Research Article

The combined effects of resistance training and pineapple extract on intratumoral NF-κB, LIN28B, and systemic TNF-α in a murine melanoma model

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Abstract

This study investigated the effects of resistance training and pineapple extract consumption on intratumoral NF-κB and LIN28B gene expression and serum TNF-α levels in a murine C57 melanoma model. Twenty C57BL/6 mice were allocated into four groups (n=5/group): melanoma tumor control (MT), MT with resistance training (MT+RT), MT with pineapple extract (MT+PJ), and MT with combined intervention (MT+RT+PJ). The RT protocol and PJ administration (300 mg/kg/day via gavage) were conducted for six weeks' post-tumor induction. Serum TNF-α was quantified by ELISA, and tumor gene expression of NF-κB and LIN28B was analyzed via RT-PCR. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. All three intervention groups exhibited a significant downregulation of NF-κB and LIN28B gene expression in tumor tissue compared to the MT control group ($p<0.05$). Conversely, serum TNF-α levels were significantly elevated in the intervention groups relative to the control ($p<0.05$). Resistance training and pineapple extract consumption, both individually and in combination, significantly modulated pro-tumorigenic pathways by suppressing intratumoral NF-κB and LIN28B expression, despite an observed increase in systemic TNF-α.

Key Words: Resistance training; Pineapple extract; Melanoma; NF-κB; LIN28B; TNF-α; Cytokines; Mouse model.

Introduction

Melanoma is the most aggressive form of skin cancer, characterized by rapid progression, high metastatic potential, and poor prognosis. The tumor microenvironment, marked by chronic inflammation, plays a critical role in melanoma development and progression through complex interactions between tumor cells and inflammatory mediators (Amiri et al., 2005). Among key molecular drivers of melanoma malignancy are nuclear factor-kappaB(NF-κB) and LIN28B, both implicated in promoting tumor growth, invasion, and immune evasion by modulating gene expression networks (Ueda et al., 2006; Zhang et al., 2015). Elevated NF-κB activity enhances pro-inflammatory cytokine production such as tumor necrosis factor-alpha (TNF-α), which worsens tumor aggressiveness and supports tumor survival (Guarneri et al., 2017). Targeting these inflammatory signaling pathways has emerged as a promising therapeutic approach in melanoma research (Gewalt et al., 2023).

Exercise, particularly resistance training, has gained attention for its potential anti-cancer effects through modulation of systemic and tumor microenvironment inflammation. Physical activity is associated with improved immune function, reduced chronic inflammation, and favorable alterations in tumor metabolism and immune cell infiltration (Ceci et al., 2024; dos Santos et al., 2019). Exercise-induced activation of molecular pathways such as mTOR and metabolic reprogramming has been shown to hinder melanoma progression in preclinical models (Ceci et al., 2024). Moreover, physical activity can influence the expression of cytokines like TNF-α, which play dual roles in tumor biology by mediating both tumor-promoting and anti-tumor immune responses (dos Santos et al., 2019).

Pineapple extract, rich in bioactive compounds such as bromelain, has demonstrated notable anti-inflammatory and anti-cancer properties. Bromelain has been reported to inhibit key inflammatory pathways including NF-κB, reduce TNF-α levels, and induce apoptosis in various cancer models (Pezzani et al., 2023; Insuan et al., 2021).

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Studies evaluating pineapple extract in melanoma models have observed reductions in inflammatory mediators and tumor burden, suggesting that dietary interventions may complement conventional or physical activity-based therapies (Ordibehesht et al., 2020). However, the molecular mechanisms underlying pineapple extract effects on melanoma-specific inflammation and gene expression require further elucidation.

The crosstalk between exercise and nutritional interventions targeting pro-inflammatory factors in melanoma remains an emerging area of research. NF-κB and LIN28B are attractive biomarkers and therapeutic targets due to their integral role in melanoma pathogenesis by regulating oncogenic signaling and immune modulation (Guarneri et al., 2017; Zhang et al., 2015). TNF-α, a pleiotropic cytokine, is a key downstream effector and indicator of systemic inflammatory status in cancer (dos Santos et al., 2019). Investigating how resistance training combined with pineapple extract modulates these molecular and inflammatory markers in melanoma is important for developing integrated therapeutic strategies. We hypothesized that resistance training and pineapple extract consumption would individually reduce pro-tumorigenic signaling and that their combination would produce a synergistic effect, leading to a more potent downregulation of NF-κB and LIN28B gene expression and a greater modulation of serum TNF-α levels compared to either intervention alone. This study aims to investigate the effects of six weeks of resistance exercise and pineapple extract consumption on tumor NF-κB and LIN28B gene expression as well as serum TNF-α levels in melanoma-bearing C57 mice. Insight into these pathways may provide novel mechanistic evidence supporting lifestyle-based interventions to mitigate melanoma progression by targeting systemic and intratumoral inflammation

Materials and methods

Animals

In this experimental study, twenty male C57BL/6 mice aged six to eight weeks, with a weight range of 12 to 14 grams, were purchased from the Pasteur Institute to serve as the statistical sample and were transferred to the animal care facility at Baqiyatallah University of Medical Sciences Laboratory in Tehran. Following transfer, the mice were acclimated to the new laboratory environment for one week under controlled conditions: they were housed in groups of four in polycarbonate cages (20×27×47 cm) in a room maintained at an average temperature of 22±1.4°C, 55% humidity, and a 12:12 hour light-dark cycle. Throughout the study, all mice had free access to standard rodent chow, which was replenished every two days in the cage's mesh feeder, and unlimited water provided via 500 ml rodent bottles. Ethical and professional principles of animal care were strictly obser

observed; all handling and training were performed by a single individual, and procedures involving painless killing, surgery, and sampling were conducted in accordance with established ethical guidelines for laboratory animal research. This study received approval under the research ethics code IR.SSRC.REC.1401. 340 from the Azad University of Sciences and Research. Subsequently, the mice were randomly divided into four groups (n=5 per group): tumor control or melanoma tumor (MT), MT plus resistance training (RT), MT plus pineapple extract (PJ), and MT combined with both RT and PJ (MT+RT+PJ).

Cell line culture and tumor implantation (Melanoma)

The B16F10 melanoma cell line was procured from the Pasteur Institute of Iran cell bank. Cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. To establish tumor-bearing donor mice, tumor tissue was extracted from stock mice euthanized via cervical dislocation. The tumor area was sterilized with ethanol, and the tumor was aseptically dissected from the mouse's flank using forceps and scissors. The extracted tissue was then placed in a dish containing sterile phosphate-buffered saline (PBS). The tumor mass was minced into 2-3 mm^3 pieces using a scalpel blade. During this process, excess adipose tissue and vasculature were carefully removed to ensure the purity of the tumor fragments. These pieces were subsequently transferred to a sterile dish containing PBS for use in surgical implantation.

For the implantation surgery, mice were anesthetized with an intraperitoneal injection of a ketamine and xylazine mixture (prepared in a 2:1 ratio and diluted with sterile saline; total injection volume of 100 µl per mouse). Following the confirmation of profound anesthesia, mice were positioned laterally on a surgical board. A small incision was made in the shaved flank area using sterile instruments. A subcutaneous channel was then created using forceps. A single 2-3 mm^3 tumor fragment was implanted into the distal end of this channel. The incision was closed using surgical adhesive and a wound clip. Post-operatively, mice were housed individually in a temperature-controlled environment (25 °C) for recovery. The incision site was disinfected with povidone-iodine (betadine). Mice were monitored weekly for tumor growth. Throughout the study, mice were housed in polycarbonate cages (n=4 per cage) following a one-week acclimatization period in the facility. After acclimatization, mice were randomly assigned into four weight-matched groups. The research protocol was initiated one-week post-cancer cell injection, once palpable tumors were established (Dashti et al., 2014) (Table 1).

Supplement

The intervention utilized a dry ethanolic extract prepared from pineapple (Ananas comosus) parenchyma. Briefly, fresh fruit was

Table 1. Tumor weight at different groups of study (means)

groups	MT	MT+RT	MT+PE	MT+RT+PE
Means (g)	0.37	0.24	0.23	0.29

MT: Melanoma Tumor, RT: Resistance Training, PE: Pineapple extract

washed, peeled, and the parenchyma was sliced into thin rings. The rings were dried in a well-ventilated, shaded area at ambient temperature for 72 hours to prevent photochemical degradation and contamination. The dried material was then ground into a uniform powder using a mechanical grinder. For extraction, the cold-soaking method was employed. Seven grams of pineapple powder were mixed with 50 mL of 85% aqueous ethanol and stored at 4°C for 24 hours with occasional stirring. The mixture was then filtered, and the solvent was completely removed from the filtrate by evaporation in a water bath maintained at 37°C. The resulting dry extract was stored at -20°C until use. To standardize the bioactive content of the extract, the total bromelain activity was quantified using the casein digestion unit (CDU/mg) method (Gholamian et al., 2020). For the animal study, the dry extract was reconstituted in normal saline immediately before administration. The mice received the pineapple extract via oral gavage at a dose of 300 mg of dry extract per kg body weight. The control group received an equivalent volume of normal saline.

Resistance training

The animals were trained on a resistance ladder three times per week for six weeks, with each session involving climbing a 1-meter ladder set at an 85° incline with 2 cm between steps. The first week was performed without weights, and the second week with a load equivalent to 15% of the animal's body weight. Beginning in the third week, the protocol was intensified: for the first repetition of the first session, 25% of the mice's body weight was attached to its tail, with the weight increased to 50%, 75%, and 100% for subsequent repetitions. If the mice successfully carried a load, an additional 3 g was added for each successful repetition thereafter until the animal reached failure. The maximum weight carried before failure was then used to design the protocol for the next session; specifically, 50%, 75%, and 100% of this maximum weight were used for the respective repetitions, again with a 3g addition for every successful repetition. The protocol differed in that, after exhaustion, each mouse continued training with 70% of its maximum weight, ensuring each session comprised a minimum of 4 and a maximum of 8 repetitions. A 2-minute rest period was provided between repetitions, commencing once the mice reached the top of the ladder; after this rest, the appropriate weight was added to the tail, and the mice was returned to the ladder's base. If necessary, the mice's tail was gently touched to stimulate arousal (Nourshahi et al., 2013).

Laboratory measurements

Blood sampling for serum TNF-α analysis was performed 48 hours after the final resistance training session to minimize the contribution of acute, exercise-induced inflammation from the last bout. Serum TNF-α concentrations were determined using a commercial mouse-specific ELISA kit (ZellBio, Germany) according to the manufacturer's instructions. All samples were run in duplicate, and the average intra-assay coefficient of variation to ensure assay reliability

To analyze NF-κB and LIN28B gene expression, a portion of the tumor tissue was first preserved in RNAlater and stored at -20°C. RNA was then extracted using the RiboEx Total RNA isolation solution kit (GeneAll). The quality and quantity of the isolated RNA were assessed using a NanoDrop spectrophotometer and electrophoresis on a 1% agarose gel. Following confirmation of RNA purity and integrity, complementary DNA (cDNA) was synthesized using the FIRE Script RT cDNA Synthesis Kit (Solis BioDyne) and stored at -20°C. Gene-specific primers for NF-κB and LIN28B were designed using Primer3 software and synthesized by Pioneer Biotechnology; their sequences are provided in Table 2. Quantitative real-time PCR (qPCR) was performed in a 20 µl reaction volume containing 10 µl of AMPLIQON RealQ Plus 2x Master Mix Green, 1 µl of each forward and reverse primer (2 µl total), 2 µl of cDNA template, and 6 µl of nuclease-free water. The reactions were run on a Rotor-Gene Q real-time PCR cycler (QIAGEN) with the following program: initial enzyme activation at 95°C for 15 minutes, followed by 40 cycles of denaturation at 94°C for 10 seconds and a combined annealing-extension step at the temperature specified in Table 3 for 30 seconds. Finally, to confirm amplification specificity, the PCR products were analyzed via electrophoresis on a 1% agarose gel.

The expression level of the desired gene was calculated with the formula $2^{-\Delta\Delta CT}$ in the following way.

In this way, first, the threshold cycle of the desired gene of each sample was subtracted from the threshold cycle of the house-turning gene of the same sample.

Table 2. Primer sequences

Gene	Sequence
Mus musculus lin-28 homolog B (LIN28B)	Forward: 5′-ATGTGGACTGTGCGAGAAGA-3′
	Reverse: 5′-GCACTTCTTTGGCTGAGGAG-3′
Mus musculus nuclear factor of kappa light polypeptide gene enhancer in B cells 1, p105 (NF-kB1)	Forward: 5′-TTGGGAGAAGGCTGGAGAAG-3′
	Reverse: 5′-TGAACACAGGCTCATACGGT-3′
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	Forward: 5′-ACCACAGTCCATGCCATCAC-3′
	Reverse: 5′-TCCACCACCCTGTTGCTGTA-3′

(ΔCt= Ct Target-Ct Housekeeping)

In the next step, we subtract the ΔCt of each sample from the sample that needed to be compared, and multiply the negative number obtained to the power of two and obtain the relative expression of MFN1/DRP1 genes.

(ΔΔCt=ΔCt Target-ΔCt Reference) ΔΔCt- E=2

Statistical analysis

Descriptive statistics are presented as mean± standard deviation. The normality of the data distribution was assessed using the Shapiro-Wilk test, and the homogeneity of variances was verified with Levene's test. To compare differences between groups, we employed a one-way analysis of variance (ANOVA) followed by a Tukey post hoc test. A p-value of ≤0.05 was considered statistically significant for all tests. Data were analyzed using Graph Pad Prism (version 9).

Results

NF-kB gene expression

Changes in NF-kB gene expression in melanoma tumors are shown in Figure 1. Based on the results of ANOVA statistical test, there is a significant difference in NF-kB gene expression in melanoma tumors between different research groups (F=140.3, p<0.0001). The results of Tukey's post hoc test showed that all treatment groups including MT+RT, MT+PJ and MT+RT+PJ showed a significant decrease in NF-kB gene expression in melanoma tumors compared to the MT group (p<0.0001 for all). Among the treatment groups, the MT+PJ group showed a significant increase in NF-kB gene expression compared to the MT+RT and MT+RT+PJ groups (p<0.0001).

LIN28B gene expression

The changes in LIN28B gene expression in melanoma tumors are shown in Figure 2. Based on the results of ANOVA, there is a significant difference in LIN28B gene expression in melanoma tumors between different research groups (F=10.24, p=0.0006). The results of Tukey's post hoc test showed that all treatment groups including MT+RT (p=0.0154), MT+PJ (p=0.0014) and MT+RT+PJ (p=0.0013) showed a significant decrease in LIN28B gene expression in melanoma tumors compared to the MT group. The change in LIN28B gene expression in melanoma tumors was not significant between different treatment groups (p>0.05).

Serum TNF-α

Changes in serum TNF-α levels are shown in Figure 3. Based on the results of the ANOVA test, there was a significant difference

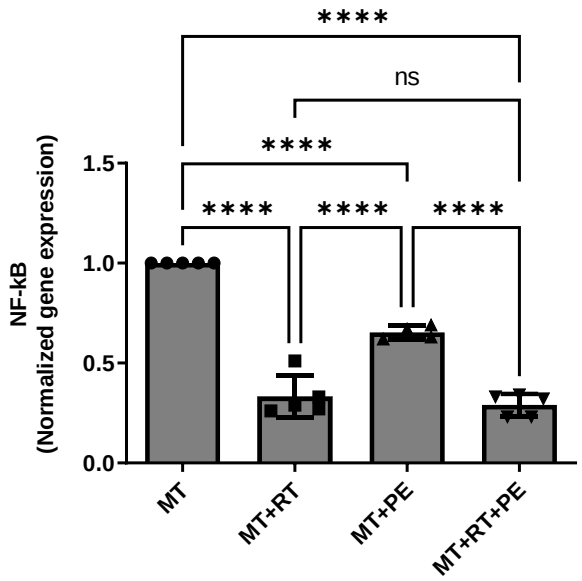

Figure 1. Expression of NF-kB at melanoma tumor at different groups of study. Data were show as means ± SD. N=5 in each group. Significant difference: *: p<0.05, **: p<0.01, ***: p<0.001, ****: p<0.0001. MT: Melanoma Tumor, RT: Resistance Training, PJ: Pineapple extract

in serum TNF-α levels between the different research groups (F=777.4, p<0.0001). The results of the Tukey post hoc test showed that all treatment groups including MT+RT, MT+PJ and MT+RT+PJ showed a significant increase in serum TNF-α levels compared to the MT group (p<0.0001 for all). Among the treatment groups, the MT+PJ and NT+RT+PJ groups showed the highest increase in serum TNF-α levels.

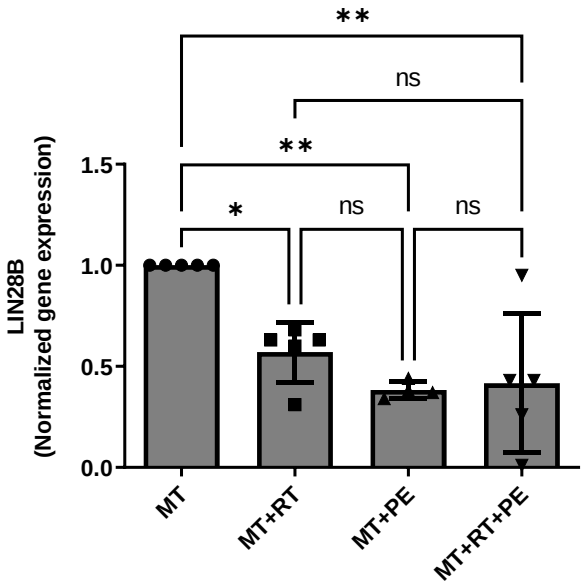

Figure 2. Expression of LIN28B at melanoma tumor at different groups of study. Data were show as means ± SD. N=5 in each group. Significant difference: *: p<0.05, **: p<0.01, ***: p<0.001, ****: p<0.0001. MT: Melanoma Tumor, RT: Resistance Training, PJ: Pineapple extract

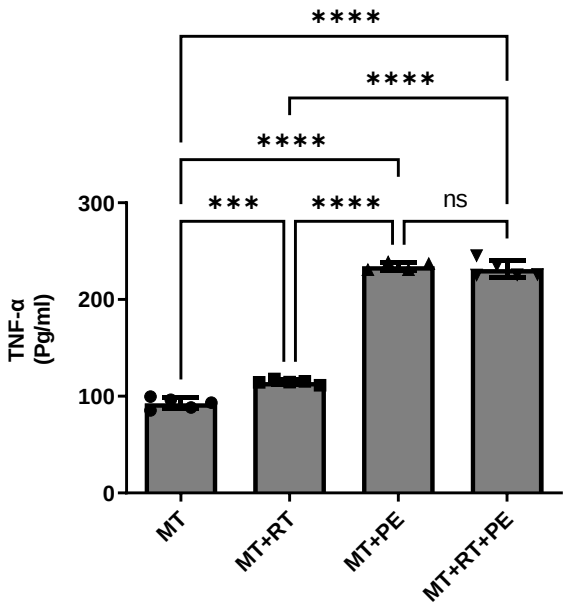

Figure 3. Serum TNF-a at different groups of study. Data were show as means ± SD. N=5 in each group. Significant difference: *: p<0.05, **: p<0.01, ***: p<0.001, ****: p<0.0001. MT: Melanoma Tumor, RT: Resistance Training, PJ: Pineapple extract

Discussion

This study provides important insights into the cellular mechanisms by which resistance training and pineapple extract consumption modulate inflammatory and oncogenic pathways in melanoma. The observed significant downregulation of NF-κB and LIN28B gene expression in tumor tissues of treated groups suggests an effective suppression of key pro-tumorigenic transcription factors that regulate inflammation, tumor growth, and metastasis. NF-κB is a well-characterized regulator of inflammatory cytokines and anti-apoptotic genes, promoting melanoma cell survival and invasiveness (Amiri et al., 2005; Guarneri et al., 2017). Resistance training and pineapple extract, rich in anti-inflammatory bromelain, likely inhibit NF-κB activation through interference with upstream signaling cascades such as IκB kinase (IKK) complex inhibition or suppression of receptor-mediated pathways including TNF receptor-associated factors (TRAFs) (Pezzani et al., 2023; Insuan et al., 2021). This suppression reduces the transcription of pro-inflammatory mediators, contributing to diminished tumor-promoting inflammation.

LIN28B, an RNA-binding protein, is implicated in melanoma progression by repressing let-7 microRNAs, thereby upregulating oncogenes and enhancing metastatic potential (Zhang et al., 2015; Gewalt et al., 2023). The decrease in LIN28B expression following interventions suggests restored let-7 activity, which ne-gatively regulates cell proliferation and invasive behavior. Exercise-induced metabolic reprogramming and pineapple bioactives may contribute to epigenetic modulation or direct transcriptional repression of LIN28B (Ceci et al., 2024). This highlights a novel pathway through which lifestyle factors exert anti-cancer effects at the molecular level.

Interestingly, while intratumoral NF-κB and LIN28B were downregulated, serum TNF-α levels increased significantly in treated groups. TNF-α acts as a pleiotropic cytokine with dual roles in cancer; it can promote tumor progression through chronic inflammation but also enhance anti-tumor immunity by activating cytotoxic lymphocytes and macrophages (dos Santos et al., 2019). The elevated systemic TNF-α may reflect a shift towards an acute immune activation state, enhancing tumor immune surveillance, possibly mediated by exercise-induced mobilization and activation of immune effector cells (Ceci et al., 2024). This pro-inflammatory systemic environment could favor tumor clearance despite reduced local tumor-promoting NF-κB activity.

Resistance exercise is known to induce the release of myokines that have systemic anti-inflammatory effects and modulate immune cell function (Ceci et al., 2024). These effects likely cooperate with pineapple extract antioxidant and anti-inflammatory properties, primarily attributed to bromelain, flavonoids, and other bioactive compounds (Pezzani et al., 2023). Bromelain inhibits NF-κB by preventing its nuclear translocation and enhances apoptosis by activating caspase pathways and upregulating tumor suppressor genes such as p53 (Pezzani et al., 2023; Ratnavelu et al., 2016). The combination of exercise and pineapple extract thus produces a synergistic effect by targeting multiple cellular pathways that disrupt tumor survival and proliferation.

The mechanisms observed align with previous studies reporting reduced tumor weight and enhanced apoptosis through exercise and dietary supplementation with pineapple extract in melanoma models (Ordibehesht et al., 2020; Gholamian et al., 2020). Resistance training likely also improves metabolic fitness by activating AMPK and mTOR signaling pathways that inhibit melanoma growth (Ceci et al., 2024). Furthermore, exercise-induced reactive oxygen species (ROS) at moderate levels act as signaling molecules to enhance immune surveillance and inhibit tumor angiogenesis (dos Santos et al., 2019). In parallel, bromelain's proteolytic activity disrupts extracellular matrix components, impairing tumor invasion and metastasis (Debnath et al., 2019).

As stated, the most intriguing finding of this study is the significant increase in systemic TNF-α levels alongside a decrease in intratumoral NF-κB gene expression. While this appears parado-

-xical given that TNF-α is a canonical activator of the NF-κB pathway, this discrepancy can be explained by the compartmentalization of inflammation and the dual role of TNF-α in cancer immunology.

First, the source and timing of TNF-α are critical. The systemic TNF-α measured 48 hours' post-exercise is unlikely to be derived from the melanoma cells themselves, where NF-κB signaling was suppressed. Instead, it is highly plausible that it originated from activated immune cells, such as monocytes and macrophages, mobilized by the repeated bouts of resistance training. Exercise is a known potent physiological stimulus for the transient release of pro-inflammatory cytokines, which can act as alarmins to prime the immune system (Pedersen & Febbraio, 2012). This exercise-induced, systemic TNF-α may reflect a state of enhanced immune alertness rather than chronic, tumor-promoting inflammation.

Second, the biological effect of TNF-α is determined by the local microenvironment. While chronic TNF-α signaling within the tumor promotes angiogenesis and metastasis, a systemic, acute-phase TNF-α response can enhance anti-tumor immunity by promoting the activation and infiltration of cytotoxic T lymphocytes and NK cells, and by inducing tumor vascular disruption (Balkwill, 2009). We postulate that the suppressed intratumoral NF-κB indicates a successful interruption of the tumor's autonomous pro-survival signaling, while the elevated serum TNF-α may signify a hostile systemic environment that favors immune-mediated tumor control. This hypothesis would align with studies showing that moderate, acute inflammation can synergize with, rather than antagonize, cancer immunotherapy.

Finally, this dissociation underscores a key limitation of our study. The precise cellular source of the elevated TNF-α and its functional impact on the tumor immune infiltrate remain unknown. Future investigations measuring immune cell populations (e.g., CD8+ T cells, Tregs, Macrophages) within the tumor via flow cytometry, alongside assessment of other systemic myokines and cytokines, are essential to resolve this paradox and confirm the immune-activating potential of our combined intervention

Conclusion

In conclusion, resistance training and pineapple extract consumption individually and combined attenuate melanoma progression by downregulating intratumoral NF-κB and LIN28B expression while elevating systemic TNF-α to promote anti-tumor immunity. This dual action—local inhibition of pro-tumor signaling with systemic immune activation—provides a mechanistic rationale for incorporating lifestyle interventions alongside conventional therapies in melanoma management.

Future work should explore signaling intermediates downstream of NF-κB and LIN28B, such as apoptosis regulators and immune checkpoint molecules, to further delineate therapeutic targets. Overall, the results underscore the translational potential of combining resistance exercise and dietary phytochemicals in integrative oncology.

What is already known on this subject?

The tumor microenvironment, marked by chronic inflammation, plays a critical role in melanoma development and progression through complex interactions between tumor cells and inflammatory mediators.

What this study adds?

Resistance training and pineapple extract consumption individually and combined attenuate melanoma progression by downregulating intratumoral NF-κB and LIN28B expression while elevating systemic TNF-α to promote anti-tumor immunity.

Organ Cross-Talk Tips:

- Resistance training and pineapple extract suppress intratumoral NF-κB and LIN28B, demonstrating systemic modulation of the tumor microenvironment.
- A distinct organ crosstalk is revealed: interventions elevate systemic TNF-α while suppressing intratumoral inflammation, indicating compartment-specific effects.

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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 there is no conflict of interest in the present research.

Ethical approval This study received approval under the research ethics code IR.SSRC.REC.1401.340 from the Azad University of Sciences and Research.

Informed consent Animal study.

Author contributions

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

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