2025. *Journal of Exercise & Organ Cross Talk*. 2025; 5 (4): 153-160. doi: 10.22122/jeoct.2025.554729.1176

Research Article

Combined resistance training and pineapple extract slow melanoma growth and alter liver apoptosis in mice

Saeid Shahrestani[1], Hossein Abednatanzi[1*], Mandana Gholami[1], Farshad Ghazalian[1]

Abstract

Melanoma is an aggressive malignancy with a high propensity for metastasis, particularly to the liver. This study investigated the individual and combined effects of resistance training (RT) and pineapple extract (PE) supplementation on primary melanoma tumor growth and the expression of hepatic apoptotic markers (Bax, Bcl-2) in a murine model. C57BL/6 mice bearing subcutaneous B16F10 melanoma tumors were allocated to four groups: Tumor Control (TC), RT, PE, and Combined (RT+PE). The six-week intervention consisted of ladder-climbing RT and/or oral PE supplementation. Tumor volume was measured throughout the study. Upon completion, hepatic Bax and Bcl-2 gene expression was analyzed via qPCR. While RT and PE alone did not significantly affect tumor volume, the Combined (RT+PE) group showed a significant reduction compared to the TC group ($p<0.05$). In the liver, all intervention groups (RT, PE, and Combined) significantly decreased pro-apoptotic Bax expression and increased anti-apoptotic Bcl-2 expression relative to the TC group ($p<0.05$). The combination of resistance training and pineapple extract exhibits a synergistic effect in reducing primary melanoma tumor growth. Furthermore, both interventions independently and collectively modulate systemic apoptotic markers in the liver, suggesting a potential role in influencing the hepatic microenvironment. This non-invasive combinatorial approach may represent a promising complementary strategy for managing melanoma progression and its systemic effects.

Key Words: Apoptosis, liver, Experimental melanoma, Resistance exercise, Tumor burden

Introduction

Melanoma is a highly aggressive form of skin cancer originating from melanocytes, characterized by its propensity for early metastasis and resistance to conventional therapies (Centeno et al., 2023). The liver is a common site for metastatic spread, which significantly complicates treatment and is a leading cause of mortality (Zane et al., 2021). Despite advancements in targeted therapies and immunotherapies, the search for effective, low-cost, and accessible adjunctive strategies to improve patient outcomes and manage systemic complications remains a critical focus in oncology research.

A critical aspect of cancer progression is the systemic interplay between the primary tumor and distant organs, even before metastasis is clinically detectable. The "seed and soil" hypothesis posits that the primary tumor can precondition distant organs, creating a favorable microenvironment (soil) for future metastatic seeds (Paget, 1889). The liver, as a major metabolic and immune organ, is particularly susceptible to these systemic changes. Therefore, investigating how interventions affect the hepatic microenvironment in the presence of a primary tumor is highly relevant for understanding their potential to influence metastatic susceptibility.

In recent years, the role of lifestyle interventions, particularly exercise, has garnered significant attention as a potential supportive care modality (Mora et al., 2023). Resistance training (RT), a form of exercise designed to improve muscular strength and endurance, has been shown to exert systemic anti-tumor effects beyond its well-documented benefits for cancer-related fatigue and quality of life (Feng et al., 2024). Proposed mechanisms include exercise-induced modulation of myokines, enhanced immune surveillance, and improved metabolic profiles, which can collectively create an unfavorable microenvironment for tumor growth (Pedersen & Saltin, 2015). Concurrently, there is growing interest in the anti-cancer properties of natural compounds. Pineapple (Ananas comosus) extract is rich in bromelain, a complex mixture of proteolytic enzymes with document anti-inflammatory, immunomodulatory

1. Department of physical education and sport sciences, SR.C., Islamic Azad university, Tehran, Iran.

*Author for correspondence: abednatanzi @iau.ir

S Sh: 0009-0002-8013-4617; H A: 0000-0001-6638-1131; M Gh: 0000-0001-8960-4123; F Gh: 0000-0002-5805-0559

Received 21 July 2025; Accepted 05 September 2025

, and pro-apoptotic activities in various cancer models (Nagaraju & El-Rayes, 2013; Nida, 2022). It's potential to selectively induce apoptosis in malignant cells positions it as a promising candidate for complementary oncology research.

The regulation of apoptosis, or programmed cell death, is a crucial mechanism often dysregulated in cancer. The balance between pro-apoptotic proteins like Bax and anti-apoptotic proteins like Bcl-2 determines a cell's susceptibility to death signals. Shifting this balance towards apoptosis is a key strategy for many anti-cancer therapies (Pistritto et al., 2016). In the context of a primary tumor, systemic signals can alter apoptotic homeostasis in distant organs like the liver. Modulating these apoptotic markers in the liver could therefore represent a critical strategy to systemically counteract the pro-metastatic environment induced by a primary tumor (Fabregat et al., 2007).

While the individual effects of exercise and natural supplements have been explored, the potential for a synergistic interaction between resistance training and pineapple extract supplementation has not been investigated. We hypothesize that combining the systemic, physiological adaptations induced by RT with the direct, bioactive properties of pineapple extract may produce a more potent anti-tumor effect on the primary tumor and favorably modulate the systemic environment in the liver. Therefore, this study aims to investigate the individual and combined effects of resistance training and pineapple extract supplementation on primary melanoma tumor volume and the expression of key hepatic apoptotic regulators (Bax and Bcl-2) as indicators of systemic effect in a murine model.

Materials and methods

Animals

In this study, thirty-two male C57BL/6 mice, sourced from the Pasteur Institute and aged six to eight weeks with a body weight between 20 and 25 grams, were utilized as the statistical population. The animals were relocated to the animal care facility within Islamic Azad University Laboratory in Yazd. After this transfer, a one-week period of acclimatization to the new laboratory setting was provided, during which the mice were kept under strictly regulated environmental conditions. They were housed in polycarbonate cages measuring 20×27×47 cm, with four mice per cage, in a room with an average temperature of 22 ± 1.4°C, 55% humidity, and a 12-hour light/12-hour dark cycle. For the duration of the study, all subjects were provided with an unrestricted supply of standard rodent food, which was refreshed every two days in the cage's mesh feeder, and had continuous access to water from 500 ml rodent bottles. All ethical and professional standards for animal care were rigorously followed; a single individual performed all handling and training, and any procedure, including painless euthanasia, surgery, and sampling , were executed in full compliance with established ethical guidelines for research on laboratory animals. The study protocol received formal approval under the research ethics code IR.IAU.YAZD.REC.1400.050 from the Azad University of Yazd. Following the acclimatization period, the mice were randomly assigned to one of four experimental groups, each containing 8 mice: a tumor control or melanoma tumor (Control) group, a tumor plus resistance training (Resistance) group, a tumor plus pineapple extract (Supplement) group, and a tumor group that received a combination of both Resistance and Supplement.

Melanoma

The B16F10 melanoma cell line was obtained from the cell bank of the Pasteur Institute of Iran. The researchers cultured these cells in RPMI-1640 medium that had been enriched with 10% fetal bovine serum (FBS) and a 1% antibiotic solution of penicillin-streptomycin. To prepare donor mice bearing tumors for the study, tumor tissue was harvested from a group of stock mice that had been humanely euthanized by cervical dislocation. The tumor site on the flank was first cleaned with ethanol, after which the tumor was carefully excised in an aseptic manner using surgical forceps and scissors. This extracted tissue was then placed into a sterile dish filled with phosphate-buffered saline (PBS). Using a scalpel blade, the main tumor mass was finely divided into small fragments, each measuring 2-3 mm^3. Throughout this mincing procedure, any surrounding non-tumorous components, such as excess fat and blood vessels, were meticulously trimmed away to guarantee the tumor fragments were pure. These prepared pieces were then moved to a fresh, sterile dish containing PBS, ready for the subsequent surgical implantation (Figure 1).

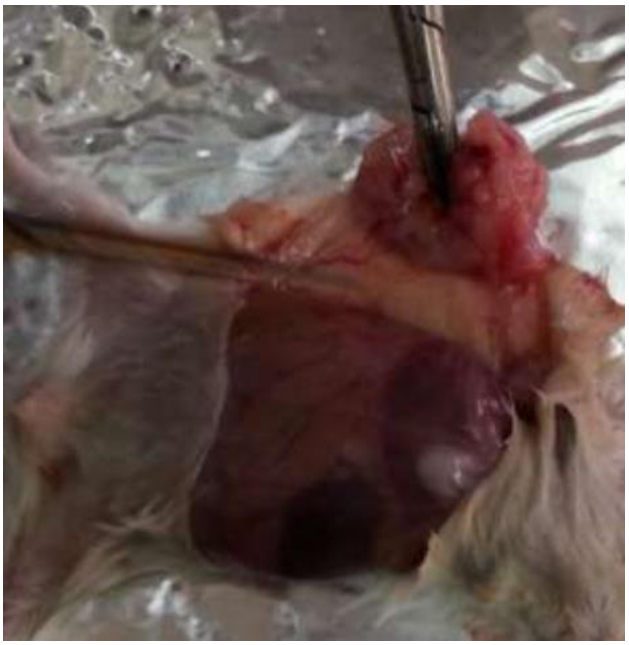

Figure 1. Melanoma tumor

For the tumor implantation procedure itself, the recipient mice were first anesthetized with an intraperitoneal injection. This injection consisted of a mixture of ketamine and xylazine in a 2:1 ratio, which was diluted with sterile saline to achieve a total administration volume of 100 µl per animal. Once a deep state of anesthesia was verified, the mice were placed on their sides on a surgical platform. A minor incision was created on the shaved flank area using sterilized surgical tools. Surgical forceps were then used to form a subcutaneous channel beneath the skin. A single prepared tumor fragment, measuring 2-3 mm^3, was implanted into the far end of this newly created pocket. The surgical wound was subsequently sealed using a surgical adhesive and secured with a wound clip. After the operation, the mice were placed in a recovery area with a controlled temperature of 25 °C and housed individually. The incision was treated with the antiseptic povidone-iodine (betadine). Tumor development was assessed on a weekly basis. For the full duration of the research, the mice were kept in polycarbonate cages, with four animals per cage, following an initial one-week period for acclimatization to the laboratory environment. After this acclimatization phase, the mice were distributed randomly into four separate groups, with the groups being balanced according to the animals' body weights. The experimental protocol officially commenced one week after the cancer cells were injected, which was the point when tangible, palpable tumors had reliably formed (Dashti et al., 2014).

Tumor volume measurement

All animals were initially weighed weekly. Tumor volume was measured in two dimensions. The largest dimension of the tumor was considered as the length (L) of the tumor and the other dimension (at an angle of 90 degrees) was considered as the width (W). After the appearance of the tumor, the length and width of the tumor were measured once a week using a digital caliper and its volume was determined using the tumor volume calculation formula [$V = (\pi/6) \times L \times W \times H$] (Figure 2) (Jones et al., 2010).

Figure 2. Tumor volume measurement

Resistance training

For a duration of six weeks, the animals participated in a resistance ladder training regimen three times each week (Table 1). Each training session required them to climb a one-meter ladder positioned at an 85-degree angle, with steps spaced two centimeters apart. The initial week of training was conducted without any additional load, while during the second week, a weight equal to 15% of each animal's body mass was introduced. Starting in the third week, the training protocol was made more demanding. The first repetition of the first session involved attaching a weight equivalent to 25% of the mouse's body weight to its tail; this load was then escalated to 50%, 75%, and 100% for the following repetitions. Following any successful climb with a load, an extra 3 grams was added for every subsequent successful repetition until the animal could no longer complete the climb. The greatest weight successfully carried prior to this point of failure was then used to determine the protocol for the next session: specifically, 50%, 75%, and 100% of this maximum weight were applied for the respective repetitions, with the rule of adding 3 grams after each successful climb still in effect. A modification to the protocol was that after reaching exhaustion, each mouse continued its training using 70% of its established maximum weight. This ensured that every session included no fewer than four and no more than eight repetitions. A two-minute rest interval was allowed between repetitions, starting once the mouse had reached the ladder's summit; after this pause, the designated weight was fastened to its tail and the animal was placed back at the bottom of the ladder. When required, a gentle touch was applied to the mouse's tail to prompt it to resume activity (Nourshahi et al., 2013).

Pineapple extract

The study employed a dry extract derived from the fleshy part of the pineapple (Ananas comosus), which was produced using ethanol. The preparation process began by washing and peeling fresh pineapples, after which the inner fruit tissue was cut into thin rings. To avoid photochemical breakdown and contamination, these rings were dried for 72 hours in a shaded location with good airflow at room temperature. Following the drying phase, the material was mechanically ground into a consistent powder. The extraction itself was performed using a cold-soaking technique; this involved combining seven grams of the pineapple powder with 50 mL of 85% ethanol in water and letting it sit at 4°C for a full day, with periodic stirring. The subsequent mixture was filtered, and the liquid filtrate was then placed in a water bath at 37°C to evaporate, thereby entirely removing the solvent and yielding a dry extract. This final extract was kept in frozen storage at -20°C until it was needed.

To ensure consistency in the active components, the total enzymatic activity of bromelain in the extract was measured and

Table 1. Six-week progression of the resistance ladder training protocol.

Week	Session Load Progression	Sets & Reps	Key Rules
1	No external load.	3-4 repetitions per session.	Acclimation to the ladder.
2	Load fixed at 15% of body mass.	3-4 repetitions per session.	Introduction of constant load.
3-6	Session 1 (of the week): - Rep 1: 25% of body mass. - Rep 2: 50% of body mass. - Rep 3: 75% of body mass. - Rep 4: 100% of body mass. - Subsequent Reps: Previous load + 3g after each successful climb. Sessions 2 & 3 (of the week): - Rep 1: 50% of previous session's max. - Rep 2: 75% of previous session's max. - Rep 3: 100% of previous session's max. - Subsequent Reps: Previous load + 3g after each successful climb.	4-8 total repetitions per session.	1. Progressive Overload: After each successful climb, add 3g for the next repetition. 2. Point of Failure: The highest load successfully carried before a failed climb is recorded as the session's Maximum Load. 3. Post-Failure Continuation: After failure, the mouse continues climbing at 70% of the session's Maximum Load until 4-8 total repetitions are completed. 4. Rest: 2 minutes of rest between all repetitions.

standardized to a value of CDU/mg using the casein digestion unit (CDU/mg) method. For the purpose of the animal experiment, the dry extract was dissolved in normal saline right before it was given to the mice. The mice were administered the pineapple extract orally at a dosage of 300 mg of the dry extract per kilogram of their body weight. This dosage was selected based on its established efficacy and safety profile in prior murine models, while the control group was given the same volume of normal saline (Gholamian et al., 2020).

Laboratory measurements

Blood samples collected 48 hours after the last resistance training session. Liver was removed for measurement of apoptotic markers.

For the analysis of Bax and Bcl2 gene expression, sections of liver tissue were initially preserved in RNAlater and stored at -20°C. Total RNA was subsequently extracted from these samples using the RiboEx Total RNA isolation solution kit (GeneAll). The quality and concentration of the isolated RNA were evaluated with a NanoDrop spectrophotometer and verified through electrophoresis on a 1% agarose gel. After confirming the RNA's purity and integrity, complementary DNA (cDNA) was synthesized using the FIRE Script RT cDNA Synthesis Kit (Solis BioDyne), and the resulting cDNA was stored at -20°C. Gene-specific primers for Bax and Bcl2 were designed with Primer3 software and synthesized by Pioneer Biotechnology; the primer sequences are listed in Table 2. The specificity of all primers was confirmed by melt curve analysis following qPCR, which consistently showed single, distinct peaks for each primer pair. Quantitative real-time PCR (qPCR) was conducted in a 20 µl reaction volume, which consisted of 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 processed on a Rotor-Gene Q real-time PCR cycler (QIAGEN) using the following thermal protocol: an initial enzyme activation step 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 60°C for 30 seconds. A melt curve analysis was performed immediately after amplification, from 60°C to 95°C, with a 1°C increment per step. To further confirm the specificity of the amplification and the expected amplicon size, the final PCR products were analyzed using electrophoresis on a 1% agarose gel.

Gene expression levels were calculated using the 2^–ΔΔCT method. This process involved two primary steps. First, for each individual sample, the threshold cycle (Ct) of the housekeeping gene was subtracted from the Ct of the target gene to yield ΔCt (ΔCt = Ct Target – Ct Housekeeping). Next, the ΔCt value for each test sample was subtracted from the ΔCt value of the reference sample, resulting in a ΔΔCt value (ΔΔCt = ΔCt Target – ΔCt Reference). The final relative expression of the target genes was then determined by raising 2 to the power of the negative ΔΔCt value (Relative Expression = 2^–ΔΔCT).

Statistical analysis

The data are summarized using descriptive statistics, expressed as the mean ± standard deviation. We evaluated the normality of the data's distribution with the Shapiro-Wilk test and confirmed the homogeneity of variances using Levene's test. For the comparison of inter-group differences, a one-way analysis of variance (ANOVA) was utilized, which was then supplemented by

Table 2. Primer sequence

Gene	Sequence
Bax	Forward: 5′-CATCATGGGCTGGACACTG-3′
	Reverse: 5′-TCCCGAAGTAGGAAAGGAGG-3′
Bcl2	Forward: 5′-CTGTGGATGACTGAGTACCTGA-3′
	Reverse: 5′-GAGAAATCAAACAGAGGTCGCA-3′
GAPDH	Forward: 5′-AAGTTCAACGGCACAGTCAAGG-3′
	Reverse: 5′-CATACTCAGCACCAGCATCACC-3′

a Tukey post hoc test. For every test conducted, a p-value that was less than or equal to 0.05 was deemed to indicate statistical significance. The entire analysis was performed with Graph Pad Prism software, version 9.

Results

Tumor volume

The changes in tumor volume in the 4 study groups are shown in Figure 1. The results of one-way ANOVA test showed that there was a significant difference between the different research groups. Based on the results of Tukey's post hoc test, only the combined treatment group including resistance training and pineapple extract supplementation caused a significant reduction in melanoma tumor volume compared to the tumor control group in mice ($p<0.05$).

Bax expression at liver tissue

The results of Bax gene expression in the liver tissue of mice with melanoma tumors are shown in Figure 2. The results of Tukey's post hoc test showed that compared to the tumor control group, mono and combination treatments including resistance training alone, pineapple extract supplementation alone, and the combination of resistance training and pineapple extract caused a significant decrease in Bax gene expression in the liver tissue of mice with melanoma tumors ($p<0.05$).

Bcl2 expression at liver tissue

The results of Bcl2 gene expression in the liver tissue of mice with melanoma tumors are shown in Figure 3. The results of Tukey's post hoc test showed that compared to the tumor control group, mono and combination treatments including resistance training alone, pineapple extract supplementation alone, and the combination of resistance training and pineapple extract caused a significant increase in Bcl2 gene expression in the liver tissue of mice with melanoma tumors ($p<0.05$).

Discussion

The present study demonstrated that the combination of resistance training and pineapple extract supplementation exerted a synergistic antitumor effect in mice bearing melanoma tumors. Specifically, only the combined intervention significantly reduced tumor volume compared to the tumor control group, suggesting that concurrent mechanical and nutritional stimuli may interact positively to suppress melanoma progression. This outcome aligns with prior evidence that exercise not only enhances immune responses but also modulates the tumor microenvironment through altered cytokine signaling and myokine secretion (Pedersen & Hoffman-Goetz, 2000).

Pineapple extract, rich in bromelain, adds an additional therapeutic avenue by facilitating proteolytic degradation of extracellular matrix components and inducing apoptosis in tumor

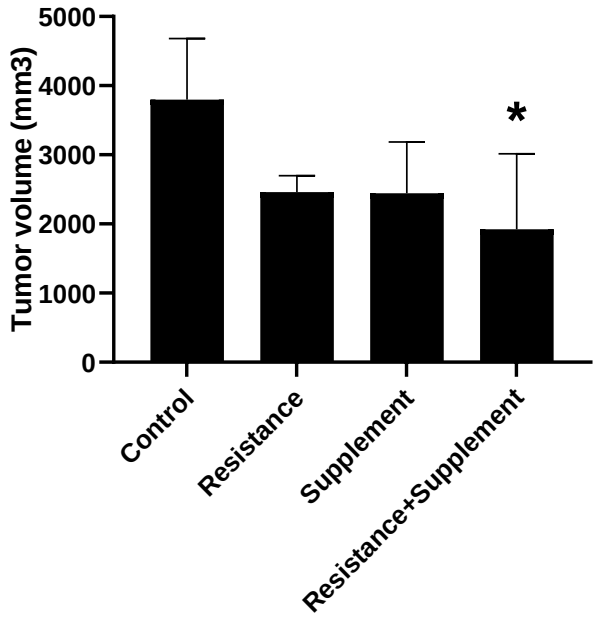

Figure 1. Changes in tumor volume (mm^3) between different study groups. Data are shown as mean ± standard deviation. *: Indicates significant difference compared to tumor control group ($p<0.05$).

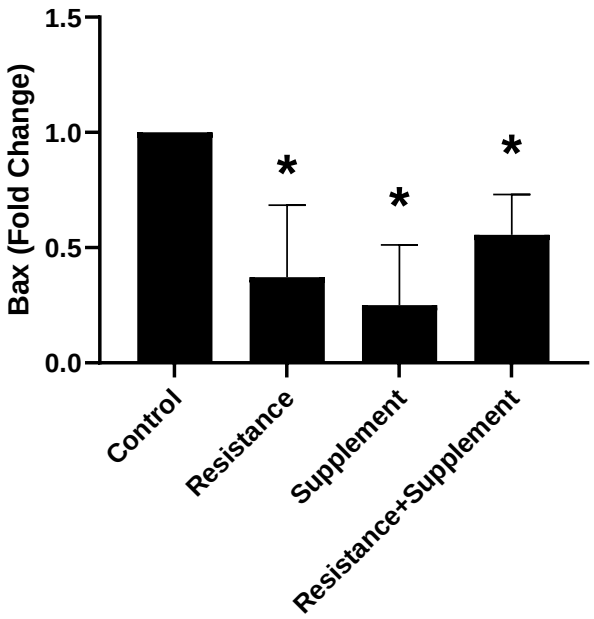

Figure 2. Bax gene expression in liver tissue of C57 mice with melanoma tumors in different research groups. Data are shown as mean ± standard deviation. *: Indicates significant difference compared to tumor control group ($p<0.05$).

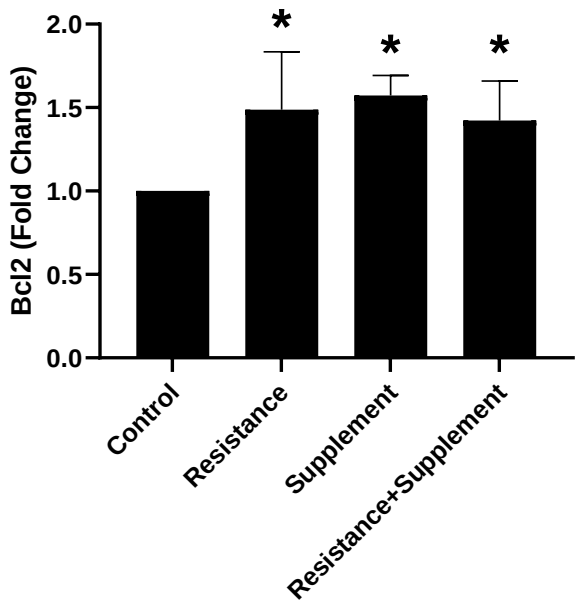

Figure 3. Bcl2 gene expression in liver tissue of C57 mice with melanoma tumors in different research groups. Data are shown as mean ± standard deviation. *: Indicates significant difference compared to tumor control group ($p<0.05$).

cells (Maurer, 2001). Thus, their integration may result in both systemic and localized suppression of tumor proliferation through complementary molecular mechanisms.

A notable finding of this investigation was the significant modulation of hepatic apoptotic regulators Bax and Bcl-2 in all intervention groups. Resistance training, pineapple extract, and their combination each decreased Bax expression while upregulating Bcl-2, indicating a shift toward cell survival signaling in the liver. While this hepatic apoptotic balance is traditionally viewed as hepatoprotective and may enhance systemic resilience against metastatic stress (Maurer, 2001), this interpretation

interpretation requires caution. In the broader context of cancer, systemic upregulation of anti-apoptotic proteins like Bcl-2 could, in theory, also enhance the survival of circulating tumor cells or micro metastases. Although our study did not find evidence of increased metastasis, this dual possibility should be acknowledged, and the net clinical benefit of such modulation warrants further investigation. Prior studies have shown that high-intensity or resistance exercise may attenuate hepatic oxidative stress, thereby preserving mitochondrial integrity and enhancing the expression of anti-apoptotic genes (Padilha et al., 2017). The present data reinforce those findings, suggesting that repeated mechanical stress during RT potentially triggers adaptive antioxidant and anti-apoptotic responses that benefit hepatic health even in the context of cancer.

The bioactive impact of pineapple extract also appears central to these observed modulations. Bromelain, the primary enzyme complex within pineapple extract, is documented to downregulate pro-inflammatory mediators such as NF-κB and TNF-α while promoting apoptotic cascades through modulation of caspase activation in tumor cells (Varilla et al., 2021). However, the paradoxical hepatic upregulation of Bcl-2 found here implies that the extract may selectively protect normal tissues while promoting selective cytotoxicity in malignant ones—a dual effect that has been noted in previous investigations using natural enzymatic extracts (Hale et al., 2002). This selective modulation may minimize collateral liver damage during elevated systemic stress induced by tumor burden, illustrating an important advantage of naturally derived adjuncts over conventional chemotherapeutic agents.

Importantly, the synergistic reduction in tumor volume observed only in the combined RT and pineapple extract group supports the concept of a multimodal intervention strategy. While the precise mechanism for this synergy remains to be fully elucidated, we can propose several plausible, non-mutually exclusive hypotheses for future validation. For instance, exercise-induced hormonal and metabolic changes, such as improved insulin sensitivity, enhanced perfusion, and altered cytokine milieu, may enhance the bioavailability or cellular uptake of phytochemicals present in pineapple extract (Pingitore et al., 2015). Concurrently, it is possible that bromelain's proteolytic activity may reduce extracellular matrix stiffness and facilitate better immune or metabolic access to the tumor site, further magnifying exercise's anti-tumor potential. Collectively, these potential mechanisms suggest that the intersection between mechanical adaptation and nutritional modulation can yield a biological synergy beyond what either intervention achieves alone. These findings provide valuable insight into the design of integrative cancer management programs emphasizing systemic health rather than tumor-centric treatment alone.

Conclusion

This study provides novel evidence that the combination of resistance training and pineapple extract supplementation exerts synergistic antitumor effects in a murine melanoma model, primarily through attenuation of tumor volume and modulation of hepatic apoptotic markers. Both resistance training and pineapple extract independently shifted the hepatic apoptotic balance by reducing Bax and increasing Bcl-2 expression, an effect that may support liver health but requires further study to understand its systemic implications in cancer. Their combination amplified these molecular adaptations and produced a significant antitumor response. The findings underscore the potential value of multidimensional, non-pharmacological interventions in supporting conventional cancer therapies. Future research should directly investigate the proposed mechanisms for synergy such as phyto-

-chemical bioavailability and ECM remodeling and explore the underlying molecular mediators, particularly myokine and cytokine interactions, in both pre-clinical and clinical models.

What is already known on this subject?

Melanoma is a highly aggressive form of skin cancer originating from melanocytes, characterized by its propensity for early metastasis and resistance to conventional therapies.

What this study adds?

Both resistance training and pineapple extract independently shifted the hepatic apoptotic balance by reducing Bax and increasing Bcl-2 expression, an effect that may support liver health but requires further study to understand its systemic implications in cancer.

Organ Cross-Talk Tips:

- Both resistance training and pineapple extract, interventions aimed at the primary tumor, independently modulated the hepatic microenvironment by reducing pro-apoptotic signals.
- The combination of training and supplementation had a dual benefit: it reduced primary tumor growth and further shifted the liver's apoptotic balance toward a more anti-apoptotic state.

Acknowledgements

None

Funding

None

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 All ethical and professional standards for animal care were rigorously followed; a single individual performed all handling and training, and any procedures, including painless euthanasia, surgery, and sampling, were executed in full compliance with established ethical guidelines for research on laboratory animals. The study protocol received formal approval under the research ethics code IR.IAU.YAZD.REC.1400.050 from the Azad University of Yazd.

Informed consent Animal study.

Author contributions

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

References

Centeno, P. P., Pavet, V., & Marais, R. (2023). The journey from melanocytes to melanoma. Nature Reviews Cancer, 23(6), 372-390. doi: https://doi.org/10.1038/s41568-023-00565-7

Dashti, A., Ebrahimi, M., Hadjati, J., & Moazzeni, S. M. (2014). Identification and Characterization of Cancer Stem Cells in Mouse Malignant Melanoma. Modares Journal of Medical Sciences: Pathobiology, 17(2).

Fabregat, I., Roncero, C., & Fernández, M. (2007). Survival and apoptosis: a dysregulated balance in liver cancer. Liver International, 27(2), 155-162. doi: https://doi.org/10.1111/j.1478-3231.2006.01409.x

Feng, Y., Feng, X., Wan, R., Luo, Z., Qu, L., & Wang, Q. (2024). Impact of exercise on cancer: mechanistic perspectives and new insights. Frontiers in Immunology, 15, 1474770. doi: https://doi.org/10.3389/fimmu.2024.1474770

Gholamian, R., Lotfabadi, N. N., & Haghiralssadat, B. F. (2020). Evaluation of antioxidant and cytotoxic effects of liposomes containing pineapple fruit extract on Melanoma skin cancer (A375 Cell Line). Journal of Shahid Sadoughi University of Medical Sciences. doi: https://doi.org/10.18502/ssu.v28i2.3480

Hale, L. P., Greer, P. K., & Sempowski, G. D. (2002). Bromelain treatment alters leukocyte expression of cell surface molecules involved in cellular adhesion and activation. Clinical Immunology, 104(2), 183-190. doi: https://doi.org/10.1006/clim.2002.5254

Jones, L. W., Viglianti, B. L., Tashjian, J. A., Kothadia, S. M., Keir, S. T., Freedland, S. J., . . . Herndon, J. E. (2010). Effect of aerobic exercise on tumor physiology in an animal model of human breast cancer. Journal of applied physiology, 108(2), 343-348. doi: https://doi.org/10.1152/japplphysiol.00424.200

Maurer, H. (2001). Bromelain: biochemistry, pharmacology and medical use. Cellular and Molecular Life Sciences CMLS, 58(9), 1234-1245. doi: https://doi.org/10.1007/PL00000936

Mora, D. C., Jong, M. C., Quandt, S. A., Arcury, T. A., Kristoffersen, A. E., & Stub, T. (2023). Supportive care for cancer-related symptoms in pediatric oncology: a qualitative study among healthcare providers. BMC Complementary Medicine and Therapies, 23(1), 104. doi: https://doi.org/10.1186/s12906-023-03924-x

Nagaraju, G. P., & El-Rayes, B. F. (2013). SPARC and DNA methylation: possible diagnostic and therapeutic implications in gastrointestinal cancers. Cancer letters, 328(1), 10-17. doi: https://doi.org/10.1016/j.canlet.2012.08.028

Nida, D. A. (2022). Literature review: cytotoxic activity of pineapple (Ananas comosus l.) against cancer cells. 4th International Conference Current Breakthrough in Pharmacy (ICB-Pharma 2022), doi: https://doi.org/10.2991/978-94-6463-050-3_18

Nourshahi, M., Babaei, A., Bigdeli, M. R., & Ghasemi Beyrami, M. (2013). The effect of six weeks of resistance training on tumor tissue VEGF and endostatin in mice with breast cancer. Journal of Sport Biosciences, 5(2), 27-46. doi: https://doi.org/10.22059/jsb.2013.35038

Padilha, C. S., Borges, F. H., Costa Mendes da Silva, L. E., Frajacomo, F. T. T., Jordao, A. A., Duarte, J. A., . . . Deminice, R. (2017). Resistance exercise attenuates skeletal muscle oxidative stress, systemic pro-inflammatory state, and cachexia in Walker-256 tumor-bearing rats. Applied Physiology, Nutrition, and Metabolism, 42(9), 916-923. doi: https://doi.org/10.1139/apnm-2016-0436

Pedersen, B. K., & Hoffman-Goetz, L. (2000). Exercise and the immune system: regulation, integration, and adaptation. Physiological reviews. doi: https://doi.org/10.1152/physrev.2000.80.3.1055

Pedersen, B. K., & Saltin, B. (2015). Exercise as medicine–evidence for prescribing exercise as therapy in 26 different chronic diseases. Scandinavian journal of medicine & science in sports, 25, 1-72. doi: https://doi.org/10.1111/sms.12581

Pingitore, A., Lima, G. P. P., Mastorci, F., Quinones, A., Iervasi, G., & Vassalle, C. (2015). Exercise and oxidative stress: Potential effects of antioxidant dietary strategies in sports. Nutrition, 31(7-8), 916-922. doi: https://doi.org/10.1016/j.nut.2015.02.005

Pistritto, G., Trisciuoglio, D., Ceci, C., Garufi, A., & D'Orazi, G. (2016). Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies. Aging (albany NY), 8(4), 603. doi: https://doi.org/10.18632/aging.100934

Varilla, C., Marcone, M., Paiva, L., & Baptista, J. (2021). Bromelain, a group of pineapple proteolytic complex enzymes (Ananas comosus) and their possible therapeutic and clinical effects. A summary. Foods, 10(10), 2249. doi: https://doi.org/10.3390/foods10102249

Zane, K. E., Cloyd, J. M., Mumtaz, K. S., Wadhwa, V., & Makary, M. S. (2021). Metastatic disease to the liver: Locoregional therapy strategies and outcomes. World Journal of Clinical Oncology, 12(9), 725. doi: https://doi.org/10.5306/wjco.v12.i9.725