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Research Article

Review the effect of eight weeks of aerobic training with gallic acid on tumor necrosis factor alpha and nuclear transcription factor kappa B in prostate tissue of rats with prostate cancer

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Abstract

Introduction: Increased inflammation in cancer-prone tissue can lead to faster progression and damage to that tissue. Although the role of exercise and antioxidants in cancer improvement has been reported, their interactive effect is not yet well understood. Therefore, the aim of the present study was to investigate the effect of eight weeks of aerobic training (AT) with gallic acid (GA) on tumor necrosis factor alpha (TNF-α) and nuclear transcription factor kappa B (NF-kB) levels in prostate tissue of rats with prostate cancer (PC).

Methods: 40 male rats (age 10- 12 months and weight 260- 300 g) with prostate cancer (with the LNCaP cell line) were randomly assigned to the following groups: 1) cancer control (PCa), 2) sham (solvent of GA/(Sh)), 3) GA, 4) AT, and 5) AT+GA. Also, to investigate the effect of PC induction on the research variables, 8 healthy rats were assigned to the healthy control (HC) group. The AT groups ran three sessions per week at an intensity of 15 m/min on a 15 degree incline for 30-60 minutes for eight weeks. The GA groups also consumed daily 20 mg/kg GA orally.

Results: The results showed that in the AT, GA and AT+GA groups, the levels of TNF-α and NF-kB were significantly lower than PCa group. The levels of TNF-α and NF-kB in the AT group were significantly lower than GA group. Also, in the AT+GA group, they were significantly lower than AT and GA groups.

Conclusion: It seems that although AT and GA alone have a reducing effect on some inflammatory markers. However, these two (AT and GA) can enhance each other's effect on reducing inflammatory markers in prostate tissue following PC.

Keywords:
Exercise, Gallic Acid, Inflammation, Prostate Cancer

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1. Introduction

Prostate cancer (PCa) is known as the second most common cancer in men worldwide. Data show that the number of these patients has increased from 13.69 per 100,000 in 1990 to 15.37 per 100,000 in 2021. It is predicted that by 2040 the number of people with this disease will almost double. In other words, although the number of deaths from this disease has decreased with the progress of medical science; however, due to the increase in the aging population, the increase in environmental factors continues to increase the number of new people with this disease to the extent that it is considered a social problem (Chu, 2025). Data show that with increasing age and genetic characteristics of people, metastasis occurs in prostate cells; In other words, changes in the function of lymphocytes and monocytes following PCa can generate infiltrating cells and ultimately lead to tumorigenesis (Nowroozi, 2017; Donate-Moreno, 2020). More specifically, it seems that the increase in M1 macrophages can increase the activation of nuclear transcription factor kappa B (NF-kB); this transcription factor, upon translocation to the nucleus, can lead to the transcription of inflammatory factors such as tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1b), and ultimately expose the prostate tissue to necrosis and apoptosis (Driscoll, 2025). -On the other hand, researchers have shown that regular and long-term exercise has long been used as a suitable solution for chronic diseases, including cancer. In such a way that increasing the level of physical activity reduces the risk of cancer and plays a role in improving the quality of life of these patients (Webber, 2024). It is believed that regular physical activity can be effective in reducing inflammation and oxidative stress. It has been reported that aerobic exercises for eight weeks and five sessions per week can lead to a decrease in pro-inflammatory cytokines such as TNF-α, NF-κB, IL-6 and lipid peroxidation in rats with PCa (Veras, 2023). In another review study, researchers also stated that long-term exercise can lead to a decrease in oxidative stress and an increase in antioxidant capacity in prostate cancer (Rebillard, 2013). Also, in a study, researchers showed that regular and long-term exercise can lead to modulation of extracellular signal-regulated kinase 1/2 (ERK1/2) in patients with PCa (Liu, 2025). In a study, researchers also showed that high-intensity interval training (HIIT) can lead to reduction of TNF-α and IL-6 in an X-ray-exposed cancer model (Parastesh, 2022). Although the favorable role of physical activity in improving inflammation in PCa has been clearly demonstrated, in practice, it seems that due to the progressive nature of this disease, there is not enough time to benefit from sports activities. Therefore, researchers in the field of sport nutrition are using natural antioxidants for better efficiency. One of these antioxidants is gallic acid (GA). GA is a polyphenol found in plants such as tea, grapes, berries and other fruits that has beneficial effects on stopping carcinogenesis in various tissues (Verma, 2013). It is believed that GA can be beneficial in cancer through several mechanisms. In such a way that phenolic compounds in GA can be beneficial in cancer, including PCa, by inhibiting cell migration, metastasis, modulating apoptosis, regulating the cell cycle, improving angiogenesis and modulating the expression of oncogenes (Jiang, 2022). Studies have been conducted in this field. For example, a study showed that GA consumption could lead to increased expression of anti-inflammatory cytokines IL-4, IL-10, decreased IL-1, IL-6, IL-12, IL-17, IL-23, TGF-β and TNF-α in a TNBS-induced ulcerative colitis model (Zhu, 2019).

In addition, another study reported a decrease in the expression of NF-kB, TNF-α and TGF-β in cisplatin-induced liver injury (Saif-Elnasr, 2023). Given the favorable role of exercise and GA in improving inflammatory factors in cancer, a review of past studies shows that an effective treatment method that can provide the best treatment method in these patients is still not well known. In addition, it seems that, given the limitations of long-term studies and the long-term effects of exercise, it seems that combining exercise with natural antioxidants can provide researchers with a more favorable treatment method. Given the limited information regarding the combination of exercise and GA on inflammatory markers, the present study was conducted to investigate the simultaneous effect of eight weeks of aerobic training (AT) combined with GA consumption on TNF-α and NF-kB in prostate tissue of rats with PCa.

2. Materials and Methods

In this experimental study, 42 Wistar rats were purchased from the Pasteur Laboratory Animal Breeding and Reproduction Center in Tehran; then, these animals were kept in the Fundamental Exercise Physiology Laboratory of Pishtazan Institute of Higher Education in Shiraz for one week to adaptation to the new environment. It is worth noting that all ethical issues regarding work with laboratory animals in this study were conducted in accordance with the Helsinki Rules and under the supervision of the Biomedical Research Ethics Committee of Marvdasht University (with ethics code IR.IAU.M.REC.1403.494). Rats were kept in standard conditions in terms of light, temperature 22- 24 degrees Celsius, relative humidity 55- 60 percent, 12-hour light and 12-hour dark cycle, in transparent, washable polycarbonate cages with free access to water and special animal food.

Induction of PCa disease

To induce PCa in rats, first, LNCaP and TSP-1-EnSCs cell lines were ordered from the Pasteur Institute of Iran under standard conditions and appropriate culture medium containing all nutrients for cell life; then, the cells were propagated and maintained in 1640 RPMI supplemented with 5% FBS manufactured by Life Technologies, Canada. Then, to prepare a solution for injection into the prostate gland, 1 × 6 × 10 LNCaP cells were suspended in 75 μl of 1640 RPMI, 5% FBS, and 75 μl of Matrigel (Collaborative Biomedical Products, Bedford, Massachusetts). Then, the rats were anesthetized using a combination of *ketamine* and *xylazine*, a transverse incision was made at the bottom of the abdominal cavity. After cutting the superficial and deep muscles, the abdominal muscles were cut, and the bladder and seminal vesicles were released through the incision to expose the dorsal lobe of the prostate. The prepared suspension was then carefully injected into the subcutaneous space on the right side of the prostate through a Hamilton gauge needle. Then, 4-0 absorbable sutures manufactured by Supa Company, Iran, were used to close the wound. Also, during the research period and after surgery, OTC solution was used to disinfect the suture site (MC Klogh et al., 2013). Subsequently, 35 rats with prostate cancer were randomly divided into groups 1) patient control (PCa), 2) sham (salvage gallic acid), 3) GA, 4) AT, and 5) AT + GA. Also, to investigate the effect of prostate cancer induction on the research variables, 7 healthy rats were placed in the healthy control group.

Training protocol

First, the PCa rats were familiarized with a treadmill specifically for rats and exercise for one week. The familiarization was that the rats ran on a treadmill without an incline for 10 minutes a day during this one week. Then, according to the study of McClugh et al., (2013); the PCa rats ran on treadmill for 60 minutes a day at a speed of 15 meters per minute on a 15-degree incline. It is worth noting that the training was conducted for eight weeks and three sessions per week. Also, to comply with the principle of overload, the training was 30 minutes in the first to fourth weeks and increased to 60 minutes from the fourth to eighth weeks (McClugh et al., 2013).

Preparation of Gallic Acid

Gallic acid in the present study purchased from Sigma-Aldrich, USA. Then, 20 mg/kg of GA was dissolved in food and water flavoring daily and fed to rats (Ojo et al., 2023).

Dissection and sampling

Finally, 48 hours after the last training session and in a 12-hour fasting state, rats were anesthetized using a combination of *ketamine* (55 mg/kg) and *xylazine* (25 mg/kg); to ensure anesthesia and analgesia, pain detection tests such as squeezing the tail, hind limbs, and gentle tapping on the abdomen of rats were used. Lack of response to these tests was considered a sign of complete analgesia and anesthesia. Subsequently, the abdominal cavity of the rats was opened with a size 20 surgical blade, and after removing the connective tissues, the prostate tissue of the rats was carefully extracted. The prostate tissue was immediately placed in special tissue preservation microtubes and immersed in a nitrogen tank for 10- 15 minutes. After immersion in the nitrogen tank, the tissues were transferred to a temperature of -80°C.

Gene expression assay

In this study, TNF-α and NF-kB levels were measured using qReal Time PCR. For this purpose, a small amount of homogenized tissue was first used for RNA synthesis; RNA synthesis in this study was performed using the FavorPrep™ Tissue Total RNA Kit with catalog number (FATRK 001) made in Taiwan. Next, to assess the percentage of RNA purity, a spectrophotometric method with a wavelength of 260 nm used, and if the concentration was desirable, the samples used for cDNA synthesis using the Thermo Scientific Fermentase Kit with catalog number (K1621); then the samples combined with pre-designed primers whose efficiency has been previously evaluated on the PUBMED site, and then the samples placed in the Real Time PCR machine with Step One bread made in Italy. At the end of the various temperature and time cycles of the device, the variable values along with the internal control gene Total Binding Protein (TBP) evaluated based on the threshold cycle (Ct). Finally, the formula 2 - ΔΔCt used to quantify the data.

Table 1. Sequences of primers used in the study

Genes	Primer Sequences	Sizes (bp)
TBP	*Forward: 5'-GCGGGGTCATGAAATCCAGT-3'*	*147*
	Reverse: 5'-AGTGATGTGGGGACAAAACGA -3'	
NFKB	*Forward: 5'-AGGCCATTGAAGTGATCCAG -3'*	*128*
	Reverse: 5'-GAGCTCATCTATGTGCTGTCTT -3'	
TNF-α	Forward: 5'- ATGGGCTCCCTCTCATCAGT-3'	106
	Reverse: 5'- GCTTGGTGGTTTGCTACGACG-3'	

Statistical analysis

In the descriptive statistics section, data were presented based on mean and standard deviation. Also, the Shapiro-Wilk test was used to check the normality of the data distribution. Then, considering the normality of the data distribution, one-way analysis of variance test was used to check the difference between groups, and to determine the location of the difference between groups, Tukey's post hoc test was used in SPSS software version 22 and a significance level of 0.05.

3. Results

The results of one-way ANOVA test showed that there was a significant difference in the levels of TNF-α (P=0.001 and F=133.89) and NF-kB (P=0.001 and F=65.612) in the study groups. The results of Tukey's post- hoc test in Figure 1 showed that the levels of TNF-α in the PCa (P=0.001) and Sham (P=0.001) groups were significantly higher than the HC group. Also, in the PCa group, it was significantly higher than Sham group (P=0.009). But in the GA (P=0.001), AT (P=0.001) and AT+GA (P=0.001) groups, it was significantly lower than the PCa group. Also, in the AT (P=0.001) and AT+GA (P=0.001) groups, it was significantly lower than the GA group. In addition, in the AT+GA group, it was significantly lower than AT group (P=0.001).

The levels of NF-kB in the PCa (P=0.001) and Sham (P=0.001) groups were significantly higher than HC group. It was also significantly higher in the PCa group than Sham group (P=0.001). But in the GA (P=0.001), AT (P=0.001) and AT+GA (P=0.001) groups, it was significantly lower than PCa group. It was also significantly lower in the AT (P=0.001) and AT+GA (P=0.001) groups than GA group. In addition, in the AT+GA group, it was significantly lower than AT group (P=0.001) (Figure 2).

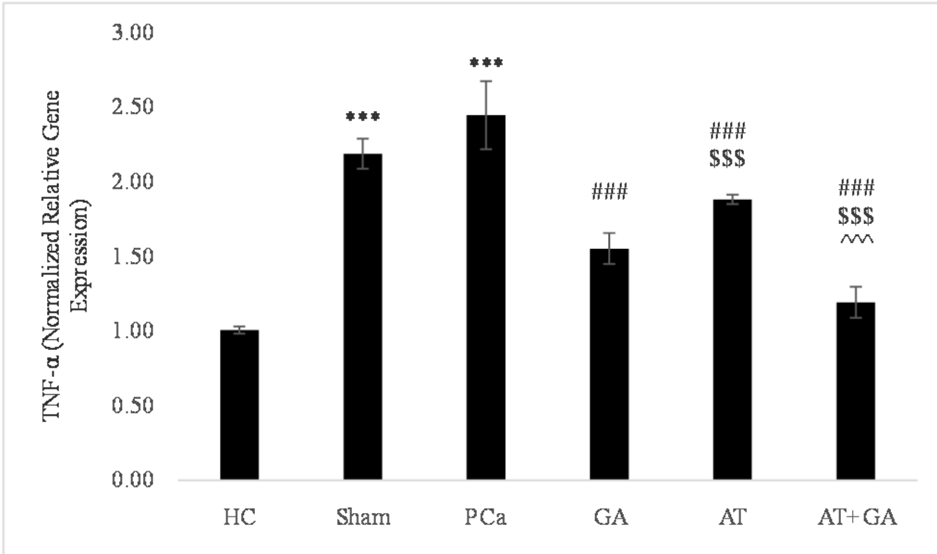

Figure 1. TNF-α gene expression levels in prostate tissue of rats in the studied groups
*** (P=0.001) significant increase compared to HC group; ### (P=0.001) significant decrease compared to PCa group; $$$ (P=0.001) significant decrease compared to GA group; ^^^ (P=0.001) significant decrease compared to AT group

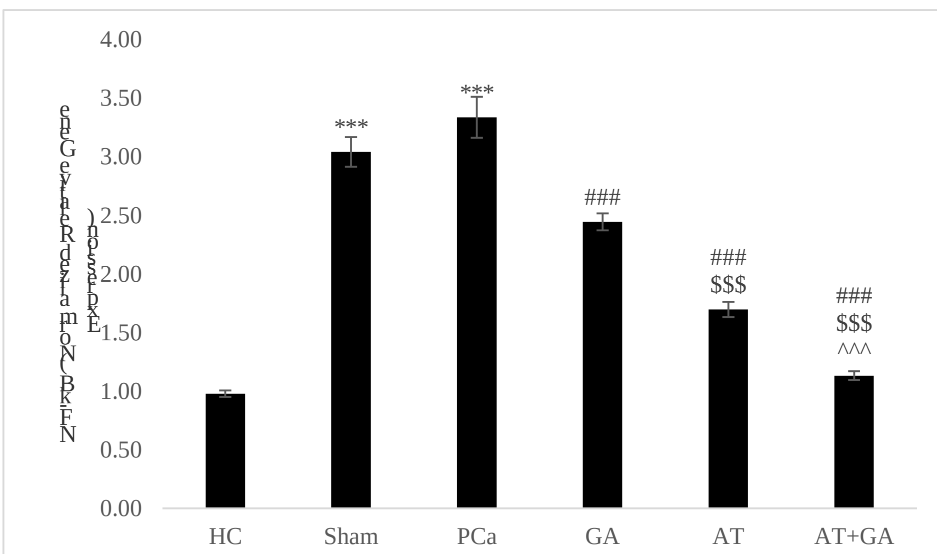

Figure 2. NF-kB gene expression levels in prostate tissue of rats in the studied groups

*** (P=0.001) significant increase compared to the HC group; ### (P=0.001) significant decrease compared to the PCa group; $$$ (P=0.001) significant decrease compared to the GA group; ^^^ (P=0.001) significant decrease compared to the AT group

4. Discussion

The results showed that in the AT group, the levels of TNF-α and NF-kB were significantly lower than PCa group. The data show that long-term exercise can play a role in cancer through various mechanisms. However, in relation to the effect of exercise specifically on inflammatory factors, it seems that regular and long-term exercise can improve the function of regulatory cells by down-regulating membrane metalloprotease 1 (MCP-1), granulocyte-colony stimulating factor (G-CSF) and Flt-3 ligand, T cells and natural killer cells, regulating and modulating CD8+ cells, leading to improved function of regulatory cells. This ultimately leads to the modulation of M1 and M2 type macrophages. Finally, inflammatory and anti-inflammatory factors are modulated following exercise. Finally, these events result in a reduction in tumor volume in cancers such as breast cancer and PCa (Sun, 2025). In addition, a review study stated that regular exercise can lead to increased release of inflammatory factors such as IL-6 and TNF-α from skeletal muscles. These two factors then attack cells that are metastasizing and can activate apoptosis mechanisms in them. Therefore, another mechanism of tumor volume reduction following exercise could be apoptosis induction (Chen, 2025). Studies have been conducted in this field. For example, in a study conducted on men with colon cancer; the results showed that intense and moderate exercise led to improved quality of life, reduced tumor volume, and improved exercise performance; intense exercise for 12 weeks had no significant effect on reducing hs-CRP and sTNFαR2. While moderate to low intensity aerobic exercise led to a decrease in hs-CRP (Brown, 2025). In another study, researchers showed that regular exercise could lead to inhibition and reduction of platelet-stimulating factor 4 and ultimately inhibition of metastasis in CT26 cancer cells induced in an animal model (Tobias, 2023). Also, in a study, researchers showed that regular exercise can lead to inhibition of metastasis and tumorigenesis by suppressing the expression of NF-κB (Ji, 2025). Therefore, it seems that exercise can play a role in reducing inflammation and tumor inhibition both by the mechanism of effect on tumors and by the mechanism of effect on myokines.

The results showed that in the GA group, the levels of TNF-α and NF-kB were significantly lower than PCa group. GA, with the chemical formula 3, 4, 5-trihydroxybenzoic acid, can act as a potential phenolic compound and a strong antioxidant. In other words, in addition to antioxidant effects, it can control the cell cycle by regulating the cell cycle, up-regulating cyclins D and E. Also, GA, by the mechanism of down-regulating cyclooxygenases, can lead to a decrease in the activity of M1-type macrophages. This pathway ultimately leads to a decrease in NF-kB expression and protects tissues from inflammation induction and tumor growth. In addition, GA seems to lead to cancer cell death by the mechanism of increasing TNF-α-dependent apoptosis (Verma, 2013). In line with the present study, researchers showed that the consumption of 100 mg/kg GA can lead to a decrease in NF kB, TNF α, TGF β and improve liver function in conditions of liver injury with cisplatin (Saif-Elnasr, 2023). Also, in another study, researchers showed that GA can lead to a decrease in oncogenes and ultimately inhibit metastasis by inducing apoptosis in cancer cells (Jiang, 2022). In another study, researchers showed that GA and its components can lead to an improvement in the expression of cell cycle regulatory genes such as P75, P53 and P21. In addition, a decrease in cyclooxygenase 2 and inflammatory factors was also another effect of GA (Kang, 2025).

The results also showed that in the AT+GA group, TNF-α and NF-kB levels were significantly lower than PCa group. Studies show that, although limited studies have been conducted on the simultaneous effect of exercise and GA on oxidative stress and inflammation, the simultaneous effect of these two interventions on inflammatory markers in prostate tissue following cancer induction has not been investigated. However, according to studies, it seems that aerobic exercise, by down- regulating MCP-1, G-CSF and Flt-3 ligand, regulating CD8+, and modulating M1 and M2 macrophages, leads to a reduction in inflammatory factors from the intrinsic pathway of cancer cells (Sun, 2025). Also, exercise activates the apoptosis mechanism in them by increasing IL-6 and TNF-α from skeletal muscles and their transfer to tumors (Chen, 2025). On the other hand, GA, by regulating the cell cycle, regulating the reduction of cyclooxygenases, and reducing the activity of M1 macrophages, ultimately leads to a decrease in the expression of NF-kB and TNF-α (Verma, 2013). The indications are that both have anti-inflammatory effects from the same pathways. In one study, the results showed that GA can suppress exercise-induced inflammation, and finally, both can have favorable effects on increasing antioxidant capacity in the muscle in combination (Yu, 2025). In another study, researchers showed that curcumin and exercise have a strong synergistic effect in inhibiting cancer (Pang, 2025). In addition, in present study the levels of TNF-α and NF-kB in the AT group were significantly lower than GA group. It seems that the threshold for stimulating the expression of anti-inflammatory factors and more pathways within the tumor tissue and the myokine pathway that are more activated after exercise are among the reasons for the effect of exercise on reducing inflammatory factors (Sun, 2025; Chen, 2025); Although the effect of GA also seems to be dose-dependent and was not investigated in this study. However, since it was significantly lower in the AT+GA group than AT and GA groups, it seems that these two interventions can enhance each other's effects in reducing inflammatory factors. Given the more favorable effect of exercise compared to GA, it seems that the lack of investigation of different doses of GA along with exercise is a limitation of the present study. Therefore, it is suggested that different doses be compared in future studies. Considering the antioxidant role of GA and the contrasting effects of exercise on inflammation and oxidative stress, it seems that the lack of evaluation of these markers is another limitation of the present study. Therefore, it is suggested that more related pathways be evaluated in future studies. Given the need to prove changes in tumorigenic and pathological studies, the lack of evaluation of prostate tissue pathology was another limitation of the present study. Therefore, it is suggested that pathology and physiologic studies be evaluated together in future studies.

۵. Conclusion

It seems that although AT and GA alone have a reducing effect on some inflammatory markers, the two (AT and GA) can enhance each other's effect on reducing inflammatory markers in prostate tissue following PCa.

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

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