JOURNAL OF NUTRITION FASTING AND HEALTH

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

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ARTICLEINFO

Article type:
Research Paper

Article History:
Received: 24 Jul 2023
Accepted: 02 Dec 2023
Published: 15 Jan 2024

Keywords:
Glioblastoma multiform
miR-21
P53

ABSTRACT

Introduction: Glioblastoma multiforme is the foremost common harmful tumor of the central nervous system that specifically influences the brain and is resistent to common therapies such as surgery, radiotherapy and chemotherapy. The aim of this study was to examine the viability of perseverance preparing and Nano-curcumin supplementation on the expression of miR-21 and P53 qualities in brain tumor tissue in a creature demonstrate of glioblastoma multiforme.

Methods: In this experiment, 35 8-week-old male Wistar rats were divided into seven groups with 5 rats each: healthy control group, 4-week-old healthy, control group cancer, 4-week-old cancer group and training group, Nano-curcumin group and training-Nano-curcumin group. Cancer cells were injected into the right frontal cortex of mice using a pump at a depth of 2.5 mm. One week later, mice entered the treadmill training program (4 weeks) and Nano-curcumin was administered orally at a dose of 80 mg/kg (28 days). Gene expression was measured using real-time fluorescent quantitative PCR and used for analysis.spss software.

Results: The expression of miR-21 gene in the training group, Nano-curcumin, and training group Nano-curcumin was lower than that of the control cancer at 4 weeks (P = 0.001). Moreover, the expression of P53 gene in the Nano-curcumin training group and Nano-curcumin training group was higher in cancer cells and 4-week blood-eating cancer than in the control group (P = 0.001).

Conclusion: Endurance training and curcumin administration appear to reduce tumor growth in mice with brain tumors by modulating the expression of miR-21 and p53 genes.

► Please cite this paper as:
Naghizadeh N, Riyahi Malayeri Sh, 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. J Nutr Fast Health. 2024; 12(1): 26-35. DOI: 10.22038/JNFH.2023.73964.1455.

Introduction

Brain tumors, particularly dangerous tumors, are among the foremost terrifying maladies that straightforwardly influence the brain. Brain tumors are isolated into two sorts: essential and auxiliary (systemic) brain tumors (1). Glioblastoma multiforme (GBM), the most dangerous tumor of the central nervous system, originates from glial tissue and is resistant to commonly used therapies such as surgery, radiotherapy, and chemotherapy (2). The normal survival time of glioblastoma multiforme patients who get standard care treatment is roughly 15 months (1, 2).

Later studies have resulted in the belief that microRNAs play a crucial part within the start and movement of cancer (3). A few miRNAs act as tumor silencers or oncogenes and play key parts in tumor cell expansion and tumor cell apoptosis (4) MicroRNAs (miRs) suppress their target genes through binding the 3′ untranslated regions of messenger RNAs. (5). One of the

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biomarkers in cancer determination and treatment is miR-21; which is found on chromosome 17 and is known as an oncogene protein activator. It has been detailed in numerous threatening tumors, counting glioblastoma, and is included in tumor movement (6). Laboratory studies considers on a few sorts of cancer have appeared that the devastation of miR-21 stifles cell expansion and tumor development, and decreases the intrusion of metastasis (4). The results of a study showed that the diminishment of miR-21 expression moreover decreases tumorigenic potential in glioblastoma cell lines (7). A few miRs have been reported to be included within the p53 pathway, which are either controlled by p53 or act specifically to quell the expression of p53 or its downstream effectors, showing the significance of miRs within the p53 pathway (5). P53 could be a translation factor and tumor silencer protein that plays a part amid the cell cycle, counting transmission of cell messages, cell reaction or harm and recovery, DNA stability and genomic Stability (9, 8). The P53 quality is found on the brief arm of chromosome number 17 and its disturbance and inactivation leads to cancer (6). Later investigate has revealed that P53, in expansion to having an administrative part in apoptosis, cell cycle capture, and cell maturing, conjointly through supporting the activity of cancer prevention agents, too plays a skillful role (10). MiR-21 applies its oncomiR work by hindering apoptosis. Erasure of miR-21 sensitizes cells to apoptosis actuated by DNA-damaging specialists, within the nearness or nonattendance of p53 (5).

On the other hand, curcumin, the organically dynamic substance of turmeric, has different possibilities in terms of usefulness, which influences the work of numerous translation components, development variables, and receptors due to its polyphenolic dynamic substance. In addition, curcumin has low poisonous quality and it has been appeared that it performs a wide run of therapeutic capacities, counting antioxidant, anti-inflammatory, antimicrobial impacts, treatment of diabetes, Alzheimer's, and anti-cancer through numerous cellular pathways (10, 11). It moreover can change the cell cycle and pathways included in multiplication, apoptosis, relocation, intrusion, angiogenesis, and metastasis. Mechanically, curcumin balances a few atomic targets and applies its anticancer properties either by changing quality expression, actuation, or signaling pathways or by coordinating interaction and diminishes a few side impacts related with chemotherapy (12). A few prove has affirmed the antitumor impact of curcumin and its work on tumor cells (13, 14). Ponders have appeared that the utilization of curcumin and nano-curcumin, in expansion to a critical increment within the expression of the P53 quality, leads to cell cycle capture and apoptosis (15,10). In a study, Wang et al. (2017) appeared that curcumin can initiate apoptosis and diminish the movement of cancer cells by reregulating miR-21/Akt (16). Too, sports and cancer considers appear that regular exercise can have useful impacts in preventing and controlling cancer (17). Aerobic exercises is a vital non-pharmacological instrument that has an anti-tumor impact and can diminish tumor development, act as a tumor silencer, and control quality expression through distinctive components such as quieting quality expression (18). in a research, it was appeared that sports exercises increase P53 (19). In a review article that investigated the aerobic metabolism of P53 and cancer, it was expressed that the components directed by P53 control mitochondrial breath additionally offer assistance keep up genomic soundness (20). The results of a study showed that endurance training together with nano curcumin supplementation caused cell cycle capture and apoptosis by influencing the p21-p53 pivot (10). The study of Soltani et al (2019) appeared that Aerobic exercise can can diminish MIR-21 (4). Moreover, 8 weeks of high-impact work out diminished P53 and MIR-21 in individuals with prostate cancer (6). Nowadays, one of the critical issues that analysts have focused on is examining the impact of diverse intercessions such as Aerobic exercise and home grown supplements and their impacts on the development, improvement and conceivably restraint of the cancerous mass (21). Considering the useful impacts of preparing action on the avoidance of Cell senescence and apoptosis handle as well as positive and antioxidant and anticancer impacts of nanocurcumin supplement (10). This question is raised whether the combination of sports movement and the utilization of nanocurcumin supplements can have a more noteworthy impact on the diminishment of glioblastoma brain tumor tissue

than either of them alone. According to the searches, no comprehensive ponder was found that explored this issue. In spite of the fact that no study was found in this field, a few ponders have examined the synchronous impact of Aerobic exercise and curcumin on brain work. Therefore, the purpose of this study is the effectiveness of endurance training and nanocurcumin supplementation on miR-21 and P53 quality expression in brain tumor tissue of a creature show of glioblastoma multiforme.

Methods

The present study is experimental; which was done at the Creature Center of Research facility Sciences, Baqiyat Elah University of Medical Sciences. This study has been looked into and endorsed by the ethical committee of the Borujerd Islamic Azad College with code IR.IAU.B.REC.1400.29. Since it was not conceivable to get to human subjects due to space, ethics, and time limitations, subsequently, animal subjects (male Wistar rats) were utilized. Concurring to the enlightening of the Iranian Society for the Protection of Laboratory Animals, the examined creatures were kept independently in cages. The statistical population of male Wistar rats and its sample size included 35 rats. The test estimate was decided with G*Power program based on the factual strategy of investigation of change and alpha blunder level of 0.05 and control of 0.85 with 35 tests (10). Rats with an approximate age age of eight weeks and a weight extend of 200±20 grams were gotten from the Pasteur Research facility Creature Breeding Center (Tehran, Iran) and after the animals were transferred to the sports physiology laboratory. All creatures were kept within the same and ideal conditions of research facility creatures (temperature 22±2 °C, relative mugginess 45-50 and light-dark cycle 12:12) and they had free access to standard research facility nourishment and water. After a week of getting utilized to the environment, the rats were arbitrarily partitioned into 7 bunches of 5 included: Basic healthy control group, healthy control for 4 weeks, Basic cancer control, 4-week cancer control, cancer + nanocurcumin, cancer + endurance exercise and cancer + aerobic exercise + nanocurcumin group were divided. One week after the Induction of cancer cells within the frontal cortex of rats, nanocurcumin supplement was arranged and gavage was performed concurring to the informational (22). For endurance training, rats were to begin with arranged for running for one week on a treadmill for rodents (DSI 5-lane show, made in Iran). At that point, a 4-week exercise protocol was executed with an escalated of 18 meters per minute for 25-40 minutes per day with reiteration of 5 sessions per week (balanced high-impact convention) (Table 1) (23).The control groups (basic healthy, healthy 4 weeks, basic cancer and 4 weeks cancer) did not get any movement or supplements. At the end of the interventions of the exercise and supplementation groups, the mice were transferred to the laboratory. The basic healthy control and basic cancer control groups were anesthetized and sacrificed with peritoneal injection of xylosin and vaccinia 48 hours after the last training session (at the end of 4 weeks) to determine the basic values of the studied genes in the first week. At that point, the brain tissue of all rats was expelled beneath sterile conditions and instantly solidified in fluid nitrogen at -70 degrees Celsius. At that point for tissue staining and processing, tumor estimate estimation and RNA (RiboNucleic Corrosive) extraction and cDNA (Complementary deoxyribonucleic corrosive) as well as primers designing and the examination of gene expression utilizing Real-time PCR method, the tests were data analysis and Information examination was kept up.

Table 1. Endurance training protocol

Endurance Training	Weeks	Intensity	Duration	frequency
Aerobic Treadmill	1	18 m/min	25 min/day	3 day/ week
	2	18 m/min	30 min/day	3 day/ week
	3	18 m/min	35 min/day	3 day/ week
	4	18 m/min	40 min/day	3 day/ week

Cancer Cell Culture

C6 mouse glioblastoma cells were gotten from the National Center for Hereditary Assets. Cells were to begin with refined. To culture C6 cells, an RPMI cell culture medium was utilized. To begin with, C6 cells were refined in a carafe in RPMI medium (Roswell Stop Dedication Founded), 300 mg/ml penicillin (Sigma, America), 720 mg/ml streptomycin (Jabarban Hayan Pharmaceutical), and 2 g/L sodium bicarbonate 10% (Merck,

Germany). The ultimate volume of the cell culture medium was 1000 ml, and its pH was balanced to1.7. At that point it was neutralized with PBS (buffered saline Pho) (Gibco, America) and 0.025% trypsin-EDTA arrangement and with 10% FBS medium. The arrangement was centrifuged at 1200 rpm for 5 minutes and the cells were isolated. The Initial density for cell culture was considered to be 100,000 cells/cm2. At long last, 10 microliters of trypan blue color (0.4% weight-volume) and 90 µl of cell suspension and neobar slides were used for cell counting and viability. The rate of recolored cells (blue) was decided as the rate of dead cells.

Cancer Tumor Induction

To induce cancer, the refined cells of C6 creature glioma blastoma were utilized (24). In such a way that for tumor induce, the animals were anesthetized by intraperitoneal infusion of ketamine (100 mg/kg) and xylazine (10 mg/kg) (4). To begin with, animal hair was shaved. At that point, the creature was settled by putting the bars interior the ears and upper teeth to the stereotaxic gadget (Stelting 1, show 200195504). After making a skin cut within the back of the cranium and evacuating the periosteum concurring to Swansen's enlightening, utilizing an mixture pump and a stereotaxic gadget, the proper frontal cortex of the rats was decided on the bone with the taking after facilitates and gradually infused into the rats brain for 10 minutes in a volume of 10 microliters with a concentration of 5x105 cells/30 µL. At that point the bone was closed utilizing wax and the skin was sutured utilizing cotton string. After relinquishing the creatures, the brain tissue was sent to the research facility for recoloring and tissue preparing (25).

Preparation and Gavage of Nano Curcumin Supplement

One week after the affirmation of cancer within the rats, concurring to the instructions, nano curcumin supplement was given 5 days a week for 28 days with a dose of 80 mg/kg for cancer + nano curcumin, cancer + Exercise + nano curcumin groups utilizing an affront syringe based on the weight of each mouse. To get ready chitosan nanoparticles supplement, chitosan (500 mg) was Solved in 2% v/v acidic corrosive arrangement (50 ml) and blended with curcumin in ethanol (1 mg/ml).15 ml of 1% weight-volume TPP arrangement was included to it. At that point the arrangement was blended for 1 hour and centrifuged at 10,000 rpm for 30 minutes. To get chitosan nanoparticles encased in curcumin. Commercial nano curcumin fabricated commercially by Exir Nano Sina Company (Tehran, Iran) was utilized as a comparative test of item quality. For each creature, after planning the item, 80 mg per kilogram of body weight was utilized (22).

RNA Extraction and cDNA Production

To extricate add up to RNA, it was homogenized at a proportion of 1 to 10 in Isol RNA-reagent Lysis concurring to the enlightening of the pack (Qiagen, Germany). In arrange to remove protein components, the resulting product was centrifuged at 4C for 10 minutes at 12000 rpm. The supernatant was expelled and blended with chloroform with essential Isol at a proportion of 0.5 to 1. The item was centrifuged at 4C for 15 minutes at 12,000 rpm and the mineral and watery parts were isolated, the RNA containing portion was evacuated and blended with isopropanol at a proportion of 0.5 to 1 and cleared out for 10 minutes at room temperature and after that centrifuged at 4C for 10 minutes at 12,000 rpm. The plate containing RNA was broken down in 20 µL of Free-RNAs water. RNA concentration was measured employing a nono drop gadget and the proportion of 260 to 280 between 1.8 and 2 was characterized as ideal immaculateness. After extricating RNA with tall virtue and concentration from the hippocampus of all examined tests, cDNA amalgamation steps were performed according to the manufacturer's convention (Fermentas, USA) and after that the synthesized cDNA was utilized to perform the invert translation response.

Designing Primers and Checking the Expression of miR-21 and P53 Genes

Refined water containing lyophilized preliminary 10 microliters, Primer Forward and Primer Revers 0.5 microliters each, cDNA, 1 microliter and DEPC Water 8 microliters were utilized to plan groundworks. For Biagen, the entire RNA of the cells was extricated concurring to the Cinagen convention utilizing the q RT-PCR strategy utilizing Kiazol arrangement. The quality of extricated RNAs was assessed by spectrophotometry. To plan single-stranded cDNA, Oligo dt groundwork and invert translation chemical were performed agreeing to the pertinent convention. Each PCR response was

performed in an ABI Step One machine agreeing to the manufacturer's protocol. Real-time PCR response cycles for qualities were performed at three temperatures of 94, 60, and 72 degrees Celsius. The Melting chart was done to check the precision of PCR responses. Dissolving chart was done to check the exactness of PCR responses. GAPDH (Glyceraldehyde-3-phosphate dehydrogenase) and U6 were utilized as reference qualities for P53 and miR-21. The expression levels of control and exploratory qualities were measured together (Table 2).

Table 2. Sequence of primers used

Gene	Forward primer	Reverse primer	Product lenght	Accession number
U6	5′-GCGCGTCGTGAAGCGTTC-3′	5′- G TGCAGGGTCCGAGGT-3′		
mir-21	5′-TGGATACGACTCAACATCA-3′	5′-TGGATACGACAAAAATATGGA-3′		
GAPDH	5′-CAAGTTCAAGGGCACAGTCA-3′	5′-CCCCATTTGATGTTAGCGGG-3′		
P53	5′-TCCCCTCCTTTCTTGCCATT-3′	5′- CAGAGACCCAGCAACTACCA-3′	170 nt	NM_030989.3

Statistical Analysis

To begin with, the Shapiro-Wilk test was utilized to check the normality of the data dispersion. Considering the normality distribution of the data, a one-way investigation of change was utilized to check the difference between the groups, Levene's test was utilized for the homogeneity of changes, and Tukey's post hoc test was utilized on the difference that there was a contrast. data analysis was done utilizing the SPSS software version 26 and charts from Excel with significant level (p≤0.05).

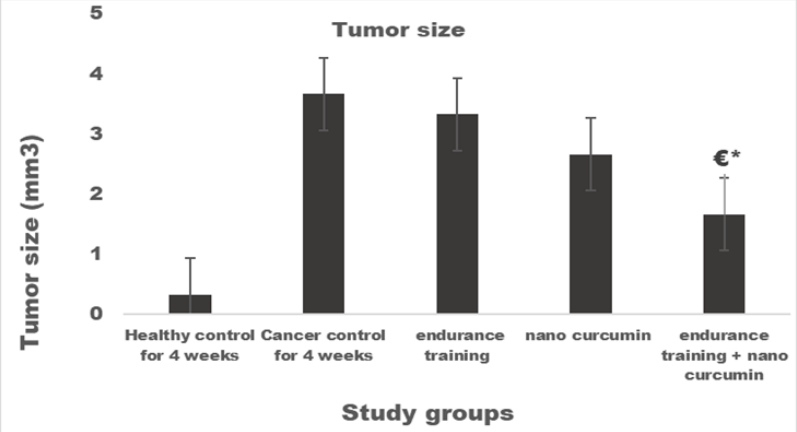

Figure 1. Tumor size in different groups.(* p ≤ 0.05)*A significant decrease in the cancer + endurance training + nano curcumin , compared to the 4-week cancer control group , (€ p ≤ 0.05)€ Significant reduction in the training of the cancer + endurance training + nano curcumin compared to the cancer + endurance training.

Results

According to the results of one-way analysis of variance of the one-way examination of fluctuation for tumor development rate, it appeared that there's a noteworthy distinction between the bunches (sig=0.001, F=16.50). Agreeing to the results of Tukey's post hoc test, the tumor growth rate within the preparing + nano curcumin gather was altogether to the results diminished compared to the 4-week cancer control group and preparing cancer (P=0.001) (Figure 1). In any case this diminishment within the nano curcumin group and the preparing gather was measurably noteworthy (P ≤ 0.05).

In addition, there was a significant difference between groups in the expression of miR-21 (sig = 0.001, F = 55.79), thus exercise and nanocurcumin each had a different expression of miR-21 (P<0.001) and exercise had. + nanocurcumin interaction showed a decrease in the expression of miR-21 gene in Tukey post hoc test (P=0.001) (Table 3) (Figure 2)

Regarding the expression of the p53 gene, there was a difference between groups in a single analysis of different experiments (sig = 0.001, F = 22.123). Tukey's post hoc test showed that the training effect, nanocurcumin effect, and training effect caused an increase in P53 gene expression in the nanocurcumin group (P = 0.001) (Table 3) (Figure 3).

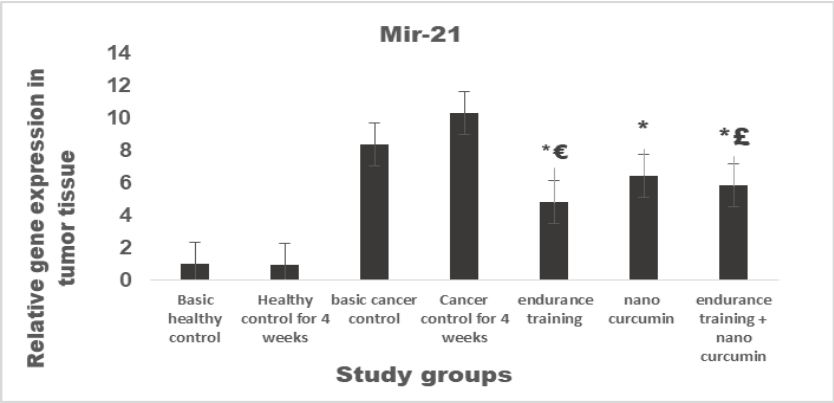

Figure 2. miR-21 gene expression in different groups.(* p ≤ 0.05)*significant reduction of cancer + endurance training, cancer + nano curcumin and cancer + endurance training+ nano curcumin compared to the Cancer control for 4 weeks.(€ p ≤ 0.05) € significance of cancer + endurance training and cancer + endurance training + nano curcumin compared to the basic cancer control.

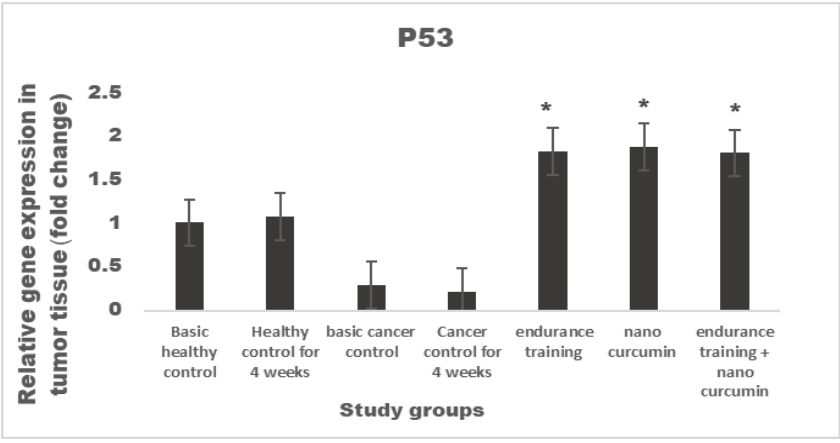

Figure 3. p53 gene expression in different groups. (*p≤0.05) *significant Increase in cancer + endurance training, cancer + nano curcumin and cancer + endurance training + nano curcumin compared to basic cancer control and Cancer control for 4 weeks

Table 3. Tukey's post hoc test for gene Mir-21 and P53

Groups	Groups	Mir-21 P Value	P53 P Value
Basic Cancer Control	Cancer control for 4 weeks	0.070	0.950
	endurance training	0.001*	0.001*
	nano curcumin	0.091	0.001*
	endurance training + nano curcumin	0.011*	0.001*
Cancer Control for 4 Weeks	endurance training	0.001*	0.001*
	nano curcumin	0.001*	0.001*
	endurance training + nano curcumin	0.001*	0.001*
Endurance Training	nano curcumin	0.195	1.000
	endurance training + nano curcumin	0.691	1.000
Nano Curcumin	endurance training + nano curcumin	0.966	1.000

Discussion

The results appeared that 4 weeks of perseverance preparing and nano-curcumin supplementation altogether diminished tumor development and did not alter (non-significant diminish), mir-21 expression quality and expression P53 expression within the preparing, nano-curcumin, and preparing + nano-curcumin groups compared to the 4-week cancer control gather.

The discoveries of the think about expressed that the induction of cancer in rats caused a diminish in tumor development, which was more significant within the preparing + nanocurcumin gather than within the training group and the

nanocurcumin group; which appears the impact endurance exercise together with the utilize of nanocurcumin. In line with the results of the present study, Betof et al. (2013) showed that high-impact endurance exercise can decrease tumor development in cancer groups up to two times compared to other groups (26). Additionally, regarding the effect of two interventions (physical activity and nanocurcumin), Delfan et al. (2020) showed that 5 weeks of endurance training and taking 100 mg/kg curcumin inhibited the growth and development of cancer cells by affecting intra-tissue mechanisms (27). Parvareh et al. (2023) expressed in their study that the synchronous utilize of sports exercises (resistance-endurance) and the utilization of nano curcumin supplement by hindering mRNA and STAT5 quality through the JAK-STAT pathway driven to the decrease of GBM tumors in rats (28). exercises and curcumin, as components that cause apoptosis, by ceasing mitosis, anticipate the movement of the cell cycle in dangerous tumors through distinctive signaling pathways, counting the pathway of cell multiplication, tumor silencer qualities and passing receptors (DR4, DR5) and advance restrains tumor cells (29,30,31).

Agreeing to the research results, the variable sum of miR-21 within the endurance exercise group, nano curcumin gather, and nano curcumin + exercise group was essentially lower than the 4-week cancer group. which is reliable with the results of Dufresne et al. (2018), Amani-Shalamzari et al. (2020), Soltani et al. (2019) and Esmatabadi et al. (32,33,34,4). But it was conflicting with the results of Jio et al. (2019) and Baggish et al. (2014) (35, 36). Within the studies, it has been found that the expression of miR-21 diminishes altogether after exercise (32, 33, 6, 4). The instrument of the impact of sports movement and particularly high-impact exercise on miRs has not been well characterized. But likely sports action controls miRNAs included in cell multiplication, intrusion, and metastasis (17). In expansion, Mir-21 may be a negative tumor suppressor of modified passing (PDCD4) and downstream direction of signaling targets in cell lines. By decreasing Mir-21 expression inside cancer cells, work out reestablishes PDCD4 action and limits cancer cell multiplication (4). Curcumin, having a dynamic component by interatomic with proteins and adjusts their expression and action, such as translation components, cell survival variables, angiogenesis, and different signaling pathways, can possibly direct the expression of a few miRNAs included in cancer (34). Prove has appeared that nano curcumin represses the development of cancer cells by down-regulating the expression of miR-21 and diminishing the number of cells within the G2/M stage of the cell cycle (34, 37, 38). The number of available studieson the combined impact of both intercessions, physical action and curcumin on mir-21 is exceptionally few, but a few studies have detailed the impact of these two mediations on diminishing the expression of miR-1, miR-133, miR-30, and mirR-199 (39, 40).

The results of the current research about the expression of the P53 quality within the cancer + exercise group, nano curcumin group and nano curcumin + preparing gather were significantly higher than the fundamental cancer control group and 4 weeks cancer. The results of this study are in line with The results of Akbarpour et al. (2022), Ju et al. (2019), Asghari Rekabard et al. (2018(, Nakayama et al. (2011), Pourjafarian et al. in conjunction with endurance training on p53 quality (6,10,35,41,42). But it was conflicting with our results of Ma et al. (2013) (5). The particular biological role of P53 is exceptionally complex, but P53 primarily secures the genome from transformations or hereditary changes. When defects are found in DNA, the P53 protein is phosphorylated and stabilized and actuates downstream pathways to halt the cell cycle, repair DNA, or actuate apoptosis (9). In an investigation, it was found that hereditary pathways are controlled by P53 amid sports exercises (43). In a review article on P53, aerobic metabolism and cancer. They expressed that the mechanisms controlled by p53 can interfere in the genes that coordinate the two main energy production pathways of aerobic metabolism and also help maintain genomic stability (9). Curcumin influences the function of numerous transcription factors, development factors and their receptors, cytokines, proteins and qualities directing cell expansion and apoptosis; and represses the expansion and survival of tumor cells (10). In line with the current study, in a research, they explored the utilization of curcumin at a dosage of 360 mg three times a day for 10 to 30 days in patients with colorectal cancer, which come about in a diminish within the serum concentration of TNF-α, an increment

within the apoptosis of tumor cells, and an increment within the event of p53 within the tumor got to be (42). A study has also shown that tolerance and promotion of nanocurcumin, in addition to increasing p53, may also cause cancer death by inhibiting cell growth and development, arresting the cell cycle and apoptosis, possibly affecting cell death (10).

Conclusion

According to the current findings, regulation of miR-21 and p53 gene expression and consumption of nanocurcumin after endurance training can reduce tumor volume through cell arrest cycle and apoptosis in mice with tumor cells. It prevents and slows down the development of cancer.

Acknowledgment

The creators of the article would like to precise their appreciation to all the individuals who have cooperated in this venture within the inquire about established and sports physiology research facility of Baqiyatullah College. This investigate was done without budgetary help.

Conflict of Interest

The creators thusly announce that there's no conflict of intrigued within the show consider.

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