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The Simultaneous Effect of Linum Usitatissimum Supplementation and Aerobic Training on 6-Methylguanine and ATP in the Endothelial Aorta and Heart Tissues in Rats Poisoned with H2O2

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Abstract

***Background and Objective*:** As a high-energy demanding tissue, the heart is exposed to a high level of ROS molecules such as H2O2, leading to cardiovascular disorders through damaging macromolecules such as DNA and disrupting ATP production. Hence, this study aimed to investigate the simultaneous effect of aerobic exercise (Ae) and *Linum Usitatissimum* (Lu) supplementation on DNA damage and ATP synthesis in heart and aorta endothelial tissues in rats poisoned with hydrogen peroxide (H2O2).

Material and Methods: 56 male Wistar Albino rats were randomly divided into 7 groups, including HC (Healthy Control), TC (Toxicated Control), Lu1 (Received 5 mg/kg of Lu), Lu2 (Received 10 mg/kg of Lu), Ae (Received only Aerobic Exercise), Ae Lu1, and Ae Lu2. Then, all groups got poisoned by H2O2 except HC. Next, they received *Linum Usitatissimum* (Lu) supplementation and Low-Intensity Interval Training (LIIT). Finally, 24h after the last treatment session, the level of 6-methylguanine (6MG) and ATP were measured via the ELISA technique in cardiovascular tissue.

Results: The findings determined that Lu supplementation and Ae significantly diminish the 6-methyl guanine level in endothelial ($F=111.3$, $P=0.0008$, $\eta=0.9823$) and heart cells ($F=147.9$, $P=0.0005$, $\eta=0.9867$). Also, the ATP level was increased significantly in endothelial ($F=342.6$, $P=0.0003$, $\eta=0.9942$) and heart cells ($F=135.1$, $P=0.0013$, $\eta=0.9854$). However, no considerable changes were found for both factors in groups who received Ae or Lu singularly.

Conclusion: The study showed that concurrent administration of Lu and Ae could exert dynamic cardio protective properties through their antioxidant effects.

Keywords: Toxicity [MeSH], Mitochondria [MeSH], Cardiovascular Diseases [MeSH], Herbal Medicine [MeSH], Rehabilitation [MeSH], Exercise [MeSH]

Highlights

- Administration of Linum Usitatissimum and aerobic exercise could exert dynamic cardioprotective properties through their antioxidant effects.
- Linum Usitatissimum and aerobic exercise significantly improve the 6-methyl guanine level in endothelial and heart cells.
- The interaction of Linum Usitatissimum and aerobic exercise significantly increased the ATP level in endothelial and heart cells.

Introduction

Cardiovascular disorders are one of the most prevalent life-threatening diseases on the globe. Based on reports, energy depletion and DNA damage in response to oxidative stresses play essential roles in the progression of cardiovascular, coronary diseases, ischemia-reperfusion, and heart failure disorders (1). These aberrations initiate or increase cellular death in cardiac tissues, leading to severe diseases and worsening the illness condition. In this regard, many studies have shown a high level of 6-methylguanine (a marker of DNA damage) and a low level of ATP in cardiac and related endothelial cells in patients with ischemia-reperfusion and heart failure illnesses (2). Moreover, the researchers have displayed attenuation of oxidative-induced death in cardiomyocytes, accompanies by a better prognosis in related patients (3).

Oxidative stresses could be formed in many physiologic and pathologic conditions, especially in high-energy demanding tissues such as the heart. The oxidative stresses producing reactive oxygen species (ROS) have been identified to be involved in many diseases, including cardiac disorders, as the oxidative stress markers are found elevated in cardiovascular diseases (4). Hydrogen peroxidase (H_2O_2) is one of the most prominent ROS engaged in the pathophysiology of cardiac illnesses. That is because of the high energetic demands of heart tissue supplied through oxidative phosphorylation (5). Hence, the heart tissue subsequently will be exposed to a high level of oxidative stresses so that ROSs are linked to different cardiac pathologic disorders, including hypertrophy and ischemia (6). The ROSs, especially H_2O_2, are the main factors leading to cellular apoptosis, necrosis, and tissue failure (7). The integrity of the genome is an essential factor for cell survival. The complexity of DNA replication and repair systems is responsible for maintaining this integrity (8). In addition to DNA damage caused by normal metabolism, further damages are caused by oxidative stresses. The damaged-DNA-induced cell death is just one of many biological consequences of oxidative stresses, including H_2O_2 (9). Studies show that H_2O_2 can impair nucleotide bases and biological responses immediately after DNA damage, including DNA repair and cell cycle arrest (10). More importantly, DNA damage activates caspases protein, a downstream target of the signaling network in DNA damage that gets stabilized and activated to stimulate the expression of pro-apoptotic genes (11, 12).

Moreover, recent evidence suggests that regular exercise has a considerable ameliorative role in cardiovascular diseases, notably its protective effects against oxidative stress-related damages (13, 14). Thus, this association has made a strong linkage between sedentary and various illnesses, especially cardiovascular diseases. Cardiovascular tissue is highly vulnerable to oxidative stress due to high oxygen consumption and insufficient antioxidant system (3,5). Hence, aerobic exercise has been identified to strengthen the antioxidative defense system, heart muscle, and blood volume, so that it has reported up regulating antioxidants enzymes (15).

Aerobic exercise (Ae) reduces mitochondrial oxidant production and increases mitochondrial antioxidant enzyme activity (13). de Meirelles et al reported (2014) reported that factors involved in cardiac cell survival pathways are significantly increased during aerobic exercise in the individual cells (14). Moreover, it has been indicated that aerobic exercise could reduce the risk of injury,

oxidative stress, and inflammatory signaling in cardiac cells (15). Hence, exercise efficiently can decrease the production of ROSs such as H_2O_2 through improving antioxidant systems (16).

The Flaxseed or *Linum Usitatissimum* (Lu) belongs to the *Linaceae* family that grows widely in tropical and subtropical regions (17). It is one of the oldest cultivated crops in the world for its fiber, seeds, oil, and by-products (18). The flaxseed is also a rich source of vegetarian unsaturated omega-3 fatty acids (PUFA) and contains 50% alpha-linoleic acid, an omega-3 fatty acid. This plant is recognized as one of the most important medicinal herbs and has been scientifically paid attention to containing beneficial fatty acids, lignans, fiber, protein, and vitamins (19). These omega-3 fatty acids are vital for the proper function of the brain, nervous system, kidney, and sexual health (20). The most considerable lignan present in this plant, the Secoisolariciresinol diglucoside (SDG), also shows antioxidant, anti-apoptotic, anticoagulant, antiviral, antibacterial properties, and cytotoxic effects on some human cancerous cells, as well (21). Likewise, it has been indicated that Lu proteins effectively remove hydroxyl radicals, improving endothelial function due to their high arginine levels (22). Furthermore, regarding reports, Lu extract has been found to have high antioxidative traits because of contained vitamins and lignans (23-25).

Based on what is implied here, the current study aimed to investigate the simultaneous effect of aerobic exercise and flaxseed extract on apoptosis and DNA damage of endothelial aortic and heart tissue poisoned rats with H2O2. So that, the toxicity of hydrogen peroxide led to increased apoptosis as well as oxidative stress in the target cells. As oxidative stress could efficiently trigger DNA lesions and subsequently increase apoptosis in specific cells (26), we administered the Lu and aerobic exercise to rats to analyze their accompanying effects on attenuation of apoptosis in cells imposed to extensive oxidative stress. It is not far to efficiently use herbal medicine in therapeutical and preventive approaches in cardiovascular patients.

Materials and Methods

- ***The animals***

The ethics committee approved the whole experimental protocol in this study of Islamic Azad University, Mahallat Branch (IR.IAU.ARAK.REC.1399.043). It was done under the NIH (National Institutes of Health) guide for the care and use of laboratory animals (No. 80–23), which emphasized minimal animals being sacrificed and minimal pain imposed during the study.

The male Wistar Albino rats (10-12 weeks, 200 ± 20 g) were selected and purchased from Pasteur, Tehran, Iran. Based on various treatments, the rats were randomly and equally divided into 7 groups (n=8), including 1) Healthy Control (HC) who received no Lu extract and no Ae, 2) Lu1 (received 5 mg/kg of Lu supplementation), 3) Lu2 (received 10 mg/kg of Lu supplementation), 4) Ae (received only Ae), 5) Ae Lu1 (received 5 mg/kg of Lu supplementation as well as Ae), 6) Ae Lu2 (received 10 mg/kg of Lu supplementation as well as Ae), and 7) Toxicated Control (TC with no treatment). Afterward, they were separated into separate cages with optimized temperatures to 22-27 °C at the university's Animal Care Facility. They were alternatively exposed to 12 hours of light and 12 hours of darkness during adaption and study periods with constant free access to water and food.

- ***The poisoning of Rats by hydrogen peroxide***

The peroxide hydrogen was used to poison the rats (27, 28), which was prepared from product oxidants 9% (Grape Oxidant 6 Number 1 Atusa 60 ml) purchased from Atusa Company, Tehran, Iran. The primary substance weighted 60 mg was transferred into a box with a volume of 125.123 mm^2 covered by a barrier net to prohibit oral usage by rats so that hydrogen peroxide was distributed throughout the cage air. The animals were entered into the cage at each turn so that rats inhaled the air inside the cage for 3 hours a day for one week.

- ***Treatments of rats***

The poisoned rats were treated with plant extract and aerobic exercise. The group that intoxicated control got intoxicated by H2O2. The Lu1 group received 5 mg/kg of herbal extract. The Lu2 group received 10 mg/kg of herbal extract. The Ae group underwent aerobic exercise. The Ae Lu1 group received 5 mg/kg of herbal extract as well as aerobic exercise. The Ae Lu2 group received 10 mg/kg of herbal extract as well as aerobic exercise. The HC group did not receive H_2O_2, herbal extract, and aerobic exercise. Although the extract was bitter, no sweetener was not used due to eliminating any probable chemical interactions. The extract was orally administered daily using a syringe to rats for 28 days (4 weeks), and groups Ae Lu1, Ae Lu2 received extract after every aerobic exercise session during weeks 2 and 3.

- ***The Low-Intensity Interval Training (LIIT)***

The low-intensity interval training (LIIT) was performed through 2 separate phases so that, primarily, the rats experienced an adaptation stage for 4 days, in which the rats ran 1 min at a speed of 20-25 m/min on a rotational bar 4 times a day. Phase 2 (the main phase) had consisted of 10 repeated programs. Each program consisted of 1 min running followed by 2 min active rest (running at half-speed). Hence, each session of the main exercise program was 30 minutes per rat. The main program lasted 4 weeks, 5 sessions weekly.

- ***Preparation of Linum usitatissimum extract***

Primarily, 10 g of *Linum Usitatissimum* seeds (Pakan Bazr co, Isfahan, Iran) were thoroughly grinded. Next, the powder was mixed with petroleum ether solvent and put in a Soxhlet extractor for 10 hours for oil extraction. The sample lacking oil was wholly dried in the next step, and its methanolic extracts were purified via methanol using a Soxhlet extractor for 16 hours. The resulted yellow solution was as methanolic extract was kept at 50° C for 5 hours. After thorough evaporation of existed methanol, the yellow powder was remained and dissolved in normal saline. This extract is stored at 4 °C in darkness.

- ***The scarification of animals***

The tissues for molecular analysis were separated 24h after the last treating session, during which the rats have fasted for 14h. Then, the rats were passed out using ketamine (30-50 mg/kg) and xylazine (3-5 mg/kg) via intraperitoneal injection.

- ***Tissue measurements***

After assurance of anesthesia, a cleft was created at the breast of rats using a surgical blade through which the aortic endothelial and heart tissue were taken out and washed thoroughly by normal saline. Then, the tissues got immediately frozen by liquid nitrogen and stored at -80 °C. To homogenate collected tissue, after defrosting at RT, pieces of the left ventricle and beginning parts of the aortic artery were separated. The tissue was transferred into 2 ml microtubes, as 500 µl of lysis buffer (EPX-99999-000) is needed for 100 mg of tissue, through 615-705 µl of lysis buffer for 123-141 mg of tissue samples. Moreover, the lysis buffer contained antiprotease that prohibited protein denaturation. Then a 5 mm stainless steel bead was added to microtubes. Finally, the microtubes were transferred into the TissueLyser device (QIAGEN) by which Homogenization of sample was performed for 2 minutes at 25 Hz followed by centrifuge at 4 °C for 10 minutes. Subsequently, the supernatant was poured into new microtubes, and the sample was diluted at ration 10 mg protein/ml using 1X PBS. The product was kept at -80 °C. Eventually, we quantitatively assessed the level of 6-methylguanine (pg/ml) as a marker of DNA damage and ATP (µM/ml) in both cells via ELISA (Mabtech, Sweden).

- ***Statistical analysis***

The Kolmogorov-Smirnov test was used to determine the normality of the distribution. All results were expressed as mean±standard deviation. In order to analyze the data and investigate the inconsistencies of the observation amongst different groups, the two-way analysis of variance ANOVA method was used, which was

then followed by the LSD post hoc test. Biochemical data were analyzed using the Prism 8 software at a statistically significant level ($P \leq 0.05$).

Result

- ***The Lu and Ae attenuates the DNA damage in aortic endothelial and heart tissue***

The intragroup analyzes showed that the *Linum Usitatissimum* supplementation and aerobic exercise significantly reduced the levels of 6-methylguanine (6MG) in aortic endothelial (F=111.3, *P*=0.0008, η =0.9823) and heart tissue (F=147.9, *P*=0.0005, η =0.9867). Though based on intergroup analyses, the groups Lu1, Lu2, Ae, and AeLu1 for aortic endothelial cells and groups Lu1, Lu2, and Ae, for heart tissue cells, have been demonstrated did not show any differences in the level of 6MG compare to TC. On the contrary, the group Ae Lu2 for aortic endothelial cells and Ae Lu1 and Ae Lu2 for heart tissue cells showed a significantly lower level of 6MG (Figure 1). Thus, the most considerable response was observed when both interventions were simultaneously administered, especially in a high dose of *Linum Usitatissimum*.

Table 1. The mean concentration of 6MG in different groups receiving Lu and Ae in aortic endothelial and heart tissue cells. 2-way ANOVA analyzed the data.

Groups		Mean	F	*P*.value	η
Aortic endothelial	**HC**	0.97 ± 0.03	111.3	0.0008	0.9823
	Lu1	1.88 ± 0.04			
	Lu2	1.72 ± 0.05			
	Ae	1.88 ± 0.05			
	Ae Lu1	1.61 ± 0.04			
	Ae Lu2	1.50 ± 0.03			
	TC	1.99 ± 0.11			
Heart Tissue	**HC**	1.05 ± 0.06	147.9	0.0005	0.9867
	Lu1	1.92 ± 0.05			
	Lu2	1.74 ± 0.03			
	Ae	1.95 ± 0.02			
	Ae Lu1	1.57 ± 0.06			
	Ae Lu2	1.48 ± 0.02			
	TC	2.04 ± 0.05			

*Healthy Control (HC) who received no Lu extract and no Ae, Lu1 (received 5 mg/kg of Lu supplementation), Lu2 (received 10 mg/kg of Lu supplementation), Ae (received only Ae), Ae Lu1 (received 5 mg/kg of Lu supplementation as well as Ae), Ae Lu2 (received 10 mg/kg of Lu supplementation as well as Ae), Toxicated Control (TC with no treatment). F: Statistical parameter of analysis of variance. *P*: significant statistical level. η: Effect size.

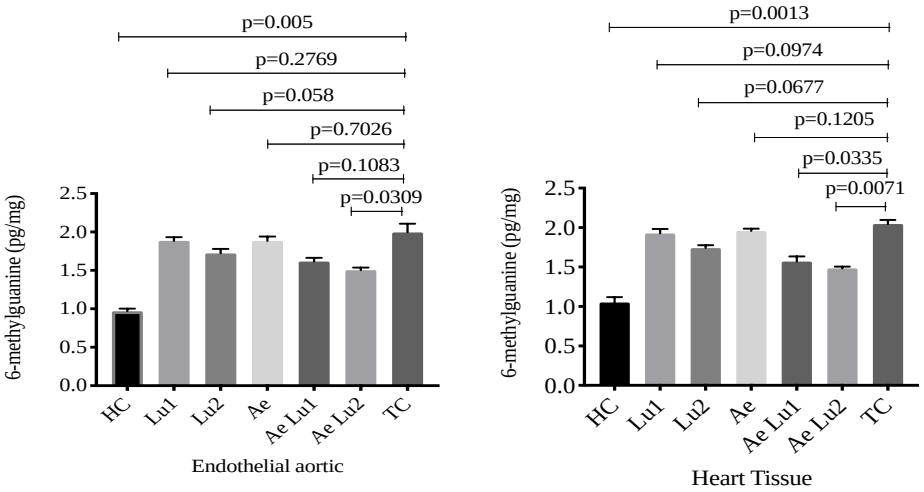

Figure 1. The mean concentration of 6-methylguanine in different groups receiving Lu and Ae.

*Healthy Control (HC) who received no Lu extract and no Ae, Lu1 (received 5 mg/kg of Lu supplementation), Lu2 (received 10 mg/kg of Lu supplementation), Ae (received only Ae), Ae Lu1 (received 5 mg/kg of Lu supplementation as well as Ae), Ae Lu2 (received 10 mg/kg of Lu supplementation as well as Ae), Toxicated Control (TC with no treatment).

- ***The Lu and Ae heighten the ATP level in studied tissue***

Moreover, the intragroup analysis presented that the *Linum Usitatissimum* extract and aerobic exercise also increased ATP levels in the studied groups in both aortic endothelial (F=342.6, *P*=0.0003, η =0.9942) and heart tissue (F=135.1, *P*=0.0013, η =0.9854). Although, the intergroup analyzes displayed that the level of ATP did not differ statistically significant in Lu1, Lu2, and Ae groups for both cell types, while a significantly higher level of ATP was found in the Ae Lu1 and Ae Lu2 groups for both tissue types (Figure 2).

Table 2. The mean concentration of ATP in different groups receiving Lu and Ae in aortic endothelial cells.

Groups		Mean	F	*P*.value	η
Aortic endothelial	**HC**	1.27 ± 0.03	342.6	0.0003	0.9942
	Lu1	0.33 ± 0.01			
	Lu2	0.43 ± 0.03			
	Ae	0.235 ± 0.05			
	Ae Lu1	0.58 ± 0.02			
	Ae Lu2	0.74 ± 0.04			
	TC	0.27 ± 0.02			
Heart Tissue	**HC**	1.39 ± 0.08	135.1	0.0013	0.9854
	Lu1	0.38 ± 0.07			
	Lu2	0.55 ± 0.01			
	Ae	0.23 ± 0.03			
	Ae Lu1	0.77 ± 0.03			
	Ae Lu2	0.31 ± 0.01			
	TC	598.8 ± 59.36			

*Healthy Control (HC) who received no Lu extract and no Ae, Lu1 (received 5 mg/kg of Lu supplementation), Lu2 (received 10 mg/kg of Lu supplementation), Ae (received only Ae), Ae Lu1 (received 5 mg/kg of Lu supplementation as well as Ae), Ae Lu2 (received 10 mg/kg of Lu supplementation as well as Ae), Toxicated Control (TC with no treatment). F: Statistical parameter of analysis of variance. *P*: significant statistical level. η: Effect size.

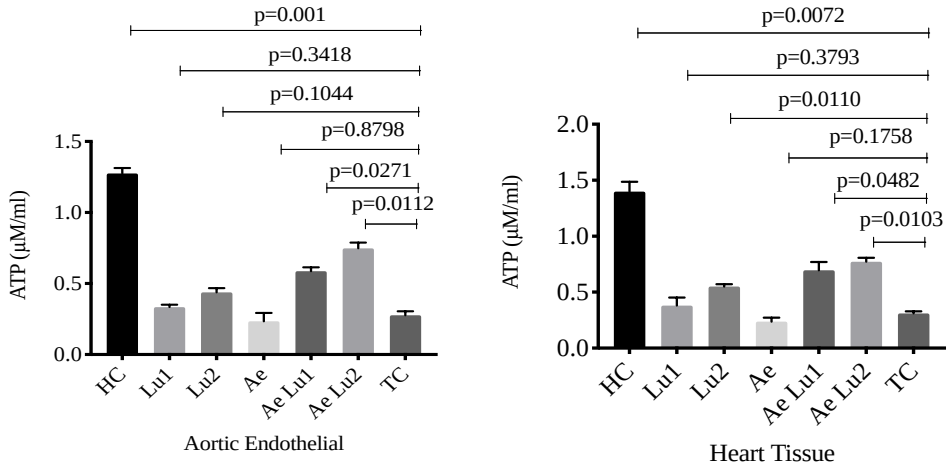

Figure 2. The mean level of ATP is displayed in different groups.

*Healthy Control (HC) who received no Lu extract and no Ae, Lu1 (received 5 mg/kg of Lu supplementation), Lu2 (received 10 mg/kg of Lu supplementation), Ae (received only Ae), Ae Lu1 (received 5 mg/kg of Lu supplementation as well as Ae), Ae Lu2 (received 10 mg/kg of Lu supplementation as well as Ae), Toxicated Control (TC with no treatment).

Discussion

Due to beneficial properties such as a lack of side effects, therapeutic approaches refocus on herbal therapies to prevent or improve diseases. Some known herbs have undergone many studies by which their pharmacologic characteristics have been proved (29). The *Linum Usitatissimum* is one of these well-known plants with numerous activities, including anti-cancer, anti-inflammation, antioxidant, and anti-apoptosis features.

To date, researches have shown that oxidative stresses play a significant role in cardiovascular disease through directing the cardiac cells to death (30). Because oxidative stresses like H_2O_2 can seriously damage cellular macromolecules such as DNA and also trigger ATP depletion through changing mitochondria membrane permeability and speeding up the respiratory electron transport, these changes can impose the high-energy demanding cardiac cells to stress, which eventuate in the activation of apoptotic cascade and cellular death (31). The antioxidant-promoting effect of exercise has been shown in many studies (13). Aerobic exercise has been found to protects cells against oxidative stress through strengthening the antioxidant system, such as up regulation of antioxidant enzymes and free radical scavengers (14, 15). The advantages of exercise are mediated via adaptation phenomenon, including modifying alterations in cardiorespiratory and musculoskeletal systems and body metabolism, which is best in aerobic exercise (14, 16).

Moreover, the antioxidant properties of *Linum Usitatissimum* have been verified in healthy cells (23, 32). Likewise, it has been displayed that *Linum Usitatissimum* exerts an anti-apoptotic solid effect on the healthy cell. In this regard, one of the most important mechanisms that *Linum Usitatissimum* executes its productive cellular effects is suggested to be its antioxidative trait (33). As noted, contained chemicals in this plant, such as lignans, have potential antioxidant effects responsible for attenuating apoptosis in normal cells. As we know the cardiovascular disorders such as ischemia-reperfusion, cardiac hypertrophy, and heart failure are discerned by extensive death of cardiomyocyte cells in these patients (34).

The present results displayed that both aerobic exercise and *Linum Usitatissimum* extract declined the DNA damage marker, 6-methylguanine, and led to a higher level of ATP in cells. As observed, the most desirable response was seen when both interventions were administered concurrently. A high concentration

of plant extract was significantly effective without any exercise. In contrast, we did not recognize any significant alteration when aerobic exercise was applied without herbal extract. Thus, it can be seen here that these interventions could enhance each other's effects so that we may obtain the aimed therapeutical outcome with less concentration of herb accompanied with aerobic exercise. The current study demonstrated that the methanolic extract of *Linum Usitatissimum* could reduce the severity of DNA damage, so that it might be suggested that antioxidant and anti-inflammation features of compounds existing in herbal extract could lessen the free radicals and ROS s such as H_2O_2 that firmly damage the cell genome and deplete mitochondrial ATP. As the H_2O_2 was implemented to poison rats, studies show that hydrogen peroxide, as one most potential detrimental molecules harms DNA via oxidative molecules' production and inhibits DNA repair systems (35, 36). These oxidants result in alterations of purine and pyrimidine bases, which cause a single-chain and double-chain breakdown of the DNA molecule (36). hence it could be reported that molecules such as lignans and Secoisolariciresinol Diglucoside (SGD) in *Linum Usitatissimum* may be able to do two main functions; 1) stimulate DNA repair systems (37) and 2) lower the ROSs molecules like H_2O_2 to prevents DNA damages and ATP synthesis disruption (38). Parallel to our study, Liu et al. mentioned that lignans molecules could effectively abate oxidative-induced DNA damages in rat liver tissue (39). Harper et al. also showed that the lignans compounds could protect cell DNA against oxidative damage (40).

Furthermore, Ghule et al. also note that Lu extracts decreased ROS products and the conservation of antioxidant enzymes in the renal artery (41). Based on our data and other studies, it could be suggested that the most probable assumption for the cardioprotective feature of *Linum Usitatissimum* could be its potential scavenging ability which is followed by minor DNA damage. In accordance with our results, Adolph et al. noted that molecule SGD lowers the cardiovascular risk factors according to its antioxidant and anti-inflammatory activities (42).

- ***Limitation***

One of the limitations of this study was the use of a short period of interventions. It was intended to reduce the pain of animals due to the methodology of the study. Also, it was meant to reduce the number of sacrifices, one of the reasons for choosing a small sample size, which can affect the study's findings. Otherwise, measuring other parameters could provide more clear findings. In addition, it has to be remembered that due to the precise control of the experimental procedure, it is difficult to generalize and compare findings with other studies, especially studies on human models.

Conclusion

This study presented that *Linum Usitatissimum* can efficiently attenuate the DNA damage and upregulate ATP production. Furthermore, it is concluded that aerobic exercise could intensify this herb's antioxidant capability in this favor. All in all, more studies are needed to elucidate the underlying mechanisms, though these findings may be a valuable achievement to modify therapeutic approaches to exploit this plant benefits in patients with cardiovascular disease.

Disclosure statement

The authors declare that no conflict of interest exists with this work.

References

1. Lee Y, Gustafsson AB. Role of apoptosis in cardiovascular disease. Apoptosis. 2009;14(4):536-48. [DOI] [PMID] [Google Scholar]

2. Favaloro B, Allocati N, Graziano V, Di Ilio C, De Laurenzi V. Role of apoptosis in disease. Aging (Albany NY). 2012;4(5):330-49. [DOI] [PMID] [PMCID]

3. Csanyi G, Miller FJ, Jr. Oxidative stress in cardiovascular disease. Int J Mol Sci.

2014;15(4):6002-8. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

4. Xiao J, Sun B, Li M, Wu Y, Sun XB. A novel adipocytokine visfatin protects against H(2)O(2) -induced myocardial apoptosis: a missing link between obesity and cardiovascular disease. J Cell Physiol. 2013;228(3):495-501. [view at publisher] [DOI] [PMID] [Google Scholar]

5. Chen K, Keaney JF, Jr. Evolving concepts of oxidative stress and reactive oxygen species in cardiovascular disease. Curr Atheroscler Rep. 2012;14(5):476-83. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

6. Aldosari S, Awad M, Harrington EO, Sellke FW, Abid MR. Subcellular Reactive Oxygen Species (ROS) in Cardiovascular Pathophysiology. Antioxidants (Basel). 2018;7(1). [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

7. He F, Zuo L. Redox Roles of Reactive Oxygen Species in Cardiovascular Diseases. Int J Mol Sci. 2015;16(11):27770-80. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

8. Somyajit K, Gupta R, Sedlackova H, Neelsen KJ, Ochs F, Rask MB, et al. Redox-sensitive alteration of replisome architecture safeguards genome integrity. Science. 2017;358(6364):797-802. [view at publisher] [DOI] [PMID] [Google Scholar]

9. Savina NV, Smal MP, Kuzhir TD, Egorova TM, Khurs OM, Polityko AD, et al. Biomarkers for genome instability in some genetic disorders: a pilot study. Biomarkers. 2012;17(3):201-8. [view at publisher] [DOI] [PMID] [Google Scholar]

10. Papamichos-Chronakis M, Peterson CL. Chromatin and the genome integrity network. Nat Rev Genet. 2013;14(1):62-75. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

11. Orth JD, Loewer A, Lahav G, Mitchison TJ. Prolonged mitotic arrest triggers partial activation of apoptosis, resulting in DNA damage and p53 induction. Mol Biol Cell. 2012;23(4):567-76. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

12. Roos WP, Kaina B. DNA damage-induced cell death: from specific DNA lesions to the DNA damage response and apoptosis. Cancer Lett. 2013;332(2):237-48. [view at publisher] [DOI] [PMID] [Google Scholar]

13. Gomes EC, Silva AN, de Oliveira MR. Oxidants, antioxidants, and the beneficial roles of exercise-induced production of reactive species. Oxid Med Cell Longev. 2012;2012:756132. [view at publisher] [DOI] [PMID] [Google Scholar]

14. de Meirelles LR, Matsuura C, Resende Ade C, Salgado AA, Pereira NR, Coscarelli PG, et al. Chronic exercise leads to antiaggregant, antioxidant and anti-inflammatory effects in heart failure patients. Eur J Prev Cardiol. 2014;21(10):1225-32. [view at publisher] [DOI] [PMID] [Google Scholar]

15. Park SY, Kwak YS. Impact of aerobic and anaerobic exercise training on oxidative stress and antioxidant defense in athletes. J Exerc Rehabil. 2016;12(2):113-7. [DOI] [PMID] [PMCID] [Google Scholar]

16. Ashrafi J, Roshan VD, Mahjoub S. Cardioprotective effects of aerobic regular exercise against doxorubicin-induced oxidative stress in rat. African Journal of Pharmacy and Pharmacology. 2012;6(31):2380-8. [view at publisher] [DOI] [Google Scholar]

17. Shim YY, Gui B, Arnison PG, Wang Y, Reaney MJT. Flaxseed (Linum usitatissimum L.) bioactive compounds and peptide nomenclature: A review. Trends in Food Science & Technology. 2014;38(1):5-20. [view at publisher] [DOI] [Google Scholar]

18. Ramesh M. Flax (Linum usitatissimum L.) fibre reinforced polymer composite materials: A review on preparation, properties and prospects. Progress in Materials Science. 2019;102:109-66. [view at publisher] [DOI] [Google Scholar]

19. Popa V, Gruia A, Raba D, Dumbrava D, Moldovan C, Bordean D, et al. Fatty acids composition and oil characteristics of linseed (Linum Usitatissimum L.) from Romania. Journal of Agroalimentary Processes and Technologies. 2012;18(2):136-40.

20. Swanson D, Block R, Mousa SA. Omega-3 fatty acids EPA and DHA: health benefits throughout life. Adv Nutr. 2012;3(1):1-7. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

21. Tripathi V, Abidi A, Marker S, Bilal S. Linseed and Linseed oil: health benefits- A review. Int J Pharm Bio Sci. 2013;3(3):434-42. [Google Scholar]

22. Herchi W, Ben Ammar K, Bou Ali I, Bou Abdollah I, Guetet A. Heating effects on physicochemical characteristics and antioxidant activity of flaxseed hull oil (Linum usitatissimum L). Food Science and Technology. 2016;36(1):97-102. [view at publisher] [DOI] [Google Scholar]

23. Szewczyk M, Abarzua S, Schlichting A, Nebe B, Piechulla B, Briese V, Richter D. U. Effects of extracts from Linum usitatissimum on cell vitality, proliferation and cytotoxicity in human breast cancer cell lines. Journal of Medicinal Plants Research. 2014;8(5):237-45. [view at publisher] [DOI] [Google Scholar]

24. Tuluce Y, Ozkol H, Koyuncu I. Photoprotective effect of flax seed oil (Linum usitatissimum L.) against ultraviolet C-induced apoptosis and oxidative stress in rats. Toxicol Ind Health. 2012;28(2):99-107. [view at publisher] [DOI] [PMID] [Google Scholar]

25. Ghule AE, Jadhav S, Bodhankar S. Effect of ethanolic extract of seeds of Linum usitatissimum (Linn.) in hyperglycaemia associated ROS production in PBMNCs and pancreatic tissue of alloxan induced diabetic rats. Asian Pacific Journal of Tropical Disease. 2012;2:405-10. [view at publisher] [DOI] [Google Scholar]

26. Owsheen S, Yang ES. The intersection between DNA damage response and cell death pathways. Exp Oncol. 2012;34(3):243-54. [view at publisher] [Google Scholar]

27. Garcia JJ, Martinez-Ballarin E, Robinson M, Allue JL, Reiter RJ, Osuna C, et al. Protective effect of beta-carbolines and other antioxidants on lipid peroxidation due to hydrogen peroxide in rat brain homogenates. Neurosci Lett. 2000;294(1):1-4. [view at publisher] [DOI] [Google Scholar]

28. Kumar S, Srivastava N, Gomes J. The effect of lovastatin on oxidative stress and antioxidant enzymes in hydrogen peroxide intoxicated rat. Food and Chemical Toxicology. 2011;49(4):898-902. [view at publisher] [DOI] [PMID] [Google Scholar]

29. Jihadi MG, Hameed I. Linum usitatissimum: Anti-bacterial Activity, Chromatography, Bioactive Compounds, Applications: A Review. Indian Journal of Public Health Research and Development. 2018;9:375-80. [view at publisher] [DOI] [Google Scholar]

30. Khoshtinat Nikkhoi S, Heydarzadeh H, Ranjbar S, Salimi F, Aghaeifard M, Alavian SM, et al. The Evaluation and Comparison of Transcriptionally Targeted Noxa and Puma Killer Genes to Initiate Apoptosis Under Cancer-Specific Promoter CXCR1 in Hepatocarcinoma Gene Therapy. Hepat Mon. 2016;16(10):e38828. [DOI] [PMID] [PMCID] [Google Scholar]

31. Sabour Takanlu J, Aghaie Fard A, Mohammdi S, Hosseini Rad SMA, Abroun S, Nikbakht M. Indirect Tumor Inhibitory Effects of MicroRNA-124 through Targeting EZH2 in The Multiple Myeloma Cell Line. Cell J. 2020;22(1):23-9. [view at publisher] [Google Scholar]

32. Abarzua S, Serikawa T, Szewczyk M, Richter DU, Piechulla B, Briese V. Antiproliferative activity of lignans against the breast carcinoma cell lines MCF 7 and BT 20. Arch Gynecol Obstet. 2012;285(4):1145-51. [view at publisher] [DOI] [PMID] [Google Scholar]

33. Ranjbar R, Karimian A, Aghaie Fard A, Tourani M, Majidinia M, Jadidi-Niaragh F, et al. The importance of miRNAs and epigenetics in acute lymphoblastic leukemia prognosis. J Cell Physiol. 2019;234(4):3216-30. [view at publisher] [DOI] [PMID] [Google Scholar]

34. Vasquez-Trincado C, Garcia-Carvajal I, Pennanen C, Parra V, Hill JA, Rothermel BA, et al. Mitochondrial dynamics, mitophagy and cardiovascular disease. J Physiol. 2016;594(3):509-25. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

35. Van Houten B, Hunter SE, Meyer JN. Mitochondrial DNA damage induced autophagy, cell death, and disease. Front Biosci (Landmark Ed). 2016;21:42-54. [view at publisher] [DOI] [PMID] [Google Scholar]

36. Jin B, Robertson KD. DNA methyltransferases, DNA damage repair, and cancer. Adv Exp Med Biol. 2013;754:3-29. [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

37. Velalopoulou A, Tyagi S, Pietrofesa RA, Arguiri E, Christofidou-Solomidou M. The Flaxseed-Derived Lignan Phenolic Secoisolariciresinol Diglucoside (SDG) Protects Non-Malignant Lung Cells from Radiation Damage. Int J Mol Sci. 2015;17(1). [view at publisher] [DOI] [PMID] [PMCID] [Google Scholar]

38. Moree SS, Rajesha J. Investigation of in vitro and in vivo antioxidant potential of secoisolariciresinol diglucoside. Mol Cell Biochem. 2013;373(1-2):179-87. [view at publisher] [DOI] [PMID] [Google Scholar]

39. Liu CM, Zheng GH, Ming QL, Chao C, Sun JM. Sesamin protects mouse liver against nickel-induced oxidative DNA damage and apoptosis by the PI3K-Akt pathway. J Agric Food Chem. 2013;61(5):1146-54. [view at publisher] [DOI] [PMID] [Google Scholar]

40. Harper A, Kerr DJ, Gescher A, Chipman JK. Antioxidant effects of isoflavonoids and lignans, and protection against DNA oxidation. Free Radic Res. 1999;31(2):149-60. [view at publisher] [DOI] [PMID] [Google Scholar]

41. Ghule AE, Jadhav SS, Bodhankar SL. Trigonelline ameliorates diabetic hypertensive nephropathy by suppression of oxidative stress in kidney and reduction in renal cell apoptosis and fibrosis in streptozotocin induced neonatal diabetic (nSTZ) rats. Int Immunopharmacol. 2012;14(4):740-8. [view at publisher] [DOI] [PMID] [Google Scholar]

42. Zhao G, Etherton TD, Martin KR, Gillies PJ, West SG, Kris-Etherton PM. Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. Am J Clin Nutr. 2007;85(2):385-91. [view at publisher] [DOI] [PMID] [Google Scholar]

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