no previous studies have reported a comparative evaluation of the effects of these drugs on 5-FU-induced toxicity in organs such as the heart and lungs.

The results of our study showed that TQ was the most effective among the therapeutic agents in significantly reducing the levels of cardiac enzymes, especially CK-MB and LDH. The antioxidant and anti-inflammatory effects of TQ, the main bioactive ingredient of black seed (*Nigella sativa*), have been proven in previous studies [13]. In a study, TQ inhibited tumor growth and enhanced the therapeutic efficacy of 5-FU in the early stages of colorectal cancer [28]. In addition, it has been shown that TQ, when used alone or in combination with 5-FU chemotherapy regimens, acts as an effective antitumor and cytoprotective agent in different tumor models [29, 30]. The cardioprotective effects of TQ nanoemulsion in ameliorating the adverse reactions of 5-FU, including elevated cardiac biomarkers CK-MB and LDH, MDA, and histopathological changes in cardiac tissue have previously been reported in rats, and our findings are almost comparable to that study [31]. However, the results of our study highlight the potential benefits of combining TQ with chemotherapy agents, especially 5-FU, which requires further *in vitro* and *in vivo* investigations.

The literature review identified only one published study on the preclinical use of SLY in treating 5-FU-induced cardiotoxicity. It was found that SLY and nano-emulsion SLY reduced cardiac enzyme levels, oxidative stress, histopathological degeneration, and the expression of pro-inflammatory markers TNF-α and COX-2 in heart tissue, significantly ameliorating cardiotoxicity caused by 5-FU in rats [12]. In line with previous research, our findings indicated the strong antioxidant potential of SLY in reducing lipid peroxidation of cellular components caused by 5-FU treatment, resulting in improved oxidative stress. Owing to the excellent biological properties of SLY as a potent anticancer flavonoid, further research on the use of SLY in 5-FU chemotherapeutic regimens in clinical and preclinical trials is recommended.

Modern pharmacological studies have shown that CUR, a natural herbal compound, has strong anti-inflammatory, antioxidant, and antineoplastic effects and can protect normal cellular integrity against chemotherapy-induced cardiac toxicity [32]. According to a study by Sarkhosh et al. [33], it was found that CUR, in combination with 5-FU, reduced toxicity in normal non-tumor fibroblast cells (L929 cell line) and reduced the possible adverse effects and toxicity caused by 5-FU. In another study, combining CUR with 5-FU significantly reduced the toxic effects of 5-FU therapy in bladder cancer cells [34]. In addition, CUR increases the anticancer properties of 5-FU against *in vitro* and *in vivo* gastric neoplasms by downregulating NF-κB and COX-2 pathways [35]. Also, Du et al. [36] provided quantitative evidence of the synergistic inhibitory effects of combining CUR and 5-FU on the growth of the human colon cancer cell line HT-29. However, although the combination of curcumin with 5-FU is widely used, additional investigations and clinical trials are necessary to confirm its beneficial effects and assess potential side effects in cancer treatment [37].

In a previous study, the addition of CIT to 5-FU-treated *Schizosaccharomyces pombe* cells controlled ROS levels, increased normal cell viability, and reduced toxicity caused by 5-FU [10]. Another research showed that CIT has antioxidant and protective effects on human endothelial cells under oxidative stress caused by hydrogen peroxide [38]. Also, the positive effects of CIT on improving the antioxidant status of the serum and reducing oxidative stress (reducing MDA levels and increasing TAC) in diabetic mice have been reported [39]. However, studies on combination therapy of CIT and 5-FU drugs are limited. To the best of our knowledge, this study is the first to investigate the *in vivo* protective effects of CIT, a key component of lemongrass (*Cymbopogon citratus*), against 5-FU-induced cardiac and pulmonary toxicity. Consistent with previous findings, our results confirmed the antioxidant and free radical-scavenging properties of CIT. While differences were observed in parameters such as CPK, MDA, and TAC levels, these differences were not found to be statistically significant.

The measurement of MDA levels in cardiac and pulmonary

tissues revealed that only SLY could significantly reduce the increased MDA levels caused by 5-FU administration in the lungs, compared to the other therapeutic compounds. The therapeutic compounds used in the present study increased the amount of TAC in cardiac tissue, demonstrating their strong antioxidant activity in ameliorating the resultant oxidative damage and cardiotoxicity caused by 5-FU. Among them, CUR showed the highest statistically significant increase in TAC, making it the most effective in increasing antioxidant capacity and neutralizing 5-FU-induced cardiotoxicity. In pulmonary tissue, CIT was found to significantly increase TAC levels compared to the other therapeutic substances, indicating its superior antioxidant capacity in protecting against 5-FU-induced pulmonary damage.

Increasing the sample size and thereby enhancing the study's statistical power could potentially convert these insignificant findings into significant ones. Alternatively, it may be worth exploring the effects of different doses or employing oral administration. Additionally, conducting a comparative evaluation of the effects of the compounds on the levels of inflammatory cytokines, combined with an analysis of the expression of important genes involved in oxidative stress, such as Nrf2, can provide valuable insights into the mechanisms underlying the effectiveness of these compounds.

CONCLUSION

Our study demonstrated that the natural compounds CIT, SLY, TQ, and CUR, in combination with 5-FU, effectively minimized the histopathological and biochemical changes caused by 5-FU treatment in the heart and lung tissues, likely through their antioxidant mechanisms. These findings suggest that these compounds can be useful and effective in mitigating the adverse effects of 5-FU administration, making them potentially useful for patients undergoing chemotherapy.

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CONFLICTS OF INTEREST

The author stated that they have no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

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