Journal of Sports Physiology and Athletic Conditioning (J.S.P.A.C) 2025; 5 (18): 51-62

*Research Article*

# Effect of Swimming Exercise and Royal Jelly on MAPK and MMP-9 Gene Expression in Lung Tissue of Benzo[a]pyrene-Induced Lung Cancer Mouse Model

**Sepideh Rajabi Baniani[1], Seyed Ali Hosseini [2]*, Mehrzad Moghadasi [3]**

1. PhD Student, Department of Exercise Physiology, Sh.C., Islamic Azad University, Shiraz, Iran
2. Department of Exercise Physiology, Marv.C., Islamic Azad University, Marvdasht, Iran
3. Department of Exercise Physiology, Sh.C., Islamic Azad University, Shiraz, Iran

**Received:** 16 November 2025
**Accepted:** 21 December 2025

## Abstract

**Introduction:** Lung cancer is one of the most prevalent cancers with a high mortality rate. Mitogen-Activated Protein Kinase (MAPK) and (Matrix Metalloproteinase-9) MMP-9 pathways play crucial roles in inflammation, oxidative stress, and cellular invasion. This study aimed to investigate the effects of swimming exercise and royal jelly on the gene expression of MAPK and MMP-9 in the lung tissue of mice with benzo[a]pyrene-induced lung cancer.

**Methods:** In this experimental study, 48 male Balb/C mice aged eight weeks were divided into eight groups: healthy control, lung cancer (BZP), , lung cancer + swimming training (ST), , lung cancer + royal jelly 50 mg/kg (RJ50), , lung cancer + royal jelly 100 mg/kg (RJ100), , lung cancer + swimming + royal jelly 50 mg/kg (ST.RJ50), and , lung cancer + swimming + royal jelly 100 mg/kg (ST.RJ100). Lung cancer was induced by intraperitoneal injection of benzo[a]pyrene at 100 mg/kg body weight. Swimming training was performed 3 days per week for 12 weeks. Royal jelly was administered intraperitoneally at doses of 50 and 100 mg/kg body weight. Forty-eight hours after the last session, mice were sacrificed, lung tissues were harvested, and gene expression of MAPK and MMP-9 was measured using real-time PCR.

**Results:** Lung cancer induction significantly increased MAPK and MMP-9 expression. Individual interventions, including swimming and royal jelly at 100 mg/kg, partially reduced MAPK and MMP-9 expression. However, the combination of swimming exercise with royal jelly, particularly at the higher dose (ST.RJ100), produced the greatest reduction in the expression of both genes.

**Conclusion**: The combination of regular exercise with royal jelly, especially at higher doses, has a synergistic effect in reducing MAPK pathway activity and MMP-9 expression. This combination may serve as a preventive and complementary natural strategy to control lung cancer progression and invasion. These findings highlight the importance of simultaneous non-pharmacological interventions with antioxidant and anti-inflammatory effects to improve molecular pathways related to cancer and enhance disease management.

**Keywords:**
Lung cancer, Mitogen-Activated Protein Kinase, Matrix Metalloproteinase-9, Royal Jelly, Swimming Exercise

***Corresponding author:** Seyed Ali Hosseini
**Address:** Department of Exercise Physiology, Marv.C., Islamic Azad University, Marvdasht, Iran
**Email:** alihoseini_57@iau.ac.ir **Tell:** 00989173027100
S A H: 0000-0001-9122-3952

## 1. Introduction

Lung cancer is one of the leading causes of cancer-related mortality worldwide, and environmental factors—particularly compounds derived from cigarette smoke and environmental pollutants—play a prominent role in its development (1). Benzo[a]pyrene (B[a]P), as one of the polycyclic aromatic hydrocarbons (PAHs), is a highly carcinogenic compound that, through its active metabolites, induces DNA damage, increases the production of reactive oxygen species (ROS), promotes chronic inflammation, and ultimately leads to the activation of cellular signaling pathways (2).

Among the most important of these pathways is the mitogen-activated protein kinase (MAPK) pathway, which comprises the major branches ERK, JNK, and p38 and plays a critical role in the regulation of cell growth, differentiation, inflammation, and cell death (3, 4). Excessive activation of the MAPK pathway can stimulate transcription factors such as AP-1 and NF-κB and, as a consequence, increase the expression of genes associated with cellular invasion, including MMP-9 (5).

Matrix metalloproteinase (MMP) pathways, particularly MMP-9, play a vital role in extracellular matrix remodeling and regulation of the tumor microenvironment (6). MMP-9 is one of the most important zinc-dependent metalloproteinases and is involved in both physiological processes (such as tissue repair) and pathological conditions (such as inflammation and cancer). Increased expression and activity of MMP-9 lead to degradation of the extracellular matrix (ECM), facilitation of malignant cell invasion, and metastasis (6–8). Studies indicate that MAPK signaling pathways can upregulate MMP-9 expression and stimulate tumor migration and growth processes, particularly under inflammatory conditions and in pulmonary diseases (9, 10). Therefore, inhibition of the MAPK pathway and regulation of MMP-9 may represent effective therapeutic targets for preventing the progression of lung cancer.

In recent years, numerous studies have shown that regular exercise and natural compounds with antioxidant properties can exert anti-inflammatory and anti-tumor effects through modulation of signaling pathways (11, 12). Regular exercise can modulate MAPK activity (13) and confer protective effects in lung cancer, including reduction of ROS levels, improvement of immune system function, and enhancement of pulmonary functional capacity (14–16). In addition, exercise can alter circulating and tissue levels of MMP-9, although the magnitude and direction of this response vary depending on health status and the presence of cancer (17, 18).

Royal jelly, a nutritious product derived from the honeybee hive, exhibits anti-inflammatory and antioxidant properties and inhibits cellular proliferation, thereby influencing cancer-related molecular pathways, including MAPK and MMP-9 (19–21). Evidence suggests that combining royal jelly with exercise or other supplements may produce stronger preventive and therapeutic effects, including reduced expression of genes associated with cancer cell growth and migration and activation of apoptotic pathways (21, 22).

Considering the pivotal roles of MAPK and MMP-9 in lung cancer progression and metastasis, along with evidence supporting the modulatory effects of exercise and royal jelly, the present study was designed to investigate the combined effects of swimming training and royal jelly on MAPK pathway activity and MMP-9 expression in lung tissue of mice with benzo[a]pyrene-induced lung cancer. This study aims to provide preclinical evidence supporting the use of these interventions as natural complementary therapeutic strategies.

## 2. Materials and Methods

In the present experimental study, which was conducted using a post-test control group design, 42 male Balb/C mice with a mean age of 8 weeks and a body weight of 18–22 g were purchased from the Laboratory Animal Breeding Center of the Pasteur Institute of Tehran and transferred to the animal laboratory of Pishgaman Institute of Higher Education in Shiraz. To allow acclimatization to the laboratory environment, the animals were housed in polycarbonate cages for one week. During this period, the mice were maintained under controlled conditions of temperature (22 ± 3°C), relative humidity (40–60%), appropriate ventilation, and a 12/12-hour light/dark cycle, with free access to food and water.

Of the 42 mice, 6 were assigned to the healthy control group, and the remaining 38 mice, after induction of lung cancer via benzo[a]pyrene injection, were allocated to the following groups: lung cancer, lung cancer + swimming training, lung cancer + royal jelly 50, lung cancer + royal jelly 100, lung cancer + swimming training + royal jelly 50, and lung cancer + swimming training + royal jelly 100.

To induce lung cancer, mice were fasted for 12 hours and then administered a single dose of benzo[a]pyrene at 100 mg/kg (Sigma-Aldrich, Germany; catalog number B1760). For this purpose, 24 mg of benzo[a]pyrene was dissolved in 1.2 mL of corn oil, and after complete dissolution, 10 international units of the prepared solution were injected into each mouse (23). Animal care and experimental procedures were performed in accordance with ethical guidelines for animal research, the standard principles for laboratory animal use approved by Islamic Azad University, Shiraz Branch, and the Helsinki Declaration.

Prior to the initiation of the main study and in a pilot experiment, 4 mice received the specified dose of benzo[a]pyrene, and 4 healthy mice served as controls. Fourteen days after benzo[a]pyrene injection, mice in both groups were anesthetized with ketamine and xylazine, sacrificed, and their lung tissues were subjected to pathological examination to confirm successful induction of benzo[a]pyrene-induced lung cancer.

Mice assigned to the swimming training, swimming training + royal jelly 50, and swimming training + royal jelly 100 groups underwent swimming exercise for 12 weeks, five sessions per week. Swimming training was performed in a specialized animal pool measuring 110 cm in width and 80 cm in depth, with water temperature maintained at 32°C. The training protocol consisted of two phases: an adaptation phase and the main training phase. During the adaptation phase, laboratory mice were familiarized with the aquatic environment and swimming exercise for 10 days. Subsequently, during the main training phase, mice exercised for 12 weeks, three sessions per week. In the first week, mice swam for 15 minutes per session. Thereafter, the swimming duration was gradually increased from 15 minutes to 30 minutes by the tenth week. During the final two weeks, the exercise duration was increased to 40 minutes per session.

To comply with the principle of progressive overload, no additional weight was applied during weeks 1 to 4. During weeks 5 to 8, a load equivalent to 2% of body weight was used, and during weeks 9 to 12, mice swam with a weight equivalent to 5% of their body weight attached to their tails. This training protocol was adopted based on previous studies with minor modifications (24, 25).

To prepare the royal jelly extract, 10 g of royal jelly was dissolved in 1000 mL of deionized distilled water, and the mixture was incubated at 50°C for 16 hours. The solution was then filtered and stored at 4°C. During the intervention period, the extract was administered daily via intraperitoneal injection at doses of 50 and 100 mg/kg (23, 26).

To minimize exercise-induced inflammatory effects, 48 hours after completion of the final training session, mice were anesthetized by intraperitoneal injection of ketamine (75 mg/kg) and xylazine (25 mg/kg) (Alfasan, Netherlands). After confirmation of deep anesthesia, the thoracic cavity was opened, and following displacement of connective tissues, the lung tissue was completely excised. The lung tissue was immediately washed and stored at −70°C.

For measurement of MAPK and MMP-9 gene expression in lung tissue, real-time polymerase chain reaction (PCR) was performed. Total cellular RNA was extracted using a column-based RNA extraction kit (FavorPrep™ Tissue Total RNA Kit, Taiwan). Gene expression levels were calculated and expressed using the ΔΔCt method. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by the least significant difference (LSD) post hoc test. All statistical analyses were conducted using SPSS software version 26, and the level of statistical significance was set at $P \leq 0.05$.

## 3. Results

Based on the results obtained from one-way analysis of variance (ANOVA), a significant difference was observed among the study groups in the expression of the MAPK gene ($F = 7.332$, $p < 0.001$) and MMP-9 ($F = 7.545$, $p < 0.001$). To identify the source of these differences, the LSD post hoc test was applied.

The results of the post hoc analysis indicated a significant increase in MAPK levels in the BZP, RJ50, RJ100, and ST groups compared with the healthy control group. In contrast, MAPK levels in the RJ100, ST, RJ50, ST.RJ50, and ST.RJ100 groups were significantly reduced compared with the BZP group. Furthermore, MAPK gene expression in the ST.RJ50 and ST.RJ100 groups was significantly lower than that observed in the RJ50 and RJ100 groups. In addition, MAPK gene expression in the ST.RJ100 group was significantly reduced compared with the ST and RJ100 groups (Figure 1).

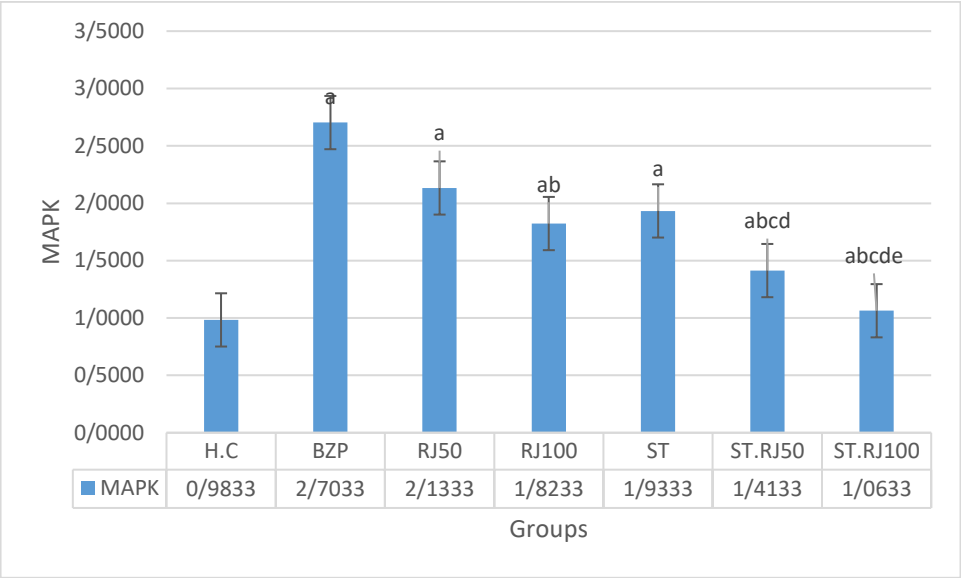


**Figure 1. Changes in MAPK gene expression among the study groups;**
**a:** significant difference compared with the healthy control (HC) group;
**b:** significant difference compared with the benzo[a]pyrene (BZP) group;
**c:** significant difference compared with the RJ50 group;
**d:** significant difference compared with the RJ100 group;
**e:** significant difference compared with the swimming training (ST) group.

In the analysis of changes in MMP-9, the results of the Bonferroni post hoc test indicated a significant increase in MMP-9 levels in the BZP, RJ50, RJ100, and ST groups compared with the healthy control group. The level of MMP-9 in the ST.RJ50 and ST.RJ100 groups was significantly lower than that observed in the BZP, RJ50, and RJ100 groups. In addition, MMP-9 gene expression in the ST.RJ100 group was significantly reduced compared with the ST group (Figure 2).

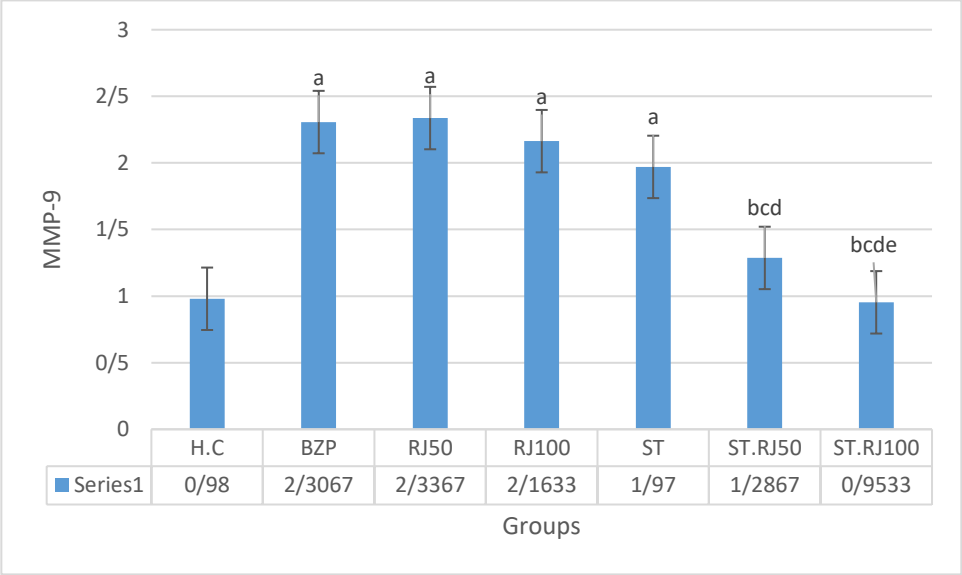


**Figure 2. Changes in MMP-9 gene expression among the study groups;**
**a:** significant difference compared with the healthy control (HC) group;
**b:** significant difference compared with the benzo[a]pyrene (BZP) group;
**c:** significant difference compared with the RJ50 group;
**d:** significant difference compared with the RJ100 group;
**e:** significant difference compared with the swimming training (ST) group.

## 4. Discussion

The findings of the present study demonstrated that induction of lung cancer with benzo[a]pyrene resulted in a significant increase in the expression of MAPK and MMP-9 genes in lung tissue. The elevation of MAPK under these conditions indicates excessive activation of the MAPK pathway, which is associated with increased oxidative stress, inflammation, and tumor growth (4). In parallel, the increase in MMP-9, as a zinc-dependent metalloproteinase, reflects extensive degradation of the extracellular matrix (ECM) and facilitation of cancer cell invasion and metastasis (6–8). Previous studies have also confirmed that MMP-9 is regulated by several complex signaling pathways, particularly MAPK branches (JNK and p38) and the transcription factors NF-κB and Smad3 (27, 28).

Under inflammatory or cancerous conditions, excessive stimulation of these pathways—especially by TNF-α or benzo[a]pyrene—can markedly increase MMP-9 expression and thereby exacerbate cellular invasion and metastasis through ECM degradation (27, 29).

With respect to the effects of royal jelly supplementation, the results indicated that the 50 mg dose of royal jelly did not exert a significant effect on MAPK or MMP-9 gene expression, whereas the 100 mg dose led to a significant reduction in MAPK expression compared with the benzo[a]pyrene group, without a significant effect on MMP-9. It has been reported that royal jelly can modulate cancer-related molecular pathways, including MAPK. For instance, Cooperola et al. (2023) reported that royal jelly, alone and in combination with Aloe vera, activated apoptotic pathways via MAPK signaling in lung cancer cells by increasing BAX expression and decreasing BCL-2 levels, ultimately resulting in reduced glycolysis and inhibition of cell proliferation (21).

In addition, Fazeli et al. (2018) demonstrated that royal jelly reduced cell viability, inhibited migration, and decreased MMP-9 expression by approximately 50% in bladder cancer (5637) cells, while exerting no effect on MMP-2 expression (22). The discrepancy between the findings of the present study and those reported by Fazeli et al. may be attributed to differences in cancer tissue type, experimental models, and intervention protocols.

Evaluation of the effects of swimming training revealed that MAPK gene expression was significantly reduced following the intervention compared with the benzo[a]pyrene group. Consistent with these findings, previous evidence indicates that regular physical activity can modulate the MAPK pathway and exert anti-inflammatory and protective effects in lung cancer, including reductions in ROS levels, improvements in immune responses, and enhancement of pulmonary functional capacity (13, 30). Regular exercise is also associated with activation of endogenous antioxidant systems, leading to reduced oxidative stress in lung tissue, primarily through increased activity of key antioxidant enzymes (31).

A notable finding of the present study was the synergistic effect of combining swimming training with royal jelly supplementation, such that this combined intervention resulted in a simultaneous reduction in MAPK and MMP-9 gene expression. This synergistic effect is likely mediated through modulation of MAPK branches (p38 and JNK), inhibition of the NF-κB pathway, and attenuation of oxidative stress in lung tissue. Royal jelly, owing to its antioxidant and anti-inflammatory constituents such as 10-hydroxy-2-decenoic acid (10-HDA), flavonoids, and polyphenols, appears to potentiate the beneficial effects of exercise in reducing ROS and regulating signaling pathways. Previous studies have also supported the additive effects of antioxidant interventions; for example, it has been reported that the combination of aerobic exercise with antioxidant supplementation reduces the expression of RAS and ERK genes in muscle tissue and enhances the ability of exercise to inhibit signaling pathways associated with cancer cell growth and progression (20, 32). Concurrently, exercise training, through enhancement of immune function and increased antioxidant capacity, may reduce MMP-9 expression and thereby limit cellular invasion and metastasis (19, 22, 33).

Overall, the combination of exercise training and royal jelly, by concurrently reducing MAPK activity and MMP-9 expression, exerts synergistic effects in attenuating inflammation, oxidative stress, and extracellular matrix degradation, which may substantially inhibit lung cancer progression and metastasis (22, 34). These findings suggest that the concurrent use of exercise interventions and natural antioxidant supplements may serve as a preventive strategy and complementary therapeutic approach in the management of lung cancer. Furthermore, the results demonstrated that the higher dose of royal jelly (100 mg), when combined with swimming training, exerted a stronger modulatory effect on MAPK and MMP-9 gene expression, such that the reductions observed in the combined ST.RJ100 group were significantly greater than those observed with swimming training or 100 mg royal jelly alone, indicating a dose-dependent synergistic effect of royal jelly in enhancing the protective response against lung cancer progression.

## ۵. Conclusion

The present study demonstrated that induction of lung cancer with benzo[a]pyrene resulted in a significant increase in the expression of MAPK and MMP-9 genes in lung tissue, thereby activating signaling pathways associated with oxidative stress, inflammation, and cellular invasion. Individual interventions, including swimming training and royal jelly supplementation, were able to partially modulate MAPK and MMP-9 expression; however, the synergistic effects of combining these two interventions produced the greatest reduction in the expression of the studied genes. Moreover, the use of a higher dose of royal jelly (100 mg) in combination with swimming training exerted a stronger modulatory effect on both MAPK and MMP-9 genes, such that the reductions observed in the combined ST.RJ100 group were significantly greater than those achieved by swimming training alone or royal jelly supplementation at 100 mg. This finding indicates a synergistic effect of the higher supplement dose in enhancing the protective response against lung cancer progression. Therefore, the combination of regular exercise training and royal jelly supplementation may serve as an effective preventive strategy and a natural complementary therapeutic approach for reducing lung cancer invasion and progression. These findings suggest that non-pharmacological interventions with strong antioxidant and anti-inflammatory properties can facilitate improvement in cancer-related molecular pathways and increase the likelihood of disease control and enhanced pulmonary function. Overall, the results of this study confirm the importance of the concurrent use of exercise and natural antioxidant supplements in reducing the expression of key MAPK and MMP-9 pathways and preventing lung cancer progression and metastasis.

## Acknowledgements

This article was derived from the doctoral dissertation of the first author, a student at Islamic Azad University, Shiraz Branch. The authors express their sincere gratitude to all individuals who contributed to the execution of this study.

## Funding

This study did not receive financial support from any organization. All costs related to the research project and manuscript preparation were borne by the authors.

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

## References


1. Zhao M, Xue G, He B, Deng J, Wang T, Zhong Y, et al. Integrated multiomics signatures to optimize the accurate diagnosis of lung cancer. Nature Communications. 2025;16(1):84.

2. Smolarz B, Łukasiewicz H, Samulak D, Piekarska E, Kołaciński R, Romanowicz H. Lung Cancer—Epidemiology, Pathogenesis, Treatment and Molecular Aspect (Review of Literature). International Journal of Molecular Sciences. 2025;26(5):2049.

3. Naghizadeh, N., Riyahi Malayeri, S., Roozbahani, M., Khademi, A., Shirvani, H. The Effectiveness of Endurance Training and Nano Curcumin Supplementation on the Expression of Mir-21and P53 Genes in Brain Tumor Tissue in an Animal Model of Glioblastoma Multiform. Journal of Nutrition,Fasting and Health, 2024; 12(1): 26-35. doi: 10.22038/jnfh.2023.73964.1455.

4. Xie X, Shin YR, Kim T-S, Seong Y-S, Yi YW, Kim DJ. Identification of sinensetin as a selective inhibitor for mitogen-activated protein kinase kinase 6 and an anticancer agent for non-small cell lung cancer. American Journal of Cancer Research. 2025;15(1):113.

5. Alsharoh H, Chiroi P, Isachesku E, Tanasa RA, Pop O-L, Pirlog R, Berindan-Neagoe I. Personalizing therapy outcomes through mitogen-activated protein kinase pathway inhibition in non-small cell lung cancer. Biomedicines. 2024;12(7):1489.

6. Atkinson JJ, Senior RM. Matrix metalloproteinase-9 in lung remodeling. American journal of respiratory cell and molecular biology. 2003;28(1):12-24.

7. Chen L-H, Tsai Y-F, Wu W-T, Chiu K-L, Tsai C-W, Chang W-S, et al. Association of matrix metalloproteinase-9 genotypes with lung cancer risk in Taiwan. Anticancer Research. 2024;44(5):1845-52.

8. Gao L, Dhilipkannah P, Jiang F. Streptococcus pneumoniae infection is associated with matrix metalloproteinase-9 in lung cancer progression and brain metastases. Scientific Reports. 2025;15(1):37007.

9. Zhang H, Zhao B, Zhai Z-G, Zheng J-D, Wang Y-K, Zhao Y-Y. Expression and clinical significance of MMP-9 and P53 in lung cancer. European Review for Medical & Pharmacological Sciences. 2021;25(3).

10. Kalali D. The role of the matrix metalloproteinase-9 gene in tumor development and metastasis: a narrative review. Global Medical Genetics. 2023;10(02):048-53.

11. Marino P, Mininni M, Deiana G, Marino G, Divella R, Bochicchio I, et al. Healthy lifestyle and cancer risk: modifiable risk factors to prevent cancer. Nutrients. 2024;16(6):800.

12. Porro C, La Torre ME, Tartaglia N, Benameur T, Santini M, Ambrosi A, et al. The potential role of nutrition in lung cancer establishment and progression. Life. 2022;12(2):270.

13. Yang L, Morielli AR, Heer E, Kirkham AA, Cheung WY, Usmani N, et al. Effects of exercise on cancer treatment efficacy: a systematic review of preclinical and clinical studies. Cancer research. 2021;81(19):4889-95.

14. Luo Z, Wan R, Liu S, Feng X, Peng Z, Wang Q, et al. Mechanisms of exercise in the treatment of lung cancer–a mini-review. Frontiers in Immunology. 2023;14:1244764.

15. SH M-H, Musavi N. The effect of 12 weeks of submaximal swimming training on immunoreactivity of Ras and Raf-1 in lung epithelial cells of Wistar rats exposed to carcinogen NNK. 2020.

16. Williamson D, Gallagher P, Harber M, Hollon C, Trappe S. Mitogen-activated protein kinase (MAPK) pathway activation: effects of age and acute exercise on human skeletal muscle. The Journal of physiology. 2003;547(3):977-87.

17. Gibala MJ, McGee SL, Garnham AP, Howlett KF, Snow RJ, Hargreaves M. Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1α in human skeletal muscle. Journal of applied physiology. 2009;106(3):929-34.

18. Messina G, Tartaglia N, Ambrosi A, Porro C, Campanozzi A, Valenzano A, et al. The beneficial effects of physical activity in lung cancer prevention and/or treatment. Life. 2022;12(6):782.

19. Ababd ZVM, Chaman NH, Hosseini M, Maleki A. Aerobic Exercise and Nano-curcumin Supplementation Prevent cancer symptom development through MAPK/ERK pathway. 2023.

20.Rullman E, Olsson K, Wågsäter D, Gustafsson T. Circulating MMP-9 during exercise in humans. European journal of applied physiology. 2013;113(5):1249-55.

21. Giganti MG, Tresoldi I, Sorge R, Melchiorri G, Triossi T, Masuelli L, et al. Physical exercise modulates the level of serum MMP-2 and MMP-9 in patients with breast cancer. Oncology letters. 2016;12(3):2119-26.

22. Oršolić N, Jazvinšćak Jembrek M. Royal jelly: biological action and health benefits. International journal of molecular sciences. 2024;25(11):6023.

23. Miyata Y, Sakai H. Anti-cancer and protective effects of royal jelly for therapy-induced toxicities in malignancies. International journal of molecular sciences. 2018;19(10):3270.

24. Kul Köprülü T, Gezer B, Erkal Çam B. The impact of apoptosis-inducing MAPK and glycolytic pathways modulated by Aloe vera and royal jelly in lung and colorectal cancer. Medical Oncology. 2025;42(2):51.

25. Fazili N, Soheili ZS, Malekzadeh-Shafaroudi S, Samiei S, Alipoor SD, Moshtaghi N, Bagheri A. Royal Jelly Decreases MMP-9 Expression and Induces Apoptosis in Human 5637 Bladder Cancer Cells. Journal of Cell & Molecular Research. 2021;13(1).

26. Rashedi F, Heidarnia E, Hosseini SA. Swimming training and royal jelly effects on caspase-3 expression in lung cancer mice. Journal of Physical Activity and Hormones. 2025;6(1):14-8.

27. Fei Z, Li D, Li K, Zhou M, Li Y, Li Y, Sun Z. Detraining after tumor-bearing accelerates tumor growth while continuous training decreases tumor growth in mice. Journal of Traditional Chinese Medical Sciences. 2020;7(1):75-81.

28. Mirdar S, Arab A, Hedayati M, Hajizade A. The effect of pregnant rat swimming on hypoxia-inducible factor-1α levels of neonatal lung. Tehran University Medical Journal. 2012;69(12).

29. Shirzad M, Kordyazdi R, Shahinfard N, Nikokar M. Does Royal jelly affect tumor cells? Journal of HerbMed Pharmacology. 2013;2(2):45-8.

30. Yao J, Xiong S, Klos K, Nguyen N, Grijalva R, Li P, Yu D. Multiple signaling pathways involved in activation of matrix metalloproteinase-9 (MMP-9) by heregulin-β1 in human breast cancer cells. Oncogene. 2001;20(56):8066-74.

31. Cho SJ, Chae MJ, Shin BK, Kim HK, Kim A. Akt-and MAPK-mediated activation and secretion of MMP-9 into stroma in breast cancer cells upon heregulin treatment. Molecular medicine reports. 2008;1(1):83-8.

32. Liu A, Li X, Hao Z, Cao J, Li H, Sun M, et al. Alterations of DNA methylation and mRNA levels of CYP1A1, GSTP1, and GSTM1 in human bronchial epithelial cells induced by benzo [a] pyrene. Toxicology and Industrial Health. 2022;38(3):127-38.

33. Radak Z, Zhao Z, Koltai E, Ohno H, Atalay M. Oxygen consumption and usage during physical exercise: the balance between oxidative stress and ROS-dependent adaptive signaling. Antioxidants & redox signaling. 2013;18(10):1208-46.

34. Fashi M, Alinejad HA, Mahabadi HA. The effect of aerobic exercise in ambient particulate matter on lung tissue inflammation and lung cancer. Iranian journal of cancer prevention. 2015;8(3):e2333.

35. Du T, Wang W, Zhang R. Royal jelly and doxorubicin suppressed tumor cells in the xenograft model of lung cancer via the STAT3/FOXM1/ATG7 signaling pathways in athymic nude mice: a biochemical, immunohistochemically and molecular approach. Toxicology Research. 2025;14(2):tfaf042.

36. Aslan A, Gok O, Beyaz S, Can MI, Parlak G, Gundogdu R, et al. Royal jelly regulates the caspase, Bax and COX-2, TNF-α protein pathways in the fluoride exposed lung damage in rats. Tissue and Cell. 2022;76:101754.

37. Mohammadi H, Mohammadian B, Najafzadeh Varzi H, Shahriari A. Evaluation of the effect of royal jelly on histopathological and biochemical changes in the lungs of rats following arsenic trioxide toxicity. Iranian Veterinary Journal. 2024;20(2):92-101.

38. Benoot T, Piccioni E, De Ridder K, Goyvaerts C. TNFα and immune checkpoint inhibition: friend or foe for lung cancer? International Journal of Molecular Sciences. 2021;22(16):8691.

39. Dong Y, Sun N, Qiang Y, Wang Y, Yuan Y, Li M. TNF-α inhibites non-small cell lung cancer cells proliferation by targeting THRIL in a FTO-YTHDF2-dependent manner. Archives of Biochemistry and Biophysics. 2025:110438.

40. Sobo-Vujanovic A, Vujanovic L, DeLeo AB, Concha-Benavente F, Ferris RL, Lin Y, Vujanovic NL. Inhibition of soluble tumor necrosis factor prevents chemically induced carcinogenesis in mice. Cancer immunology research. 2016;4(5):441-51.

41. signalling via TNF receptor 1 and TNF receptor 2 in the tumour microenvironment. Current opinion in immunology. 2024;86:102409.

42. Riyahi Malayeri S, Hoseini M. The Effect of Acute Exercise on Vaspin and Chemerin Levels in Obese Men. jbrms 2021; 8 (1) :58-66

43. Torrey H, Butterworth J, Mera T, Okubo Y, Wang L, Baum D, et al. Targeting TNFR2 with antagonistic antibodies inhibits proliferation of ovarian cancer cells and tumor-associated Tregs. Science signaling. 2017;10(462):eaaf8608.

44. Tam EM, Fulton RB, Sampson JF, Muda M, Camblin A, Richards J, et al. Antibody-mediated targeting of TNFR2 activates CD8+ T cells in mice and promotes antitumor immunity. Science translational medicine. 2019;11(512):eaax0720.