Journal of Sports Physiology and Athletic Conditioning (J.S.P.A.C) 2025; 5 (18): 1-14

Research Article

Investigating the Effect of 12-Week Swim Training and Vitamin C Supplementation on TGF-β Expression in Lung Tissue of Mice with Lung Cancer

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Received: 1October2025
Accepted: 25 November2025

Abstract

Introduction: Lung cancer involves dysregulation of key signaling pathways, including transforming growth factor-beta (TGF-β). This study examined the effect of 12-week swim training (ST) and vitamin C (VC) supplementation on TGF-β expression in the lung tissue of mice with lung cancer.

Methods: 42 male Balb/c mice were assigned to seven groups: healthy control (HC), lung cancer control (LC), VC50, VC100, ST, ST+VC50, and ST+VC100. Lung cancer was induced by benzo[a]pyrene injection. The ST protocol was conducted for 12 weeks, 3 sessions/week. VC was administered orally daily. TGF-β mRNA expression was measured using real-time PCR. Data were analyzed by independent t-test and two-way ANOVA with Bonferroni post-hoc test ($p \leq 0.05$).

Results: Cancer induction significantly increased TGF-β expression in the LC group (2.44 ± 0.14) compared to HC (1.00 ± 0.025; p=0.001). ST alone significantly reduced TGF-β (1.76 ± 0.10) versus LC (p=0.002). A significant interaction was found between ST and VC on TGF-β reduction (p=0.028), with the lowest expression in ST+VC100 (1.05 ± 0.06) and ST+VC50 (1.12 ± 0.11) groups.

Conclusion: The combination of ST and VC synergistically reduces TGF-β expression in a lung cancer model, suggesting a promising complementary therapeutic strategy.

Keywords:
Lung cancer, Benzo[a]pyrene, TGF-β, Swimming training, vitamin C

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1. Introduction

Lung cancer, as one of the deadliest types of cancer worldwide, is responsible for a significant number of cancer-related deaths [1, 2]. Numerous risk factors, including exposure to carcinogens such as benzo[a]pyrene (BaP) and nicotine, play a role in its pathogenesis [3, 4]. Lung carcinogenesis is a complex multi-stage process characterized by disruptions in key cellular signaling pathways such as transforming growth factor-beta (TGF-β), hypoxia-inducible factor (HIF-1α), and p53 [5, 6, 7]. Among these pathways, TGF-β is a multifaceted cytokine with a dual role; it acts as a tumor suppressor in early stages, but in advanced disease, by inducing the epithelial-mesenchymal transition (EMT) process, metastasis, and immune evasion, it becomes a pro-tumor factor [6]. Therefore, regulating TGF-β expression could be a promising therapeutic strategy in lung cancer management.

In recent years, non-pharmacological interventions such as physical activity and diets rich in micronutrients have gained attention as complementary approaches alongside conventional cancer therapies [8, 9]. Regular exercise, particularly aerobic exercises like swimming, exerts its anti-tumor effects through multiple mechanisms, including improving immune function, reducing inflammation, modulating tumor growth signaling pathways, and inhibiting angiogenesis [10, 11]. Studies have shown that exercise can reduce tumor growth in animal models of lung cancer. Specifically, swim training inhibits angiogenesis and reduces tumor growth by modulating the HIF-1α/VEGF pathway [12]. Furthermore, evidence suggests that exercise can affect TGF-β levels in various tissues [13].

On the other hand, vitamin C, as a potent antioxidant and essential cofactor for numerous enzymes, has shown significant protective effects against cancer [14, 15]. The anti-cancer mechanisms of vitamin C include neutralizing oxidative stress, inhibiting HIF-1α factor activity, inducing apoptosis in cancer cells, and enhancing the immune system [16, 17]. Interestingly, recent studies indicate that vitamin C can also modulate the TGF-β signaling pathway. For example, ascorbic acid has been shown to promote the TGF-β-induced myofibroblast phenotype [18] and suppress breast cancer cell metastasis by inhibiting EMT [19]. Additionally, vitamin C can help stabilize and activate p53, which is a negative regulator of the TGF-β pathway, by competing for the binding of HIF-1α and p53 to the E3 ubiquitin ligase CBL [20].

Despite independent evidence of the beneficial effects of exercise and vitamin C on cancer and the TGF-β pathway, the combined effect of these two interventions on TGF-β expression in the lung tissue of mice with lung cancer has not been well investigated. Can the combination of swim training and vitamin C supplementation have a synergistic effect on regulating this key cytokine? This research is designed to investigate the effect of 12 weeks of swim training and vitamin C supplementation on TGF-β expression in the lung tissue of mice with lung cancer. The hypothesis is that combining these two interventions can modulate TGF-β expression more effectively than either alone by modulating related signaling pathways, thereby increasing the therapeutic potential in the lung cancer model. The results of this study could pave the way for the application of combined exercise and micronutrient protocols as an adjuvant strategy in lung cancer control.

2. Materials and Methods

Study Design and Animals

In all experiments, the guidelines of the Helsinki Declaration for animal care were followed. This study has the ethical code IR.IAU.SHIRAZ.REC.1403.027. In this experimental study, a post-test design was used, involving 42 male Balb/c mice with an average age of 8 weeks and a weight of 18-22 grams. They were divided into 7 groups: Healthy Control (HC), Lung Cancer Control group (induced by Benzo[a]pyrene (BaP)) (LC), Lung Cancer + Vitamin C (50 mg/kg) (LC+VC50), Lung Cancer + Vitamin C (100 mg/kg) (LC+VC100), Lung Cancer + Swim Training (LC+ST), Lung Cancer + Swim Training + Vitamin C (50 mg/kg) (LC+ST+VC50), and Lung Cancer + Swim Training + Vitamin C (100 mg/kg) (LC+ST+VC100).

Cancer Induction

For this purpose, Benzo[a]pyrene was purchased from Sigma-Aldrich, Germany, with product code B1760. Based on references and a pilot study, a dose of 72 mg of Benzo[a]pyrene dissolved in 3.6 ml of corn oil was prepared and then 10 International Units of this solution were injected intraperitoneally into 4 mice in a fasting state [19]. After 14 days, lung tissue was extracted from the 4 mice that had received the Benzo[a]pyrene injection and from 4 healthy laboratory mice (These 8 mice included in the pilot were separate from the 42 main mice). The samples were sent to the pathology laboratory for examination of pathology and tumorigenicity. According to Figure-1, image A shows the lung tissue of a healthy mouse and image B shows the lung of a cancerous mouse. The arrowheads in image B indicate the presence of a tumor in the lung tissue. After confirming the induction of the disease, the mentioned dose of Benzo[a]pyrene was injected into the remaining 36 mice. According to references, weight loss and reduced mobility are other observable signs of lung cancer [19], which were clearly observed in the mice that underwent disease induction.

Development of mice model of cancer by B[a]P administration

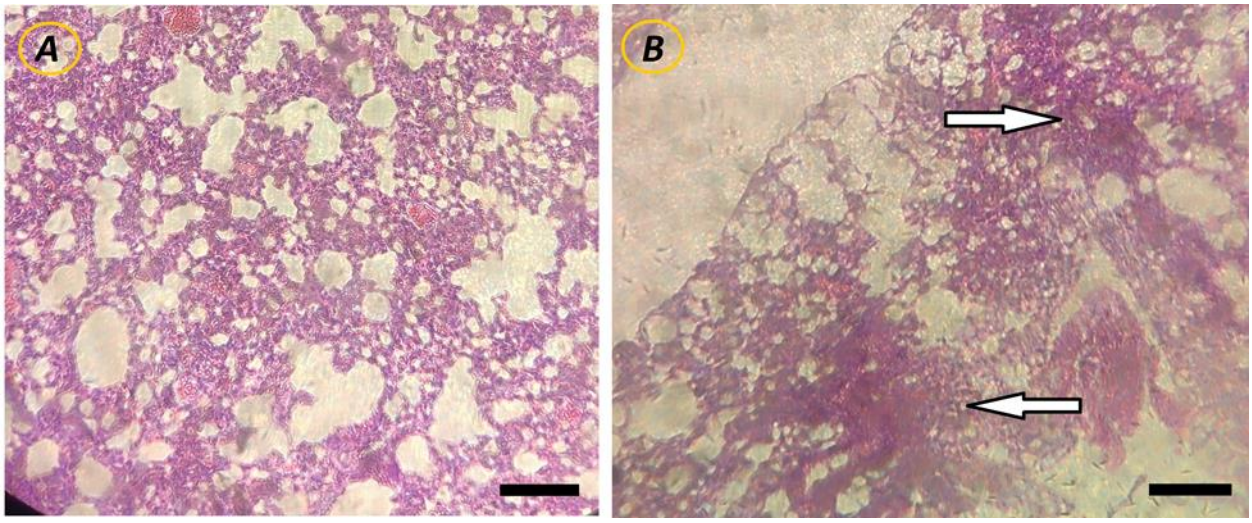


Fig 1. Representative pictures of H&E-stained lung sections. A. lung in the control group; B. lung in the B[a]P group. Arrowheads indicate tumors. Images acquired at ×100 magnification and scale bars represent 1 mm.

Exercise Protocol (Swimming Training, ST)

In this study, swimming exercise was performed according to previous studies with slight modifications. The swimming exercises were conducted in a tank (45 cm width, 80 cm length, and 80 cm height) filled with warm water (35±1°C) to a depth of 50 cm, with the water level adjusted to prevent mice from using their tails for resting [22]. The swimming training program lasted for 12 weeks, consisting of 3 sessions per week, with each session duration gradually increasing from 5 minutes to 38 minutes. The swimming protocol varied weekly throughout the 12-week period. During the first 4 weeks, the exercise intensity resembled unweighted swimming training [23,22]. From weeks 5 to 8, a tail weight equivalent to 2% of body weight was added, while weeks 9 to 12 (study completion) utilized a tail weight of 5% of body weight [24,25]. The exercise duration progressed as follows: week 1 - 5 minutes, week 2 - 8 minutes, week 3 - 11 minutes, week 4 - 14 minutes, week 5 - 17 minutes, week 6 - 20 minutes, week 7 - 23 minutes, week 8 - 26 minutes, week 9 - 29 minutes, week 10 - 32 minutes, week 11 - 35 minutes, and week 12 - 38 minutes [21].

Table 1. week swimming exercise protocol for the studied mice

Week	Duration (minutes)	Weight (% body weight)
1-4	5-14	**0**
5-8	17-26	**2**
9-12	29-38	**5**

Vitamin C administration protocol

In this study, vitamin C was administered daily via oral to the treatment groups: groups 4 and 7 received 50 mg/kg, and groups 5 and 8 received 100 mg/kg [26, 27].

Tissue Collection and Analysis

48 hours after the last training session, male Balb/c mice were anesthetized using ketamine: 100 mg/kg; xylazine: 10 mg/kg, and lung tissue was isolated and stored at -80°C. Total RNA extraction was performed using FavorPrep™ Tissue Total RNA Kit (FATRK 001, Taiwan). TGF-B mRNA was then measured by real-time PCR and calculated using the ΔΔCt method.

Table 2. Primers used in the study

Gene	Primer sequences	Size (bp)
TGF-B	*Forward: 5'- ACGTGGAAATCAACGGGATCA -3'*	152
	Reverse: 5'- GTTGGTATCCAGGGCTCTCC -3'	

Statistical Analysis

For the analysis of statistical results in this research, the Shapiro-Wilk test was used to examine the normal distribution of data in the studied groups. Descriptive data include mean and standard deviation. To investigate changes between the HC and LC groups, an independent t-test was used, and to examine the simultaneous effect of interventions, a two-way ANOVA test along with the Bonferroni post-hoc test was used. The significance level for all analyses was considered $p \leq 0.05$. Statistical analyses were performed using SPSS software version 22.

3. Results

Table 3. Mean and standard deviation of research data in the studied groups.

Group	TGF-β (Mean ± SD)
HC	1.00 ± 0.025
LC	2.44 ± 0.14
VC50	1.94 ± 0.02
VC100	1.63 ± 0.07
ST	1.76 ± 0.10
ST+VC50	1.12 ± 0.11
ST+VC100	1.05 ± 0.06

Before conducting the statistical analyses of the present study, the normality of the distribution and the normal status of the data were examined using the Shapiro-Wilk test, considering a significance level of $p \leq 0.05$. According to this test, the distribution is considered normal when the P-value is greater than the critical value at the 0.05 level. Given the reported significance level of $P \leq 0.05$, all variables in this research had a normal distribution. Furthermore, prior to the inferential analysis based on the research hypothesis, an independent t-test was conducted to examine the effect of disease induction on TGF-β, and the results are presented in Table 4. The results of this test showed that TGF-β levels in the LC group were significantly higher than in the HC group (P=0.001).

A significant difference was observed in P53 gene expression between the aerobic exercise group and the cannabis supplement group (P = 0.002), and a significant difference was also found between the aerobic exercise group and the aerobic exercise–cannabis supplement group (P = 0.001).

The lowest P53 gene expression in liver tissue was observed in the supplemented group. The interaction between these two interventions was not statistically significant. For clarity, Figure 2 is presented.

Table 4. Independent t-test for comparing the HC and LC groups.

Indicator	t	df	p-value
TGF-β	-24.26	10	0.001

To examine the interactive and simultaneous effect of these two interventions, the results of the two-way analysis of variance (ANOVA) are presented in Table 5. The results of this test showed that vitamin C did not have a significant effect on changes in TGF-β in the lung tissue of laboratory mice with lung cancer (P=0.059, F=3.05, effect size=0.14). However, swim training had a significant effect on reducing TGF-β in the lung tissue of laboratory mice with lung cancer (P=0.002, F=11.13, effect size=0.23). Furthermore, the interaction between swim training and vitamin C supplementation on reducing TGF-β levels was significant (P=0.028, F=3.97, effect size=0.10).

Table 6. Results of the two-way analysis of variance for examining the simultaneous effect of swim training and vitamin C on TGF-β levels in the lung tissue of mice with lung cancer.

Source	Sum of Squares	df	Mean Square	F	p-value	η²
VC	1.109	2	0.555	3.05	0.059	0.14
ST	2.021	1	2.021	11.13	0.002	0.23
ST*VC	1.441	2	0.721	3.97	0.028	0.18

Furthermore, to determine the type of effect of exercise on TGF-β, the results of the Bonferroni post-hoc test in Table 7 showed that TGF-β levels in the ST groups were significantly higher than in the non-exercise groups (P=0.002).

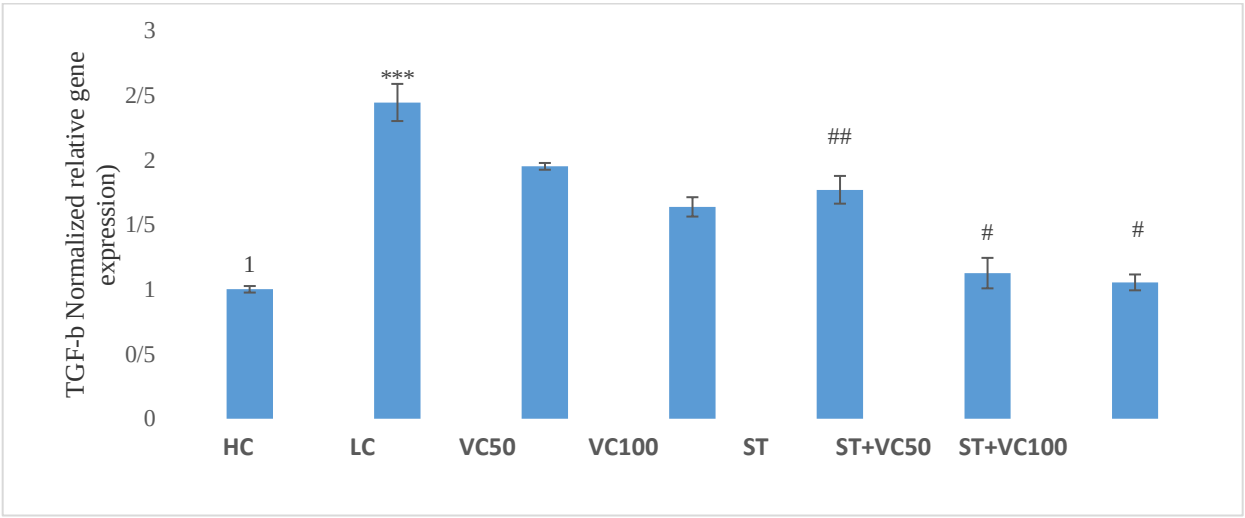
Table 8. Results of the Bonferroni post-hoc test for examining the effect of exercise on the research variables

Contrast	Mean Difference	Std. Error	Significance Level
ST vs. Non-Training	-0.45	0.13	0.002

Furthermore, given the significant interactive effect of exercise and vitamin C on the variables, the results of the Bonferroni post-hoc test and mean comparisons are presented in Table 8. In this table, cell A represents the diseased control group, cell B represents vitamin C at a dose of 100 mg/kg, cell C represents vitamin C at a dose of 50 mg/kg, cell D represents the exercise group, cell E represents exercise + vitamin C at a dose of 100 mg/kg, and cell F represents exercise + vitamin C at a dose of 50 mg/kg. The results show that the lowest TGF-β value belongs to the exercise + vitamin C 100 mg/kg group (1.05), followed by exercise + vitamin C 50 mg/kg (1.12), vitamin C 100 mg/kg (1.63), exercise (1.76), and vitamin C 50 mg/kg (1.95), respectively.

Comparing these means indicates that exercise and vitamin C at 50 mg/kg have an increasing effect on TGF-β, whereas vitamin C at 100 mg/kg leads to a decrease in the expression of this gene. Thus, the results suggest that vitamin C can modulate the effect of exercise on increasing TGF-β. Therefore, although exercise has an increasing effect on TGF-β expression, the combination of exercise with vitamin C, especially at the 100 mg/kg dose, interactively contributes to the reduction of TGF-β expression. For a better understanding of the subject, the results are presented in Chart 1.

Chart 1. TGF-β expression levels in the lung tissue of laboratory mice with lung cancer across different experimental groups.



*** (P=0.001) significant increase compared to the HC group; ## (P=0.01) and # (P=0.05) significant decrease compared to the BZP group; Vitamin C can modulate the effect of exercise on the increase of TGF-b. Therefore, although exercise has an increasing effect on the expression of TGF-b. However, the combination of exercise with vitamin C, especially at a dose of 100 mg, has an interactive role in reducing the expression of TGF-b.

4. Discussion

The findings of this study demonstrated that the induction of lung cancer with Benzo[a] pyrene (BaP) led to a significant increase in TGF-β expression in the lung tissue of the group LC compared to the HC (P=0.001). This result aligns with the well-established role of TGF-β in lung cancer progression, particularly in advanced stages where this cytokine acts as a pro-tumor factor by inducing EMT and metastasis [6].

The ST intervention alone resulted in a significant decrease in TGF-β levels compared to the LC group (P=0.002). This finding is consistent with previous studies indicating that aerobic exercise can modulate pro-tumorigenic signaling pathways, including TGF-β [10, 11]. For instance, Li et al. (2022) reported that swim training suppresses angiogenesis and tumor growth by inhibiting the HIF-1α/VEGF pathway [12]. Given the overlapping signaling pathways of HIF-1α and TGF-β [7, 28], it is probable that swim exercise reduced TGF-β expression by influencing these axes. Furthermore, exercise may prevent excessive activation of the TGF-β pathway by improving the tumor immune environment and reducing inflammation [10].

Regarding vitamin C supplementation, although its main effect on TGF-β independently was not significant (P=0.059), comparative analysis between groups revealed that VC100 significantly decreased TGF-β expression compared to the LC group. This effect could stem from vitamin C's role in inhibiting HIF-1α [16] and aiding p53 stabilization [20], both of which are considered negative regulators of the TGF-β pathway [6, 7]. The study by Zeng et al. (2019) also showed that high-dose vitamin C can inhibit EMT in breast cancer cells [19], likely through modulation of TGF-β signaling. However, the reducing effect of VC50 was lesser, indicating a dose-dependent effect of the vitamin [15, 29].

A key highlight of this study was the significant interactive effect between swim training and vitamin C supplementation on reducing TGF-β levels (P=0.028). The lowest levels of TGF-β expression were observed in the combination groups (ST+VC100 and ST+VC50). This finding suggests a synergistic effect between the two interventions. It appears that exercise and vitamin C exert their influence through complementary and synergistic mechanisms on shared pathways. Exercise, by improving blood flow and tissue permeability,

might enhance the bioavailability of vitamin C to tumor cells [30-32]. On the other hand, vitamin C, by reducing oxidative stress induced by both exercise and cancer, may create a more optimal environment for the anti-tumor effects of exercise [9, 17]. Moreover, both interventions independently can inhibit key factors like HIF-1α [12, 16], and their combination might potentiate this inhibition, consequently suppressing pro-tumorigenic TGF-β signaling more effectively.

۵. Conclusion

This study demonstrated that the combination of 12-week swim training with vitamin C supplementation, particularly at a dose of 100 mg/kg, synergistically led to a significant reduction in TGF-β expression in the lung tissue of mice with lung cancer. This combined protocol may be considered as a promising complementary therapeutic strategy for the management of lung cancer.

Acknowledgements

The results presented in this work have been taken from a student's thesis. We appreciate the department of exercise physiology of Islamic Azad University, Shiraz branch.

Funding

This study did not have any funds.

Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: Z.SH, S.A.H, M.M ; Methodology: Z.SH, S.A.H, M.M ; Software: Z.SH, S.A.H, M.M; Validation: Z.SH, S.A.H, M.M.; Formal analysis Z.SH, S.A.H, M.M ; Investigation: Z.SH, S.A.H, M.M ; Resources: Z.SH, S.A.H, M.M ; Data curation: Z.SH, S.A.H, M.M ; Writing - original draft: Z.SH, S.A.H, M.M ; Writing - review & editing: Z.SH, S.A.H, M.M; Visualization: Z.SH, S.A.H, M.M ; Supervision: Z.SH, S.A.H, M.M ; Project administration: Z.SH, S.A.H, M.M; Funding acquisition: Z.SH, S.A.H, M.M.

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