Research Article

Aerobic exercise and cannabidiol supplementation modulate prostate Akt gene expression in high-fat diet-fed rats: Mechanistic insights into obesity-driven prostate cancer risk

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Abstract

Epidemiological evidence indicates that obesity is associated with accelerated prostate cancer progression and elevated mortality rates. However, the underlying physiological mechanisms linking obesity to prostate cancer pathogenesis remain unclear. This study aimed to examine the effects of six weeks of moderate-intensity aerobic training combined with cannabidiol (CBD) supplementation on prostate protein kinase B (Akt) gene expression in high-fat diet (HFD)-induced obese male rats. Forty male Wistar rats (240 ± 20 g) were randomly assigned to five experimental groups: healthy control, HFD, HFD+exercise, HFD+CBD, HFD+exercise and CBD (n=8 per group). CBD was administered via oral gavage at 100 mg/kg, five days per week for six weeks. The aerobic exercise protocol consisted of treadmill running at progressive intensities, ranging from 15 m/min for 30 min to 27 m/min for 60 min, five days per week for six weeks. Following the intervention, prostate tissue was extracted for quantitative analysis of Akt gene expression. Statistical analysis revealed that aerobic exercise significantly modulated Akt gene expression (P=0.015). Similarly, CBD administration exerted a significant effect on Akt expression (P=0.004). However, no significant interactive effect was observed between aerobic exercise and CBD (P=0.068). These findings suggest that both aerobic exercise and CBD independently influence Akt signaling pathways, potentially through anti-inflammatory mechanisms, which may contribute to prostate cancer prevention. Further research is warranted to elucidate the precise molecular interactions involved.

Key Words: Moderate-intensity aerobic exercise, Cannabis, Prostate, High-fat diet, Akt gene

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Introduction

Obesity represents a well-established risk factor for prostate cancer (PCa) progression and mortality, with epidemiological evidence consistently demonstrating poorer clinical outcomes among obese patients (Fujita et al., 2019; Saha et al., 2023). While associations between obesity and PCa incidence remain complex and occasionally contradictory (Wilson et al., 2022), a robust body of evidence confirms that obesity significantly elevates the risk of PCa-specific mortality. Data from the American Cancer Society's Cancer Prevention Studies indicate a 20–27% increase in PCa-related death among men with BMI >30 kg/m² compared to non-obese counterparts (Fujita et al., 2019).

The adverse impact of obesity on PCa outcomes manifests through multiple interconnected biological pathways. Adipose tissue dysfunction in obesity drives systemic hormonal dysregulation—characterized by hyperinsulinemia, altered insulin-like growth factor (IGF) axis signaling, disrupted sex hormone homeostasis, and elevated leptin—alongside chronic inflammation and insulin resistance (Fujita et al., 2019; Allott et al., 2013). These factors collectively foster a tumor-promoting microenvironment. Consequently, obese men diagnosed with PCa exhibit heightened risks of disease progression, metastatic dissemination, treatment-related toxicities, and mortality (Allott et al., 2013).

Central to obesity-associated oncogenesis is the constitutive activation of the PI3K-Akt-mTOR signaling axis. This pathway is frequently dysregulated in PCa, promoting tumorigenesis, disease advancement, and therapeutic resistance through its regulation of cell survival, proliferation, and metabolism (Pungsrinont et al., 2021). The complexity of this signaling network is amplified by its crosstalk with other oncogenic cascades—including androgen receptor (AR), MAPK, and WNT pathways—which influences PCa progression and modulates response to targeted therapies (Bitting & Armstrong, 2013; Rice et al., 2019; Zhu et al., 2022). Despite advances, the precise spatiotemporal dynamics of PI3K-Akt-mTOR signaling during a

prostate tumor initiation and progression require further elucidation (Edlind & Hsieh, 2014).

Lifestyle interventions targeting obesity, such as exercise and dietary modulation, represent promising strategies to attenuate PCa progression. Emerging evidence suggests these interventions may counteract obesity-driven molecular alterations, though mechanistic insights remain limited. Moderate-intensity aerobic exercise, in particular, demonstrates potential for improving metabolic health parameters relevant to PCa. Concurrently, phytocannabinoids like cannabidiol (CBD) exhibit pleiotropic anti-tumor properties, including modulation of inflammatory and survival pathways.

Therefore, this study investigates the combinatorial effect of six weeks of moderate-intensity aerobic exercise and CBD supplementation on prostate Akt gene expression—a pivotal node within the PI3K-Akt-mTOR cascade—in a high-fat diet (HFD)-induced obesity rat model. This approach aims to elucidate potential synergistic mechanisms by which these interventions may mitigate obesity-associated PCa risk.

Materials and methods

Animals

Forty male Wistar rats (aged 10 to 12 weeks, weighing 240±20 g) were obtained from the Pasteur Institute, Tehran, Iran. The animals were provided with water and a diet specifically formulated for rats, based on caloric requirements and nutrient composition. The subjects underwent a two-week acclimation period under laboratory conditions, maintained on a 12-hour light/dark cycle, at an average temperature of 22±2°C and humidity of 50±5%. The rats were housed in ten standard rodent cages, in accordance with the animal care checklist.

Animal diet

During the two-week acclimation, rats received a standard diet (2.5 kcal/g; 19.6% protein, 3% fat, 77.4% carbohydrates) ad libitum. Post-acclimation, rats were randomized into five groups (n=8/group) and housed in same-group cages (4 rats/cage; 10 cages total). Throughout the study, all groups received their respective diets ad libitum. Food consumption was monitored by weighing provided and leftover food per cage every 48 hours. Water intake was recorded daily at the cage level. Baseline water consumption averaged 100–120 mL/cage/day (~25–30 mL/rat/day). During the high-fat diet phase, water intake increased to 180–200 mL/cage/day (~45–50 mL/rat/day) in HFD groups, while the normal-diet control group maintained baseline intake. This study's procedures were carried out under the Declaration of NIH. Ethical approval was granted by the Islamic Azad University University Ethics Committee (IR.IAU.SRB.REC.1403.136).

High-fat diet

Animals were randomized into five groups (n=8/group): normal-diet control (ND), and four HFD groups. The ND group received standard chow (2.5 kcal/g; 19.6% protein, 3% fat, 77.4% carbs) ad libitum throughout the study. HFD groups received a formulated high-fat diet (40% kcal from fat, 3.87 kcal/g; 19.6% protein, 40% fat, 40.4% carbs) ad libitum for 4 months to induce obesity. Obesity and metabolic dysfunction were validated by: Significantly higher body weight gain in HFD vs. ND ($p<0.01$). Rats were housed in same-group cages (4 rats/cage). Body weight was recorded weekly using a 0.1g-precision scale during HFD feeding and intervention periods.

Moderate-intensity aerobic training

Prior to the intervention, all rats underwent a 5-day treadmill adaptation protocol (10 min/day at 10 m/min, 0° incline) to minimize stress. The subsequent 6-week moderate-intensity aerobic training regimen consisted of treadmill running 5 days/week while maintaining continuous HFD feeding, with exercise intensity calibrated to 60–70% VO2max (validated by gas analysis in pilot cohorts). Training duration and velocity progressed weekly as follows: Week 1 at 15 m/min for 30 min; Week 2 at 18 m/min for 35 min; Week 3 at 21 m/min for 40 min; Week 4 at 23 m/min for 45 min; Week 5 at 25 m/min for 50 min; and Week 6 at 27 m/min for 60 min. Each session incorporated standardized 5-min warm-up and cool-down phases at 10 m/min (0° incline). Rats exhibiting reluctance received gentle prodding to maintain running compliance, with exclusion criteria set at >3 missed sessions/week (no exclusions occurred during the study).

Cannabidiol (CBD) supplementation

A hydroalcoholic extract of Cannabis sativa L. leaves was prepared via percolation using 70% (v/v) ethanol as the solvent. Plant material was procured in collaboration with the Faculty of Pharmacy, University of Tehran, and dried under light-protected, desiccated conditions. The resultant extract was concentrated using a rotary evaporator (45°C, 50 rpm) to remove residual solvent, followed by further dehydration under vacuum. The final extract was stored in amber glass at −20°C until use. For in vivo administration, CBD (100 mg/kg body weight) was delivered via oral gavage once daily for six weeks. In vitro applications required dilution of the extract in ethanol-distilled water (1:9 v/v). Cytotoxicity profiling and optimal non-cytotoxic dosing for cell studies were determined using the MTT assay.

Laboratory measurements

Intraperitoneal administration of ketamine (100 mg/kg) and xylazine (5 mg/kg) was performed in a total volume of 2 mL, facilitating anesthesia, cardiac blood collection, and prostate tissue sampling over an eight-hour period under veterinary super-

Table 1. Primer sequences.

Gene	Sequence	Length	Tm
Akt	F:5'-CATTGCTGACAGGATGCAGAAGG-3'	23	62.04
	R: 5'-TGCTGGAAGGTGGACAGTGAGG-3'	22	64.17
GAPDH	F: 5'-CGGGAAGACAATAACTGCACCC-3'		
	R: 5'-CGGTTAGCAGTATGTTGTCCAGC-3'		

-vision. Tissue samples were washed with physiological serum and stored at -80°C for gene expression analysis.

Gene expression analysis

Primers, designed by a genetics expert and synthesized by Pishgam Company (preparation time ~1 week), consisted of a forward primer annealing to the 5' end of the sense strand and a reverse primer annealing to the 5' end of the antisense strand for PCR amplification. Potential secondary structures and primer dimers were assessed using Primer Express 3.0 software (Table 1), and primer sequences were verified by BLAST analysis.

Prostate tissue preparation and cDNA synthesis

Prostate tissue samples were prepared in advance. For cDNA synthesis, all reagents from the kit were removed from -20°C storage, and RNA samples were taken out from -70°C storage. After thawing, they were transferred onto ice. All reagents underwent brief vortexing and spinning before use. To prepare the RT mix, the necessary components—including RT buffer, RT enzyme, Oligo dT primers, and DEPC-treated water—were combined and distributed in 0.2 mL microtubes in 19 µL aliquots. The microtubes containing RT mix and RNA samples were placed in a thermal cycler or dry block heater for temperature cycling. The resulting cDNA samples were stored at -20°C until further analysis.

Statistical analysis

Descriptive statistics, including mean and standard deviation, were used to summarize the data. For inferential statistics, an independent t-test initially compared the normal diet control group and the high-fat diet control group to assess the effects of high-fat diet intake. Subsequently, one-way ANOVA evaluated differences between groups, with Bonferroni post hoc tests identifying pairwise differences. Effect sizes (Cohen's d) were calculated for each comparison. To examine interaction effects between aerobic training and cannabis supplementation, a two-way ANOVA was conducted. This model assessed: The individual effects of aerobic training and cannabis supplementation, their combined interaction effect on the measured outcomes. The significance threshold was set at $p < 0.05$. All analyses were performed in SPSS (v25).

Table 2. Shapiro-Wilk normality test results for Akt gene expression (n=8/group).

Groups	Sig
Control	0.555
HFD	0.641
HFD+AE	0.533
HFD+CBD	0.346
HFD+AE+CBD	0.300

All p>0.05 confirm normal distribution

Results

The normality test results using the Shapiro-Wilk test for Akt expression in the studied groups are presented in Table 2. Based on the t-test results, no significant difference was observed in Akt gene expression in prostate tissue between the normal diet control group and the high-fat diet control group (P = 0.599). This indicates that high-fat diet consumption did not lead to a significant reduction in Akt gene expression in prostate tissue (Figure 1).

Based on the two-way ANOVA results, aerobic training had a significant effect on Akt gene expression in prostate tissue (P = 0.015). Cannabis supplementation also had a significant effect on Akt gene expression in prostate tissue (P = 0.004). However, the interaction between aerobic training and cannabis supplementation did not show a significant effect on Akt gene expression in the prostate (P = 0.068) (Figure 2).

Discussion

Obesity is a significant risk factor for prostate cancer, and research suggests that excess body weight plays a role in both the development and progression of the disease (Freedland et al., 2008). The underlying mechanisms involve chronic inflammation, oxidative stress, and disruptions in metabolic path-

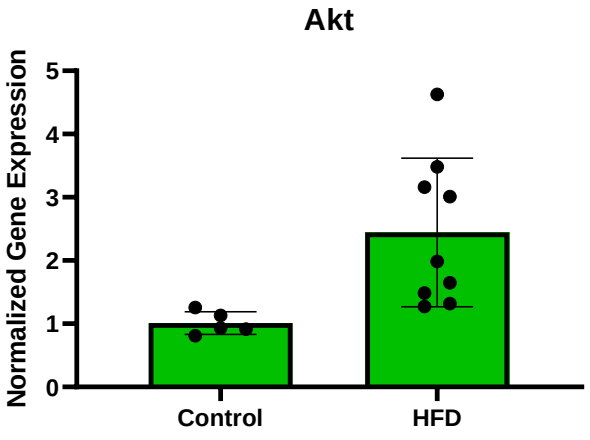

Figure 1. Akt gene expression in prostate tissue in the healthy control group and the group that fed with high-fat diet (HFD). Data were show as mean ± standard deviation.

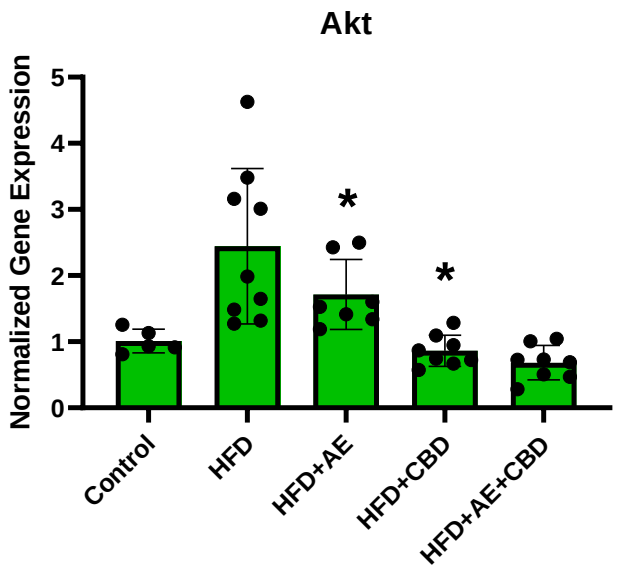

Figure 2. Akt gene expression in prostate tissue in the study groups. Data were show as mean ± standard deviation. * p<0.05. HFD: high fat diet, AE: aerobic exercise, CBD: Cannabidiol.

-ways, all of which contribute to carcinogenesis (Dharshini et al., 2023). Maintaining a healthy weight through diet and exercise may help reduce the risk of prostate cancer and improve prognosis in affected individuals. Thus, this study aimed to investigate the effect of six weeks of moderate-intensity aerobic training combined with cannabis supplementation on Akt gene expression in the prostate tissue of male rats fed a high-fat diet.

According to the findings of this study aerobic training had a significant effect on Akt gene expression in prostate tissue. Cannabis supplementation also had a significant effect on Akt gene expression in prostate tissue. However, the interaction between aerobic training and cannabis supplementation did not significantly affect Akt gene expression, though prolonged treatment might yield significance. Several studies have reported that moderate-intensity aerobic exercise significantly improves physical strength, total body fat reduction, general mental health, and blood pressure control, but it has no significant impact on fatigue, lean body mass, or overall physical health. Exercise appears to be an effective method for improving metabolic health in men with prostate cancer, with aerobic training emerging as the superior approach (Shankar et al., 2015). Furthermore, exercise has the potential to mitigate or even prevent many of the adverse effects associated with androgen deprivation therapy (ADT), ultimately improving survival rates for men with prostate cancer. The use of exercise as a management strategy for prostate cancer offers health and economic benefits, including improved quality of life and fewer complications, potentially reducing healthcare costs, enhancing productivity, and easing patient and caregiver burden (Ferlay et al., 2015). Consistent with this study, previous research has observed a positive association between increased physical activity levels and reduced prostate cancer-specific mortality and disease progression (Bolam et al., 2024). However, the molecular mechanisms underlying exercise-induced tumor suppression in prostate cancer remain largely unexplored.

Preclinical and clinical evidence highlights the beneficial effects of exercise on prostate tumor growth, identifying potential molecular mechanisms involved. It has been confirmed that physical training can reduce tumor growth and progression (Webber et al., 2024). Regarding CBD supplementation, studies indicate that CBD's effects on cell viability were not blocked by cannabinoid receptor antagonists, transient receptor potential vanilloid 1 (TRPV1) channel blockers, or G-protein-coupled receptor 55 (GPR55) agonists. This suggests that CBD operates independently of these targets in prostate cancer cells (Calheiros et al., 2024). Additionally, CBD reduced the invasiveness of highly metastatic PC-3 prostate cancer cells, while increasing E-cadherin protein expression. The ability of CBD to inhibit proliferation and invasion of prostate cancer cells indicates its potential as a future chemotherapy agent (O'Reilly et al., 2023). In alignment with the current study, other research has highlighted CBD's underlying anticancer mechanisms, which appear to be common across multiple cancer types. Studies assessing the efficacy and molecular mechanisms of CBD in cancer prevention and intervention in experimental models and clinical human trials confirm CBD's potential role in cancer therapy (Erzurumlu & Catakli, 2025; O'Brien, 2022).

Extensive research has indicated that prostate cancer (PCa) has a significant inflammatory component, with patients often being elderly individuals who exhibit weight-related disorders, most commonly obesity. Consequently, inflammation, particularly inflammatory complexes, may play a crucial role in the interaction between PCa and metabolic disorders. Researchers have discussed the potential role of each inflammatory component (sensors, molecular adaptors, and targets) in PCa pathophysiology, emphasizing the connection between inflammation and obesity and how these molecular complexes can serve as key mediators linking obesity and PCa (Pérez-Gómez et al., 2023). Furthermore, obesity is associated with high-grade and advanced prostate cancer. Although this relationship is likely multifactorial, studies suggest that obesity-induced inflammation may contribute to the progression of advanced prostate cancer. The obesity-associated microenvironment increases growth factors and pro-inflammatory cytokines, which mechanistically promote invasion, metastasis, and androgen-independent tumor growth. This review summarizes recent findings on obesity-induced inflammation, which may be linked to advanced prostate cancer. Moreover, it can introduce new therapeutic targets to mitigate prostate cancer

metastasis to bone, with a particular emphasis on the roles of interleukin (IL)-6, tumor necrosis factor (TNF) α, and IL-1β (Fujita et al., 2019).

The Akt gene encodes a serine/threonine kinase that regulates cell survival, proliferation, and metabolism. In obese individuals, chronic inflammation, elevated insulin levels, and increased adipokines (such as leptin) activate Akt via the PI3K/Akt/mTOR pathway. Overactivation of Akt promotes prostate cancer cell growth, inhibits apoptosis, and contributes to therapy resistance (Pungsrinont et al., 2021). Additionally, hormonal imbalances induced by obesity, such as elevated estrogen and reduced testosterone, may further stimulate Akt -driven oncogenic signaling. Studies indicate that prostate tumors in obese men often exhibit higher Akt activity, which correlates with poorer prognosis (Hashemi et al., 2023). Thus, targeting the Akt pathway in obese patients with prostate cancer could represent a therapeutic strategy to reduce obesity-related cancer progression. Both regular exercise and CBD oil supplementation have demonstrated potential in slowing prostate cancer progression, partly by modulating Akt signaling, a critical regulator of survival, proliferation, and metabolism. Akt hyperactivity is common in prostate cancer, contributing to tumor growth and resistance to apoptosis. Exercise activates AMPK, which inhibits Akt/mTOR signaling, thereby suppressing cancer cell proliferation and enhancing apoptosis (Rashid et al., 2011). Meanwhile, CBD oil exerts anti-tumor effects by interacting with cannabinoid receptors (CB1/CB2), leading to PI3K/Akt pathway suppression and increased oxidative stress in cancer cells. Both interventions may also reduce inflammation (via NF-κB downregulation) and improve immune surveillance. Combining exercise and CBD oil could synergistically target Akt -related oncogenic mechanisms, offering a complementary approach to prostate cancer management. Further research is required to optimize their therapeutic applications.

Conclusion

Six weeks of moderate-intensity aerobic exercise or CBD extract supplementation independently downregulated prostate Akt gene expression in a high-fat diet-induced obesity rat model ($P<0.05$ for each intervention). The absence of a significant interaction effect ($P=0.068$) suggests these interventions act through distinct mechanistic pathways rather than synergistically. Given Akt's established role as a critical regulator of the PI3K-Akt-mTOR oncogenic axis, this downregulation may attenuate obesity-associated pro-tumorigenic signaling. While these findings highlight the potential of exercise and CBD as modulators of molecular risk factors, direct extrapolation to prostate cancer prevention requires validation through:

1. In vivo tumor progression metrics (e.g., histopathology, proliferation indices)

2. Mechanistic studies confirming pathway modulation (e.g., p-Akt/Akt ratios, apoptosis assays)

3. Investigation of receptor-specific contributions (CB1/CB2 vs. TRPV1/GPR55)

Therapeutic application in humans necessitates further pharmacokinetic and efficacy studies in clinically relevant models.

What is already known on this subject?

Studies indicates that obesity is associated with accelerated prostate cancer progression and elevated mortality rates.

What this study adds?

Six weeks of moderate-intensity aerobic exercise or CBD extract supplementation independently downregulated prostate Akt gene expression in a high-fat diet-induced obesity rat model.

Organ Cross-Talk Tips:

- Exercise-induced hormonal and inflammatory changes in muscle and adipose tissue can indirectly reduce cancer-promoting signals to breast and prostate tissues.
- Aerobic exercise and cannabidiol may synergistically modulate metabolic and immune pathways, influencing gene expression in distant organs like the prostate.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study's procedures were carried out under the Declaration of NIH. Ethical approval was granted by the Islamic Azad University University Ethics Committee (IR.IAU.SRB.REC.1403.136).

Informed consent Animal study

Author contributions

Conceptualization: M.H.E., M.Gh., H.P.; Methodology: H.P., H.A.N.; Software: M.H.E., M.Gh.; Validation: H.P., H.A.N. Formal analysis: H.P., H.A.N.; Investigation: M.H.E., M.Gh.; Resources: M.H.E., M.Gh.; Data curation: M.H.E., M.Gh.; Writing - original draft: H.P., H.A.N.; Writing–review & editing: H.P., H.A.N.; Visualization: H.P., H.A.N.; Supervision: M.Gh.; Project administration: M.Gh.; Funding acquisition: M.H.E.

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