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Research Article

Long-term aerobic exercise with curcumin supplementation improves cardiac fibrosis via TGF-β1/TRAF6/CTGF signaling in brain tumor of rats

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Abstract

The aim of the present study is to investigate the effect of aerobic exercise and nano-curcumin supplementation on cardiac TGF-β1/TRAF6 and CTGF pathways in rat with brain tumors. Forty male Wistar rats were divided into 5 groups (n=8 in each) of healthy control, brain tumor, tumor + aerobic exercise (AE), tumor + nanocurcumin (N-CUR) and tumor+AE+N-CUR. Glioblastoma was injected into the rats in the frontal cortex. Nano curcumin supplement at the dose of 80 mg/kg was gavage for 4 weeks, 5 days a week. The training groups performed aerobic exercises on the treadmill for 4 weeks, 3 days a week at a speed of 18 meters per minute, for 25-40 minutes. At the end, the rats were sacrificed and TGF-β1, TRAF6, CTGF were analyzed from the myocardium by Real-time PCR method. Compared to the healthy control group, Tumor group significantly increased TGF-β1 mRNA and TRAF6 mRNA in the myocardium ($p<0.05$). Also, compared to the healthy control group, all tumor groups showed a significant increase in CTGF mRNA expression ($p<0.05$). In contrast to the Tumor group, the Tumor+AE and Tumor+AE+N-CUR groups showed a significant decrease in TGF-β1 mRNA at myocardium ($p=0.0010$ and $p=0.0002$, respectively). It seems that aerobic exercise or exercise with nano-curcumin supplement has better protective effects on the heart of tumor rats with downregulation of TGF-β1. It is suggested that different doses and various exercise modalities should be investigated to control cardiac fibrosis from the TGF-β1/TRAF6 and CTGF pathways.

Key Words: **Aerobic exercise, Nano-curcumin, TGF-β1, Cardiac fibrosis, Brain tumor**

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Introduction

Brain metastases are one of the most common and devastating neurological complications of advanced cancer (Langer & Mehta, 2005). In brain cancers, neurological deficits, cognitive disorders, and balance disorders (Newton, 2007) usually lead to the induction of a sedentary lifestyle for the patient. Increased fatigue and decreased quality of life are also among the complications of brain damage caused by cancer (Katzmarzyk et al., 2019). Physical inactivity is an established risk factor for cardiovascular disease (CVD) incidence and mortality (Kraus et al., 2019). Globally, physical inactivity is estimated to be responsible for 6% of coronary heart disease (Lee et al., 2012). Sedentary lifestyle caused by old age or disease leads to the induction of cellular damage in heart tissue. Cardiac fibrosis can be one of the results of excessive inactivity caused by the disease (Lavie et al., 2019).

Myocardial fibrosis is one of the causes of pathological destruction of the ventricles and is characterized by the proliferation of cardiac fibroblasts and deposition of extracellular matrix. Excessive deposition of collagen can lead to heart dysfunction. Myocardial fibrosis is generally considered a progressive and irreversible process that can eventually lead to heart failure or fatal arrhythmia (Deshmukh et al., 2011; Ding et al., 2013). The transforming growth factor beta 1 (TGF-β1) signaling pathway in rat myocardial fibroblasts may play a role in the development of fibrosis (Zhang et al., 2014). TGF-β1 signaling pathway includes not only canonical Smad2/3 signaling but also noncanonical signaling. TRAF6 and TAK1 are downstream signals of TGF-β1 and belong to noncanonical signaling. Activation of the TGF-β1/TRAF6/TAK1 signaling pathway can regulate the expression of connective tissue growth factor (CTGF)) and promote the proliferation of atrial fibroblasts (Gu et al., 2012).

CTGF, also called CCN2, belongs to a family of matricellular proteins that regulate various aspects of cellular function such as inflammation, tissue repair, and fibrosis (Leask, 2010). It is well known that CTGF is upregulated in a variety of fibrotic

diseases, including cardiac pathologies (Jun & Lau, 2011). Indeed, cardiac CTGF expression is increased in models of MI-induced heart failure and cardiac regeneration (Gabrielsen et al., 2007; Zhang et al., 2012). It has been stated that CTGF protein level is correlated with the degree of myocardial fibrosis in HF patients (Koitabashi et al., 2007). Despite this evidence, the role of this molecule in cardiac fibrosis remains controversial. Also, the effect of TGFβ1 and TRAF6 pathway on this index in heart tissue in conditions of disease and cancer has not been well defined.

Regular physical activity brings many physical and mental benefits for healthy and sick people at different ages (Gaetano, 2016). Regular exercise can reduce the aging process, improve mental and cognitive health, reduce the risk of physical disability, increase longevity and functional independence (Gremeaux et al., 2012). By improving physical fitness and quality of life, exercise reduces disability, hospitalization, and mortality from cardiovascular diseases. It has been reported that exercise training is necessary to reduce cardiac fibrosis and improve cardiac dysfunction after myocardial infarction. Ma et al (2021) showed that exercise training alleviates cardiac fibrosis through increasing fibroblast growth factor 21 and regulating TGF-β1-Smad2/3-MMP2/9 signaling in mice with myocardial infarction (Ma et al., 2021).

Along with exercise, the use of nano supplements, especially nano curcumin, can have cardiac protection effects. Curcumin (diferuloylmethane) is a polyphenol extracted from turmeric rhizomes. The molecular targets of curcumin are very diverse and can regulate transcription factors, growth factors and their receptors, cytokines and enzymes in different tissues. Curcumin has a wide range of effects including antioxidant effects (Abrahams et al., 2019) and anti-inflammatory (Farhood et al., 2019). This substance can be an immune regulator (Chai et al., 2020), antitumor (Ashrafizadeh, Zarrabi, Hashemi, et al., 2020), and antithrombotic (Suresh, 2020), as well as having therapeutic potential for cancer (Giordano & Tommonaro, 2019), and a variety of diseases including cardiovascular disease (Pourbagher-Shahri et al., 2021). Xue et al. (2020) confirmed the protective effect of curcumin nano-suspension on myocardial fibrosis in diabetic rats (Xue et al., 2020). However, the effects of this supplement with exercise on cardiac fibrosis have not been evaluated. Therefore, the aim of the present study is to investigate the effect of aerobic exercise and nano-curcumin supplementation on cardiac TGFβ1, CTGF, TRAF6 pathways in rats with brain tumors.

Materials and Methods

Animals

Forty 8-week-old Wistar rats (223 ± 16.99 grams) were purchased from Pasteur Institute, Tehran, Iran. The rats were placed individually in transparent polycarbonate cages (all 5 rats in one cage) under laboratory conditions of 22 ± 2 degrees Celsius and relative humidity of 55% and a 12-hour light-dark cycle. Standard pellet food and water were freely available to the rats. After one-week familiarization with the laboratory environment and training on the treadmill, the rats were divided into 5 groups (n=8 in each group), healthy control, brain tumor, tumor + aerobic exercise (AE), tumor + nanocurcumin (N-CUR) and tumor+AE+N-CUR. The study was approved by the Ethics Committee of the Islamic Azad University, Tehran, Iran under protocol number IR.IAU.SRB.REC.1401.029.

Culture of glioma cells

The C6 glioma cells of the Wistar rats (National Center for Genetic Resources) were prepared in a flask in RPMI medium (Roswell Park Memorial Institute), 300 mg/ml penicillin, 720 mg/ml streptomycin (Jabarban Hayan Pharmaceuticals) and were cultivated 2 g/liter sodium bicarbonate 10%. The final volume of the cell culture medium was 1000 ml; its pH was adjusted to 1.7. After washing, the supernatant was neutralized with PBS (buffered saline Pho) and 0.025% trypsin-EDTA solution and with 10% FBS medium. Then the solution was centrifuged at 1200 rpm for 5 minutes and the cells were separated. The initial density for cell culture was considered to be 100,000 cells/cm2. Finally, 10 microliters of trypan blue dye (0.4% weight-volume) and 90 microliters of cell suspension and neobar slide were used for cell counting and survival. The percentage of stained cells (blue) was determined as the percentage of dead cells.

Injection of glioma cells

To inject cancer cells, animals were first anesthetized using ketamine (80 mg/kg) and xylazine (10 mg/kg). cultured C6 glioma blastoma cells was injected with a concentration of 5*105 cells/30 µL by making a skin incision in the back of the skull and removing the periosteum according to Swanson's instructions using an infusion pump and a stereotaxic device in the right frontal cortex area with a depth of 2.5 mm in rats to a volume of 10 microliters. The tumor size was measured by a digital caliper after sacrificing the animals. Tumor grading was graded from 1 to 4. Grade 4 is the highest degree of damage and grade 1 is the lowest amount of tissue damage (Swanson, 2018).

Nano curcumin

500 mg of chitosan, 50 ml of 2% acetic acid solution, curcumin, ethanol (1 mg/ml) and 15 ml of 1% weight-volume TPP solution were used to prepare nano curcumin. The prepared solution was stirred for 1 hour and centrifuged at 10,000 revolutions per minute

for 30 minutes, and chitosan nanoparticles enclosed in curcumin were obtained. Finally, after preparing the product for each animal, 80 mg/kg of N-CUR was gavage for 4 weeks, 5 days a week (Vijayakurup et al., 2019).

Aerobic exercise

After confirming brain tumor, the exercise protocol was designed and started based on the protocol of Al-Jarrah et al. [29]. According to this protocol, in order to reduce stress and adapt to the conditions of the treadmill, the rats walked on the treadmill during one week at a speed of 5-10 m/min for 5-10 minutes and 3 days a week. According to Table 1, exercise groups performed aerobic exercises for 4 weeks, 3 days a week and at a speed of 18 meters per minute on a treadmill. The duration of training for adaptation in the first week was 25 minutes a day, with weekly increase of 5 minutes. This duration reached 40 minutes in the fourth week, which continued until the end of the week.

Gene expression analysis

48 hours after the last training session, Rats were sacrificed after being anesthetized with xylazine and ketamine solution. The heart tissue was immediately frozen in liquid nitrogen and kept at frizzer with -70 degrees Celsius. Heart tissue was sent to the laboratory to continue the extraction of RNA (RiboNucleic Acid). TGFβ1, TRAF6 and CTGF genes was measured after RNA extraction and cDNA (Complementary deoxyribonucleic acid) production using Real-time PCR method.

RNA extraction and cDNA production

To extract total RNA, it was homogenized at a ratio of 1 to 10 in Isol RNA-reagent Lysis according to the instructions of the kit (Qiagen, Germany). In order to remove the protein components, the resulting product was centrifuged at 4C for 10 minutes at 12000 rpm. The supernatant was removed and mixed with chloroform with primary Isol at a ratio of 0.5 to 1. The product was centrifuged at 4C for 15 minutes at 12000 rpm. The mineral and aqueous parts were separated, the RNA containing part was removed and mixed with isopropanol at a ratio of 0.5 to 1 and left for 10 minutes at room temperature and then at 4C for 10 minutes. Then it was centrifuged at 12000 rpm. The plate containing RNA was dissolved in 20 µL of Free-RNAs water. The concentration of RNA was measured using a nono drop device and the ratio of 260 to 280 between 1.8 and 2 was defined as optimal purity. After extracting RNA with high purity and concentration from all the studied samples, the stages of cDNA synthesis were performed according to the manufacturer's protocol (Fermentas, USA). Then the synthesized cDNA was used to perform the reverse transcription reaction.

Real time PCr

Table 1. Aerobic exercise training program.

	Speed (m/min)	Duration (min)	Feriquency (day/week)
Familiarization	5-10	5-10	3
Tumor induction	Injection of glioma cells (1 weeks to confirming)		
Week 1	18	25	3
Week 2	18	30	3
Week 3	18	35	3
Week 4	18	40	3

Distilled water containing 10 microliters of lyophilized primer, 0.5 microliters of forward primer and reverse primer (Primer Reverse), 1 microliter of cDNA, and 8 microliters of DEPC water were used to prepare the primers. For Biagen, the total RNA of the cells was extracted according to the Cinagen protocol using q RT-PCR method using Kiazol solution (Cinagene, Tehran, Iran). The quality of extracted RNAs was evaluated by spectrophotometry. In order to prepare single-stranded cDNA, Oligo dt primer and reverse transcription enzyme were performed according to the relevant protocol. Each PCR reaction was performed in an ABI Step One machine according to the manufacturer's protocol. Real-time PCR reaction cycles for TGFβ1, TRAF6 and CTGF genes were performed with three temperatures of 94, 60 and 72 degrees Celsius. Melting chart was performed to check the accuracy of PCR reactions. GAPDH (Glyceraldehyde-3-phosphate dehydrogenase) was used as TGFβ1, TRAF6 and CTGF reference genes. The expression levels of control and experimental genes were measured together. The fold change for each gene was determined after normalization to GAPDH using the $2^{-\Delta\Delta CT}$ method (Livak & Schmittgen, 2001).

Δ^{CT}= CTtarget –Ctreference

$\Delta\Delta^{Ct}$= Δ^{CT}test sample-Δ^{CT}control sample

Relative expression:$2^{-\Delta\Delta Ct}$

Table 2. Primer sequence.

Genes name	Primer sequences
Rattus norvegicus	Forward: GCCTGGGTTGGAAGTGGAT
TGF-β1	Reverse: GGGTTGTGTTGGTTGTAGAG
Rattus norvegicus	Forward: ACCAGTGTGAAGACCTACCG
CTFG	Reverse: CGGGACAGTTGTAATGGCAG
Rattus norvegicus	Forward: TCCACGATCAAAGCTGTCCT
TRAF6	Reverse: CGTGCCAAGTGATTCCTCTG
Rattus norvegicus	Forward: CAAGTTCAACGGCACAGTCA
GAPDH	Reverse: CCCCATTTGATGTTAGCGGG

The results are represented as the mean (±standard error of mean SEM) fold changes with respect to the sham control.

Primer sequences used are shown in Table 2.

Haemotoxylin and Eosin (H&E)

Brain tissue were removed and fixed in 4% buffered formalin. Formalin-fixed brain were embedded in paraffin, sectioned at 5-µm thickness, and stained with hematoxylin and eosin. Histological analysis was evaluated based on the scoring criteria.

Statistical analysis

All data are described as mean ± standard deviation. In order to determine the normality of the data, we use Shapiro-Wilk test. Also, homogeneity of variances was measured by Levene's test. In order to determine the significance of the difference between the variables in the groups, One Way Anova and Tukey's post hoc test were used. Data analysis was done using SPSS version 26 at a significance level of $P \leq 0.05$ and Graph pad prism software was use to drawing graph.

Results

H & E staining

A cross-section of rat's brain is shown in Figure 1 with hematoxylin and eosin stains. In the control group, the brain tissue is coherent and normal structure. In addition, the death rate of neuronal cells is very low. Examining the images in different groups showed that the tumor size was larger in the tumor group than in the other groups (p=0.0003). Also, in this group, many cells were observed in the mitosis phase, which indicates the high activity of cells in the tumor and led to an increase in angiogenesis and blood supply to the tissue. The amount of apoptosis in this group was lower compared to other groups, and parts of the tumor had necrosis, which may be due to the lack of oxygen in the center of the tumor. Examining Tumor+AE and Tumor+N-CUR groups, the changes in tumor size were less compared to the Tumor group. This was despite the fact that the combined treatment group caused a significant reduction in the damage caused by the tumor (Figure 1).

TGFβ1 gene expression

TGFβ mRNA expression is shown in Figure 2. Compared to the control group, the Tumor and Tumor+N-CUR groups showed a significant increase in TGFβ mRNA in the myocardium (p<0.0001 and p=0.0013, respectively). However, compared to the Tumor group, the Tumor+AE and Tumor+AE+N-CUR groups showed a

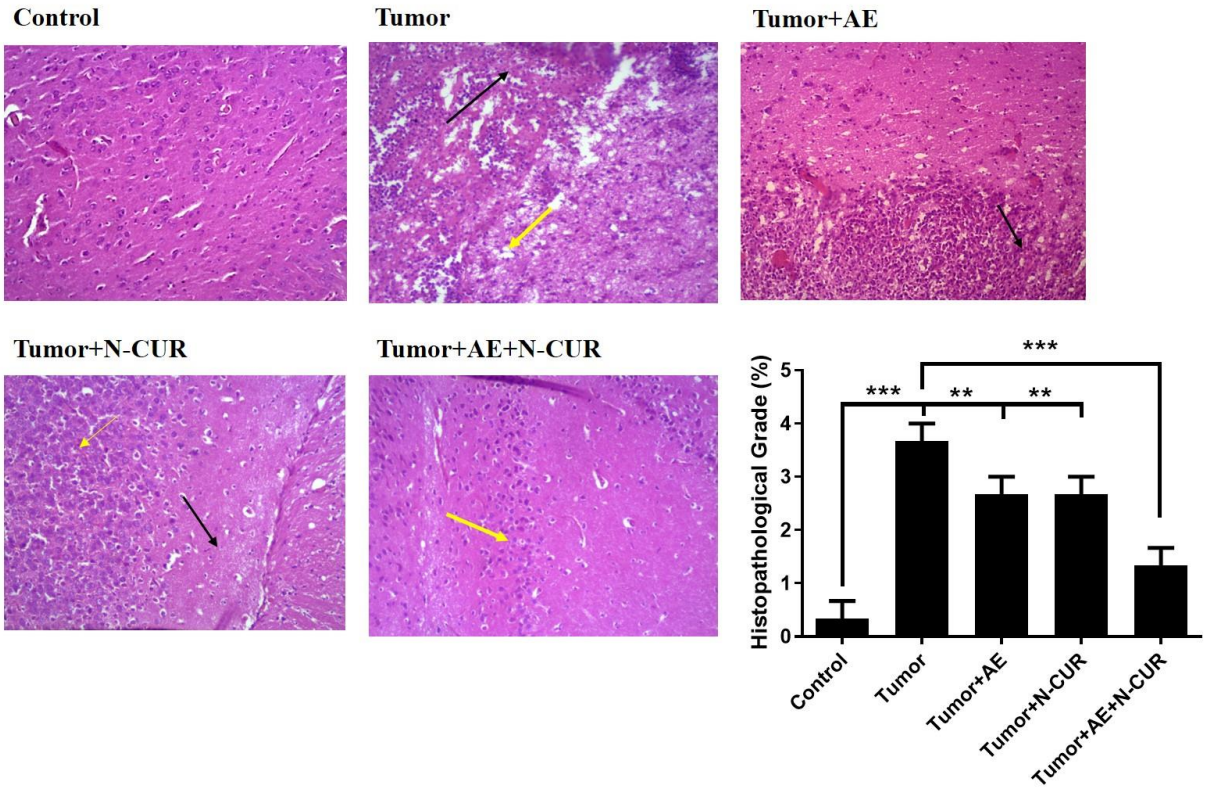

Figure 1. Induction of tumor at brain of rats in different groups. Representative images of hematoxylin and eosin (H&E, magnification 100 um). Black arrow: Necrosis area, Yellow arrow: Proliferative area. Values are expressed as mean ± SD. *:p < 0.05, **:p < 0.01, ***:p < 0.001 . AE: Aerobic Exercise, N-CUR: Nano-Curcumin.

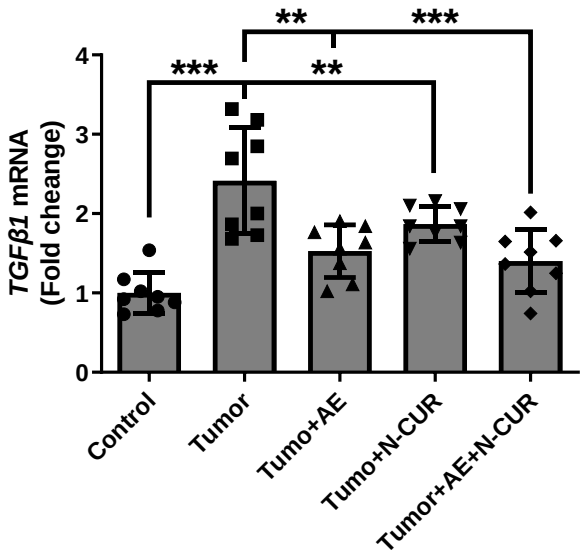

Figure 2. mRNA expression levels of the transforming growth factor (TGF)-β1 gene in the myocardium following treatment with aerobic exercise (AE) and Nano-curcumin (N-CUR) in glioblastoma (GBM)-induced brain tumor in rats. Values are expressed as mean ± SD (n = 8). *:p < 0.05, **:p < 0.01, ***:p < 0.001 . AE: Aerobic Exercise, N-CUR: Nano-Curcumin.

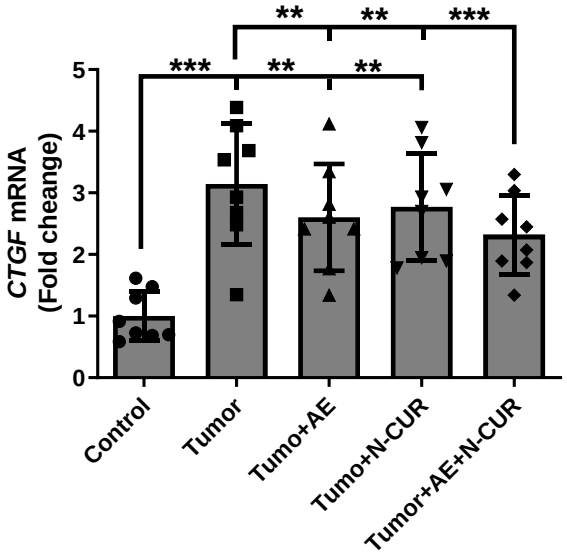

Figure 3. mRNA expression levels of the connective tissue growth factor (CTGF) gene in the myocardium following treatment with aerobic exercise (AE) and Nano-curcumin (N-CUR) in glioblastoma (GBM)-induced brain tumor in rats. Values are expressed as mean ± SD (n = 8). *:p < 0.05, **:p < 0.01, ***:p < 0.001 . AE: Aerobic Exercise, N-CUR: Nano-Curcumin.

significant decrease in TGFβ mRNA in the myocardium of rats (p=0.0010 and p=0.0002, respectively).

CTGF gene expression

CTGF mRNA expression is shown in Figure 3. Compared to the healthy control group, Tumor (p<0.0001), Tumor+AE (p=0.0021), Tumor+N-CUR (p=0.0006) and Tumor+AE+N-CUR (p=0.0151) groups showed a significant increase in CTGF mRNA expression in the myocardium. However, therapeutic interventions including exercise and supplementation or a combination of both in tumor groups could not significantly reduce CTGF mRNA expression in the myocardium (p>0.05).

TRAF6 gene expression

TRAF6 mRNA expression is shown in Figure 4. Compared to the healthy control group, only the Tumor group caused a significant increase in TRAF6 mRNA expression of the myocardium (p=0.0003). However, therapeutic interventions including aerobic exercise and Nano-Curcumin or the combination of both in tumor groups did not cause a significant decrease in TRAF6 mRNA compare to Tumor group (p>0.05). However, these therapeutic interventions prevented the excessive increase of TRAF6 in the tumor groups compared to the healthy control group.

Discussion

Cancer disease, in addition to imposing a sedentary lifestyle, it is also capable of damaging other body tissues through cellular pathways. TGF-β is a common mediator of cancer progression and fibrosis. Fibrosis can cause significant damage to multiple organs, including heart tissue (Parichatikanond et al., 2020). In

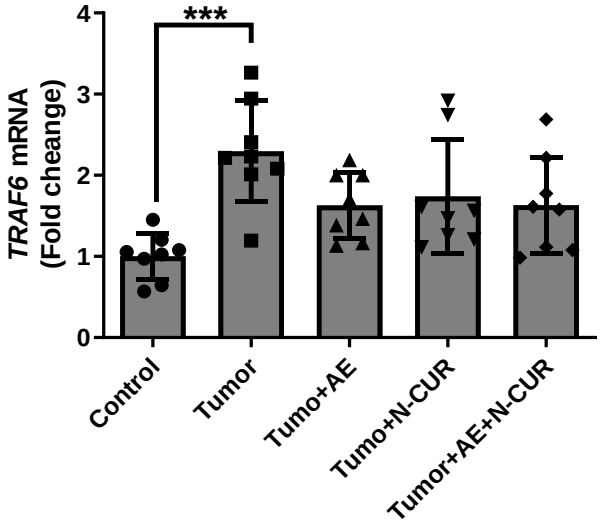

Figure 4. mRNA expression levels of the TNF Receptor Associated Factor 6 (TRAF6) gene in the myocardium following treatment with aerobic exercise (AE) and Nano-curcumin (N-CUR) in glioblastoma (GBM)-induced brain tumor in rats. Values are expressed as mean ± SD (n = 8). ***: p < 0.001. AE: Aerobic Exercise, N-CUR: Nano-Curcumin.

this study, we investigate the effect of aerobic exercise and Nano-curcumin supplementation on cardiac TGFβ1, TRAF6, CTGF pathways in rats with brain tumors.

In the current study, histological images were also used to confirm the tumor. It was found that tumor groups showed an increase in tumor size in the brain, and the largest decrease in tumor size was related to the combined treatment group. However, changes in the expression of cardiac fibrosis genes were also related to the increase in tumor severity. Destruction of the TGF-β signaling pathway often occur in tumors and cancer, and these disorders play an important role in tumor progression (Batlle & Massagué, 2019; Haque & Morris, 2017). In addition, TGF-β plays an important role in the development of fibrosis (Khan & Sheppard, 2006). Therefore, targeting TGF-β signaling pathways can be a new therapeutic strategy to treat a variety of fibrotic disorders, especially in cardiac tissue. The results of the present study showed that the tumor group had a significant increase in the expression of TGFβ, TRAF6, and CTGF mRNAs in heart tissue. As stated, the increase of TGF-β can cause the development of fibrosis. The expression of these fibrosis-related genes plays an essential role in cell differentiation that produces myofibroblasts and expands the production/deposition of ECM by myofibroblasts in fibrotic tissue (Khalil et al., 2017). In addition, TGF-β, a key growth factor in fibrosis, can regulate cell proliferation, apoptosis and migration, extracellular matrix synthesis, and fibronectin and collagen expression (Norton et al., 1997). Also, the overexpression of TGF-β can lead to the occurrence of atrial fibrosis through the regulation of CTGF expression (Liu et al., 2003), which in the tumor group of the present study, increases CTGF was aligned with TGF-β.

The exact mechanism and signal transduction pathway in the context of myocardial fibrosis is unknown. Studies in recent years have shown that the mechanisms of the renin-angiotensin-aldosterone system (RAAS), TGF-β, and inflammation and oxidative stress are mainly involved in cardiac fibrosis (Muñoz-Durango et al., 2016), but only the TGF-β pathway was evaluated in the present study. Gu et al. (2012) demonstrated that the TGFβ1/TRAF6 pathway is an important signaling pathway in Ang II-induced CTGF expression, and thus inhibition of TRAF6 may be a novel target for reversing Ang II-induced atrial fibrosis (Gu et al., 2012). TRAF6 exerts its biological effect mainly through signal transduction pathways. After TGF-β activates the TGF receptor, it promotes the ubiquitination of TRAF6, resulting in the fusion of TRAF6 with TAK1 and then the ubiquitination of TAK1 at lysine 63 and 158, thereby further activating the downstream signaling pathway (Landström, 2010). Studies have reported that TGF-β-induced activation of the TRAF6/TAK1 signaling pathway is involved in apoptosis, inflammation, and epithelial mesenchymal transformation (Gui et al., 2012).

Considering the important role of TGF-β/TRAF6 signaling in fibrosis, research focus on inhibition of this signaling pathway. In the present study, the combination of exercise training and Nano selenium supplementation caused a significant decrease in TGFβ mRNAs in heart tissue. Regular exercise, especially endurance exercise, effectively improves heart function in young and old people (Schmitt et al., 2022). Exercise training improves cardiovascular function and capacity by increasing stroke volume and cardiac output (Gusso et al., 2017). It has been stated that exercise training in the elderly population may reduce the accumulation of connective tissue (Kwak et al., 2011). Limited data suggest that exercise training may decrease collagen content in the aged heart. Collagen cross-linking in the left ventricular free wall was significantly lower in exercised rats compared to sedentary rats (Thomas et al., 1992). It has been stated that exercise training reduces plasma angiotensin concentration (Gomes-Santos et al., 2014), cardiac TGF-β1 expression, collagen deposition, and fibrosis (Ma et al., 2021). Additionally, regular moderate exercise boosts the immune system and suppresses inflammation due to its antioxidant properties. The use of curcumin supplement in nano form doubles the effect of exercise training. Therefore, the combination of these two have higher antifibrotic effects. Curcumin has been shown to decrease the expression of TGF-β to increase the levels of VE-cadherin, DDAH1, and Nrf2, and to decrease the levels of MMP-9 and ERK1/2 (Ashrafizadeh, Zarrabi, Hushmandi, et al., 2020). Consequently, endothelial-to-mesenchymal transition (EndMT) is inhibited by TGF-β to suppress endothelial cell fibrosis (Ma et al., 2020). In kidney diseases, has been shown, curcumin administration significantly reduce the expression of TGF-β1 (Zhao et al., 2019). The TGF-β signaling pathway appears to increase cell migration and motility by inducing EMT. Curcumin supplementation is associated with a reduction in the migration ability of these cells through the reduction of TGF-β and subsequent inhibition of EMT (Yin et al., 2019). Therefore, the combination of exercise and nanocurcumin has a better control on fibrosis by reducing TGF-β in cardiac tissue.

Conclusion

It seems that the combination of exercise and Nano curcumin by controlling and reducing TGF-β can improve cardiac fibrosis in different cancer models and therefore have protective effects on heart tissue. However, different exercise modalities with longer durations should be evaluated to investigate the TGF-β cell-signaling pathway in cardiac fibrosis.

What is already known on this subject?

Sedentary lifestyle caused by old age or disease leads to the induction of cellular damage in heart tissue.

What this study adds?

Combination of exercise and Nano curcumin by controlling and reducing TGF-β can improve cardiac fibrosis in different cancer models and therefore have protective effects on heart tissue.

Organ Cross-Talk Tips:

- Cardiac signals can influence brain activity and vice versa, impacting mental states and behaviors. This interaction is particularly relevant in patients with brain tumors, as emotional well-being can significantly affect recovery outcomes.

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Compliance with ethical standards

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

Ethical approval The study was approved by the Ethics Committee of the Islamic Azad University, Tehran, Iran under protocol number IR.IAU.SRB.REC.1401.029.

Informed consent Not applicable

Author contributions

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

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