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Protective Effect of Astaxanthin on Cardiac Telomere Length in Cigarette Smoke-Exposed Rats (*Rattus norvegicus*)

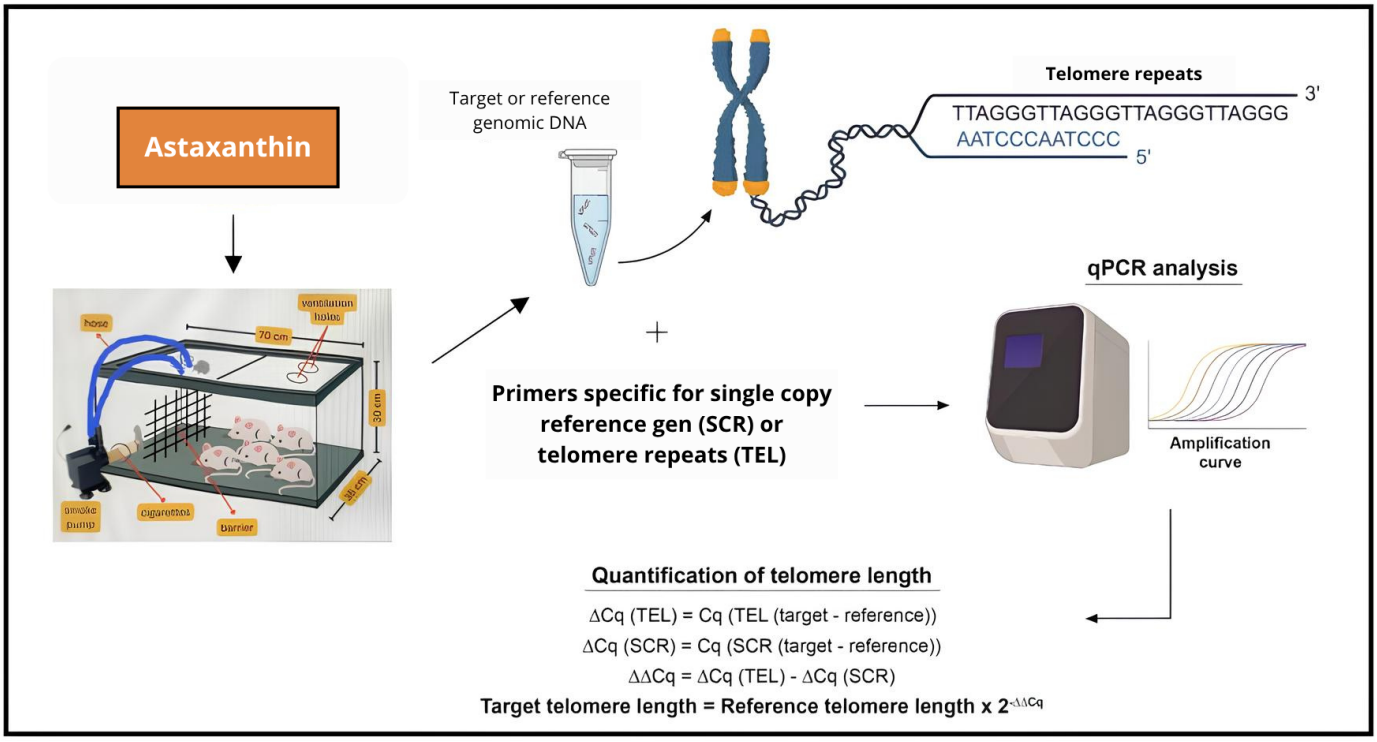
Putu Andita Ratnata[1,*], Arif Santoso[2], Firdaus Hamid[3], Aminuddin Aminuddin[4], Husni Cangara[5]

[1]Master Program of Biomedical Sciences, Hasanuddin University, Makassar, Indonesia
[2]Department of Pulmonology and Respiratory Medicine, Hasanuddin University, Makassar, Indonesia
[3]Department of Microbiology, Hasanuddin University, Makassar, Indonesia
[4]Department of Clinical Nutrition, Hasanuddin University, Makassar, Indonesia
[5]Department of Anatomical Pathology, Hasanuddin University, Makassar, Indonesia

ABSTRACT: Telomeres are repetitive nucleotide sequences that protect chromosome ends and serve as biomarkers of cellular aging and oxidative stress. Cigarette smoke accelerates telomere shortening through increased free-radical exposure, particularly in cardiac tissues. Astaxanthin, a potent antioxidant carotenoid, has been proposed to counteract telomere erosion. This study aimed to evaluate the protective effect of astaxanthin on cardiac telomere length in Wistar rats exposed to cigarette smoke.This laboratory experimental research used a Post-test Control Group Design involving 25 male Wistar rats randomly assigned to five groups: Normal, smoke-exposed control, and three treatment groups receiving astaxanthin at 12, 24, or 48 mg/kg body weight. Rats were exposed to Sampoerna Kretek cigarette smoke chronically, and astaxanthin was administered orally for 28 days. Cardiac tissue was collected on Day 29 for telomere length measurement using quantitative PCR (qPCR) based on the telomere-to-single copy gene (T/S) ratio. Cigarette smoke significantly reduced telomere length in the control group (T/S ratio ≈ 0.7; p = 0.001). Astaxanthin showed dose-dependent protection, with the 48 mg/kg dose maintaining telomere length close to normal levels (T/S ratio ≈ 1.0; p = 0.014 vs smoke control). Lower doses produced partial improvement.In conclusion, chronic cigarette smoke exposure accelerates cardiac telomere shortening, while astaxanthin, particularly at 48 mg/kg, effectively preserves telomere integrity, indicating its potential as a natural cardioprotective agent against oxidative DNA damage.

* Corresponding author.
E-mail address: putuanditaratnata@gmail.com (Putu Andita Ratnatai)

GRAPHICAL ABSTRACT



1. INTRODUCTION

Cigarette smoke has long been recognized as a major risk factor for various degenerative diseases, including cancer, cardiovascular disorders, and chronic respiratory conditions. One of the primary mechanisms underlying the health impacts of smoking is the increased production of Reactive Oxygen Species (ROS), which are highly reactive oxygen molecules that can damage essential cellular biomolecules (Boukhenouna et al., 2018). Although ROS are physiologically generated through normal metabolic processes, exposure to external sources such as cigarette smoke can markedly elevate their levels, exceeding the capacity of the body's endogenous antioxidant defense system (Zhou et al., 2021). This imbalance results in oxidative stress, a condition widely known as a key contributor to the initiation and progression of numerous chronic diseases.

The ROS components in cigarette smoke are diverse and include superoxide (O_2•–), hydroxyl radicals (•OH), and hydrogen peroxide (H_2O_2). These molecules induce oxidative damage to membrane lipids through lipid peroxidation, to proteins through amino acid oxidation, and to DNA through the formation of adducts and double-strand breaks (Silviani et al., 2022). Malondialdehyde (MDA), a commonly used biomarker of oxidative damage and a by-product of lipid peroxidation, has been shown to increase in individuals exposed to cigarette smoke (Purwaningsih et al., 2022).

Beyond direct cellular damage, ROS can also activate signaling pathways that trigger chronic inflammatory responses. Activation of the transcription factor NF-κB, for example, elevates the expression of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, further aggravating inflammation in pulmonary and cardiovascular tissues (Wu, 2024). Chronic inflammation is closely linked to accelerated cellular aging, which is mediated through telomere shortening.

Telomeres are nucleoprotein structures located at the ends of chromosomes, composed of repetitive DNA sequences (TTAGGG) and a protective protein complex known as shelterin. Their function is to maintain genome stability and protect DNA ends from damage or chromosomal fusion (Turner et al., 2019; Srinivas et al., 2020). Physiologically, telomeres shorten with each cell division, and when they reach a critical length, cells enter senescence or apoptosis as a protective mechanism against malignant transformation (Okamoto & Seimiya, 2019). However, external factors such as oxidative stress from cigarette smoke can accelerate this shortening, reducing the regenerative capacity of tissues more rapidly than natural aging (Fouquerel et al., 2019; Lagnado et al., 2021).

Several studies have demonstrated that both active and passive smokers have shorter telomeres than nonsmokers,

indicating the systemic impact of cigarette smoke on biological aging (Firmansyah et al., 2018). Telomere shortening is correlated not only with accelerated biological age but also with an increased risk of cardiovascular diseases, including coronary heart disease, cardiomyopathy, and heart failure (Deng et al., 2022; Raymond et al., 2013). In cardiac tissue, telomere shortening can impair cardiomyocytes and cardiac progenitor cells, both of which play crucial roles in tissue regeneration and repair. When these cells lose their proliferative capacity due to senescence, the heart's ability to recover from physiological or pathological stress becomes limited, accelerating disease progression (Sharifi-Sanjani et al., 2017).

Given these serious consequences, various antioxidant-based interventions have been explored to prevent or slow oxidative damage and telomere shortening. One promising candidate is astaxanthin, a natural xanthophyll carotenoid with exceptionally strong antioxidant activity. Astaxanthin, derived from the microalga *Haematococcus pluvialis* and various marine organisms, is known for its ability to neutralize ROS, protect cellular membranes, and inhibit inflammatory pathways (Ambati et al., 2010; Yuan et al., 2010).

Experimental studies have shown that astaxanthin exerts protective effects against conditions triggered by oxidative stress. In animal models, astaxanthin reduces MDA levels, increases endogenous antioxidant capacity such as superoxide dismutase (SOD), and decreases the expression of proinflammatory cytokines (Dong et al., 2013; Xia et al., 2022). Additionally, astaxanthin has been reported to reduce apoptosis in cells exposed to oxidative stress and help preserve telomere integrity by inhibiting telomere shortening caused by free radicals (Suharso et al., 2022; Tan et al., 2021).

In the context of cardiovascular health, astaxanthin shows substantial potential in mitigating oxidative damage to cardiac tissue. Several studies in Wistar rats have reported that astaxanthin supplementation is associated with improved antioxidant status, reduced ROS levels, and histological improvements in heart tissue (Mosaad et al., 2016; Xuan et al., 2016). These findings suggest that astaxanthin may play a role in protecting cardiac telomeres from smoke-induced shortening, thereby supporting cardiac function and slowing the progression of cardiovascular disease.

However, despite the growing evidence of astaxanthin's benefits against oxidative stress and inflammation, studies specifically examining its role in maintaining cardiac telomere length under cigarette smoke exposure remain limited. Most prior research has focused on its systemic antioxidant effects rather than the molecular aspects of telomere protection in heart tissue. This gap highlights an important question regarding the extent to which astaxanthin can preserve telomere integrity under chronic cigarette smoke exposure.

Based on this background, the present study aims to explore the protective effects of astaxanthin on cardiac telomere length in Wistar rats exposed to cigarette smoke. Through this approach, the study seeks to provide deeper insight into the molecular mechanisms by which astaxanthin maintains genome integrity, while also opening opportunities for its use as a nutraceutical intervention in preventing smoke-induced cardiovascular damage.

2. MATERIALS AND METHODS

2.1. Materials

The following materials were used for this study: Astaxanthin; Sampoerna Kretek cigarette smoke; rat feed (pellets); drinking water; rice husk bedding; cage labels; 70% alcohol; distilled water; alcohol swabs; 10% formalin; PCR reagent kit (insert kit); micropipette tips; disposable sample tubes; DAPI staining solution (4',6-diamidino-2-phenylindole).

2.2. Experimental design

This study was a laboratory-based experimental research employing a Post-test Control Group Design. The procedures for adaptation, maintenance, and treatment of the experimental animals were carried out at the Integrated Laboratory, Faculty of Veterinary Medicine, Hasanuddin University, Makassar. Telomere length analysis was conducted at the Hasanuddin University Medical Research Center (HUM-RC), Teaching Hospital of Hasanuddin University, Makassar.

The research subjects consisted of 25 male Wistar rats (*Rattus norvegicus*), aged 2–3 months and weighing 150–200 g. The animals were randomly assigned into five groups, each comprising five rats: a Normal group (no cigarette smoke exposure and no astaxanthin), a Control group (exposed to cigarette smoke without astaxanthin), and three treatment groups exposed to cigarette smoke and administered astaxanthin orally at doses of 12, 24, and 48 mg/kg body weight, respectively.

Following the treatment period, cardiac tissue samples were collected for telomere length analysis using quantitative PCR (qPCR).

2.3. Inclusion, exclusion, and dropout criteria

The experimental animals used in this study were male Wistar rats (*R. norvegicus*) that met the inclusion criteria of

being healthy, active, 2–3 months old, male, and weighing more than 200 g. The exclusion criteria included female rats, pregnant rats, rats weighing less than 150 g, those exhibiting anatomical abnormalities, or those showing signs of illness during the adaptation period. In addition, any rats that died during the research period were classified as dropout subjects and excluded from data analysis.

2.4. Procedure

The study began with a preintervention phase in which male Wistar rats were acclimatized for 14 days under controlled conditions to standardize their living environment and dietary intake. During the acclimatization period, the animals' health was monitored daily, body weight was measured weekly, and each rat was housed individually in a cage with standard feed (5–10 g per rat per day) and ad libitum access to drinking water. The cage environment was maintained in clean, non-humid conditions with a room temperature of 28–32 °C and adequate lighting.

Following the acclimatization period, the intervention phase commenced with the random assignment of animals into five groups. The Normal group was exposed only to ambient air and received 5 mL of distilled water per rat. The Control group was exposed to cigarette smoke from five cigarettes per day (morning and afternoon) and provided distilled water ad libitum. The three treatment groups were each exposed to cigarette smoke from two cigarettes per day and were administered astaxanthin orally at doses of 12, 24, and 48 mg/kg body weight, respectively. Smoke exposure was conducted inside a chamber box, with each cigarette burned completely within approximately 15 minutes. The cigarettes used were Sampoerna Kretek, containing 38 mg of tar and 2.3 mg of nicotine per stick.

On Day 29, all animals were anesthetized using ketamine (20 mg/kg body weight) before termination through cervical dislocation. The heart was then collected through necropsy, flash-frozen in liquid nitrogen, and stored for telomere length analysis using the qPCR method.

2.5. Statistical analysis

Normality of the telomere length ratio (T/S) data was assessed using the Shapiro–Wilk test, which confirmed that the data were normally distributed ($p > 0.05$). Homogeneity of variances across groups was evaluated using Levene's test and showed homogeneity ($p > 0.05$). Since the assumptions of normality and homogeneity were met, comparative analysis was performed using one-way ANOVA to identify differences in telomere length among treatment groups, followed by Tukey's post hoc test to determine specific group differences.

2.6. Ethical considerations

This study has received ethical clearance from the Biomedical Research Ethics Committee for Humans, Faculty of Medicine, Hasanuddin University, with the ethical approval recommendation number: 816/UN4.6.4.5.31/PP31/2025 and protocol number UH25090702. Informed consent was obtained from the subjects who participated in the study, and efforts were made to ensure the confidentiality of their identities to prevent any harm or risk. It is expected that this research will provide benefits to all parties involved, in accordance with the research benefits previously mentioned.

3. RESULTS AND DISCUSSION

Telomeres are repetitive DNA structures located at the ends of chromosomes and function as protective elements that maintain genomic integrity during replication. Telomere shortening is a biological indicator of cellular aging and oxidative damage. Cigarette smoke exposure is known to accelerate telomere shortening through increased oxidative stress, affecting various tissues, including the heart. Astaxanthin, a carotenoid compound with strong antioxidant activity, has the potential to protect telomeres from such damage. This study aims to evaluate the effectiveness of astaxanthin in maintaining telomere length in the cardiac tissue of Wistar rats exposed to cigarette smoke.

Telomere length measurement was conducted using qPCR (Figure 1). This method involves the isolation of genomic DNA from cardiac tissue of rats, followed by amplification using primers specific to telomeric sequences (TEL) and a single-copy reference gene (SCR). The cycle threshold (Cq) values for each target were used to calculate ΔCq and $\Delta\Delta Cq$, which were then converted into relative telomere length. The amplification curves (Figure 2) show positional differences between samples relative to the threshold line, reflecting telomere length variation across treatment groups. Rats were placed in partitioned cages, with cigarette smoke delivered through a pump on one side (Figure 3). This design allowed passive exposure resembling human environmental conditions. The exposure was conducted regularly to induce chronic oxidative stress.

Body weight (Figure 4) was used as an initial physiological indicator of cigarette smoke exposure and astaxanthin treatment. The results showed that the negative control group experienced a significant increase in body weight, whereas

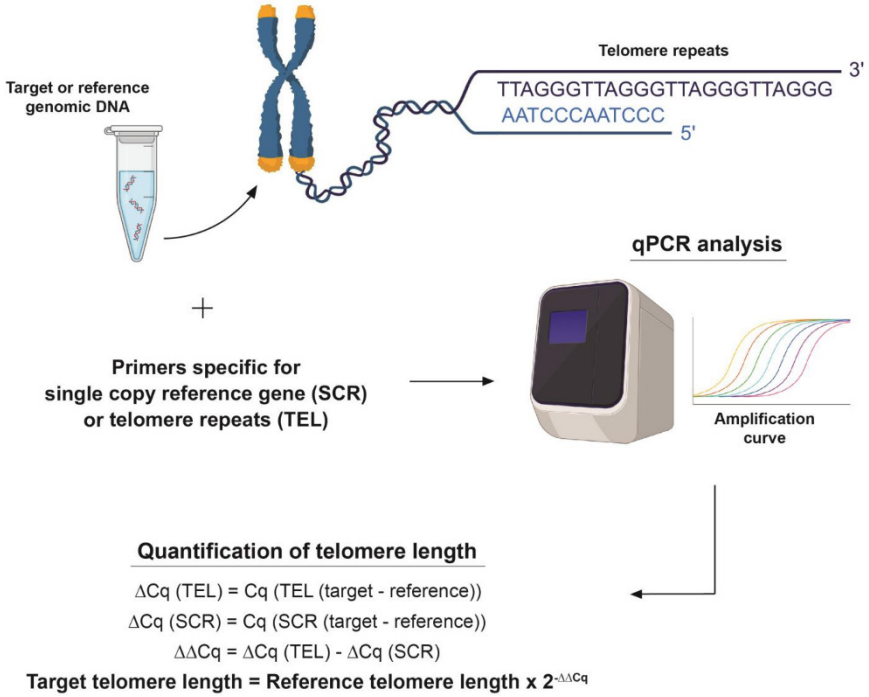


Figure 1. Schematic of telomere length quantification using qPCR (Quantitative Polymerase Chain Reaction) analysis.

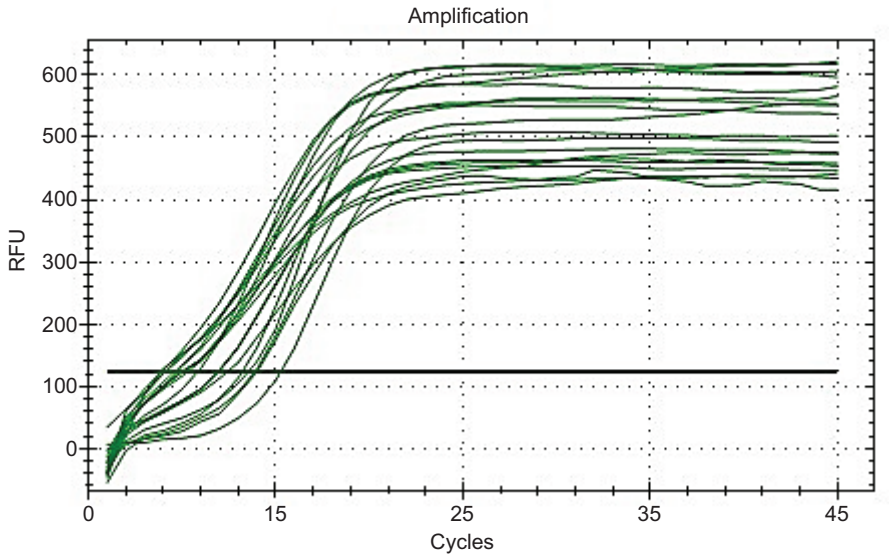


Figure 2. Amplification curve of telomere length in Wistar rat cardiac tissue using qPCR analysis.

the positive control group exhibited a decrease. The astaxanthin-treated groups displayed a recovery trend, particularly at the 48 mg dose, which produced a significant increase ($p < 0.01$). This indicates that astaxanthin may mitigate the systemic effects of cigarette smoke exposure.

The conceptual illustration (Figure 5) indicates that rats not exposed to cigarette smoke have longer telomeres, whereas smoke-exposed rats show shorter telomeres. This visual supports the hypothesis that cigarette smoke accelerates cellular aging through telomere damage induced by oxidative stress.

The qPCR data show that the negative control group had the highest telomere length ratio (~1.1), while the positive control group experienced a significant reduction (~0.7, $p = 0.001$). The astaxanthin groups receiving 12 and 24 mg showed improvement, but not a significant effect. In contrast, the 48 mg dose produced a near-normal ratio (~1.0) and

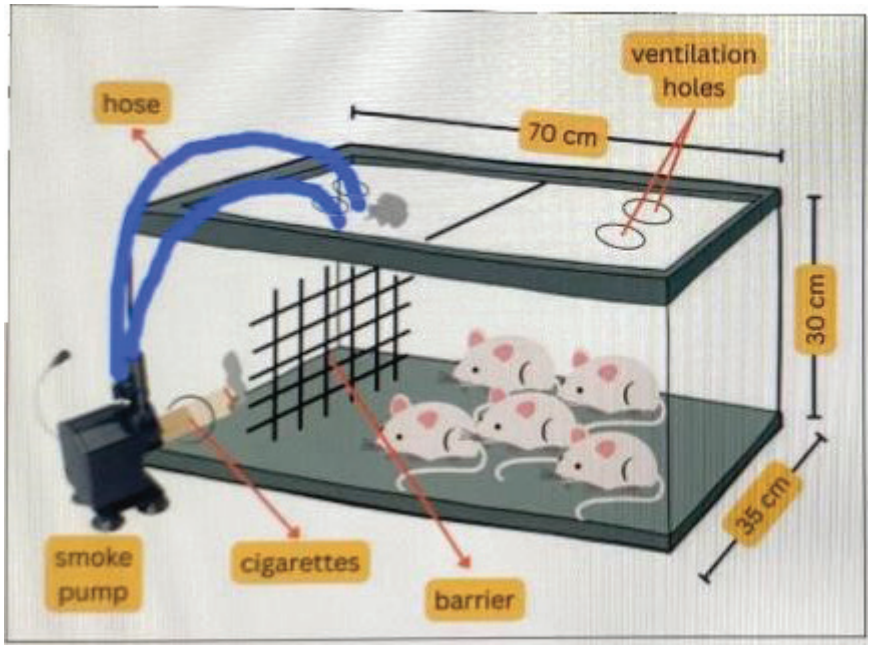


Figure 3. Experimental design for cigarette smoke exposure in Wistar rats (*Rattus norvegicus*).

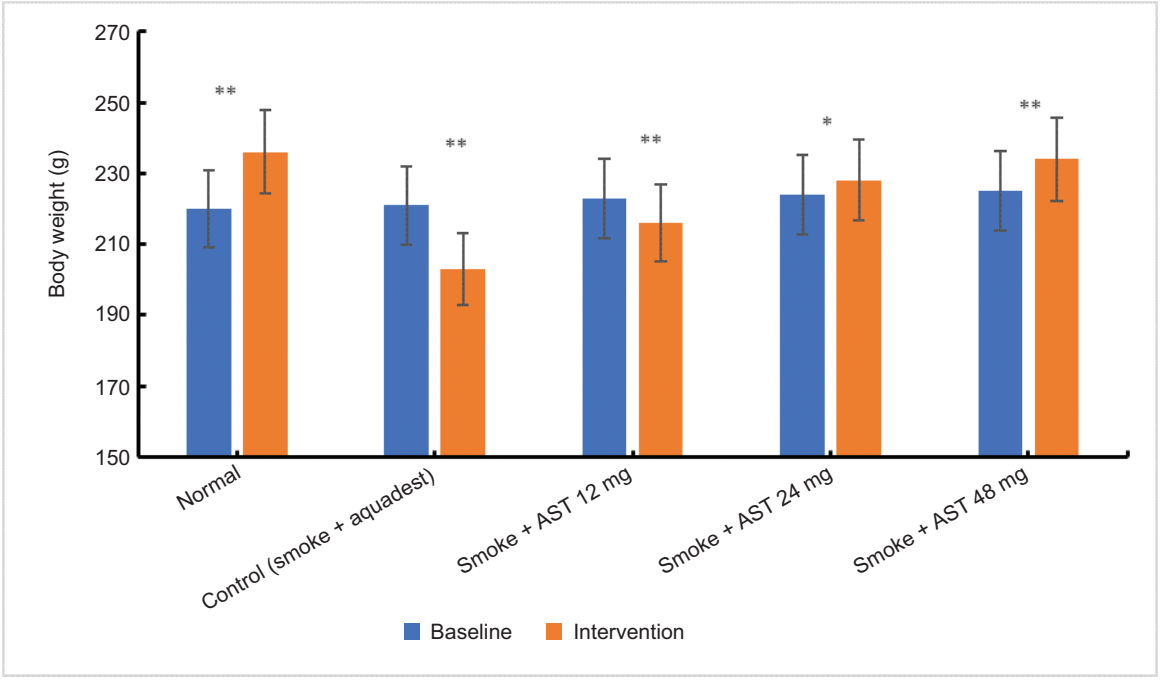


Figure 4. Body weight changes in rats (*Rattus norvegicus*). Paired t-test was used for analysis; * indicates $p < 0.05$ and ** indicates $p < 0.01$.

differed significantly from the positive control ($p = 0.014$). These findings indicate that high-dose astaxanthin effectively protects telomeres from smoke-induced damage. The results confirm that cigarette smoke exposure generates oxidative stress that triggers DNA damage and telomere shortening in cardiac tissue.

Cigarette smoke is known to be a major source of ROS, which contribute to oxidative stress and damage to lipids,

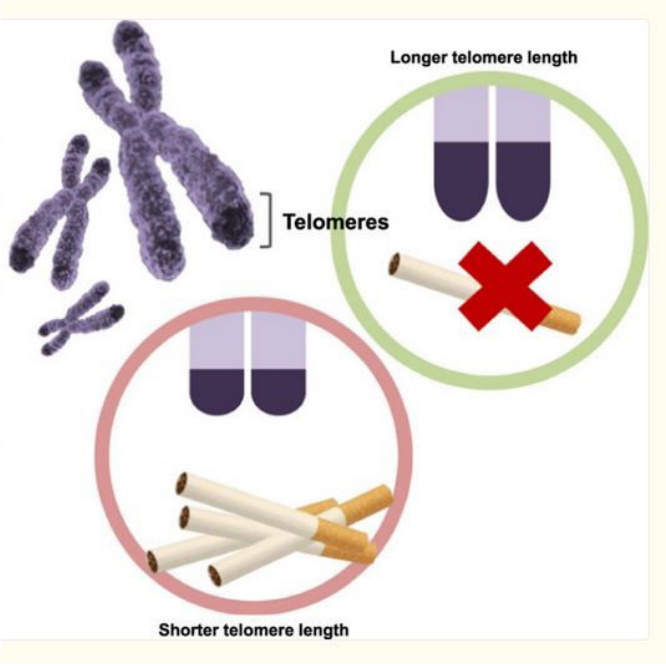


Figure 5. Effect of cigarette smoke exposure on telomere length: visual comparison between smoke-exposed and nonexposed conditions.

proteins, and DNA (Boukhenouna et al., 2018). Chronic exposure also activates inflammatory responses through increased production of proinflammatory cytokines such as TNF-α and IL-6 (Suryadinata, 2018). These conditions accelerate telomere shortening and trigger cellular senescence, a state in which cells lose their ability to renew themselves.

In cardiac tissue, cellular senescence can affect cardiomyocytes and cardiac progenitor cells that play crucial roles in regeneration and tissue repair (Moslehi et al., 2012; Mourkioti et al., 2013). These findings reinforce the evidence that cigarette smoke is a potent external factor that accelerates telomere shortening, consistent with the reports of Boniewska-Bernacka et al. (2020) and Coluzzi et al. (2014), which showed that long-term exposure to toxic smoke components increases oxidative burden, damages DNA, and accelerates the loss of telomeric sequences.

Astaxanthin administration demonstrated dose-responsive protective effects against telomere shortening. The 12 mg/kgBW dose produced a telomere length ratio of 0.46 ± 0.12, while the 24 mg/kgBW dose increased the ratio to 0.61 ± 0.07. Both remained significantly different from the normal group ($p < 0.05$), but improved compared to the

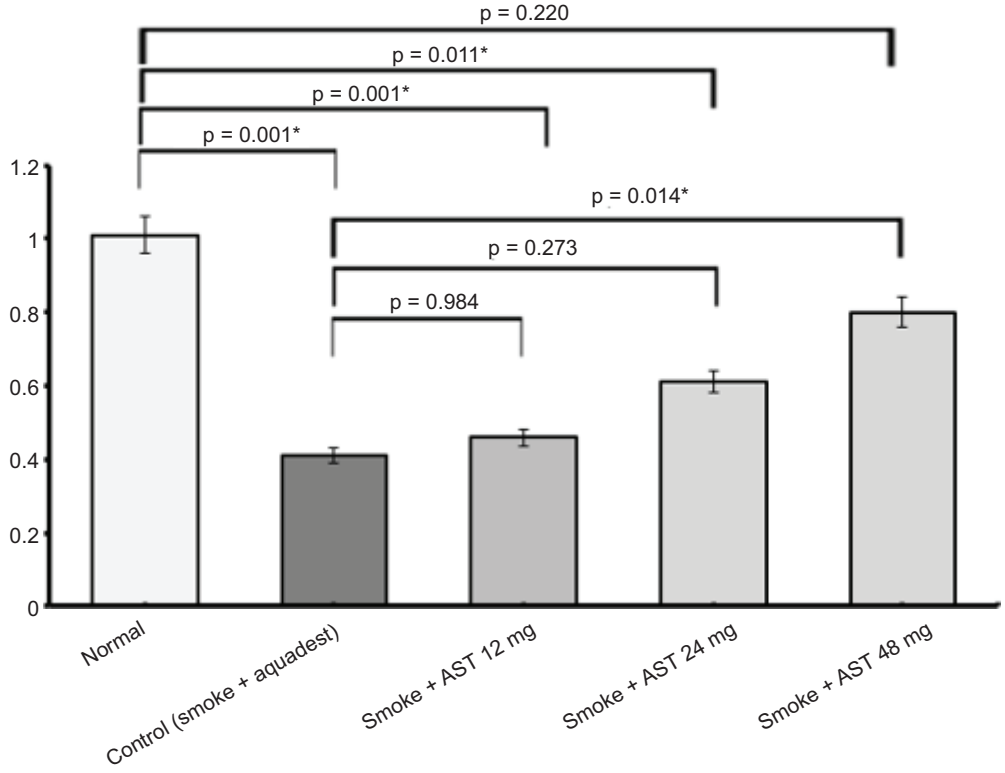


Figure 6. Comparison of mean telomere length ratio values in rat cardiac tissue. One-way ANOVA and Tukey post hoc test were used; * indicates significance at $p < 0.05$.

smoke-exposed control group. Meanwhile, the 48 mg/kgBW dose resulted in a T/S ratio of 0.80 ± 0.02, which did not differ significantly from normal ($p > 0.05$). These results indicate that the highest dose preserved telomere length close to normal despite smoke exposure.

The Tukey post hoc test further supports these findings. Telomere ratios differed significantly with 12 mg ($p = 0.001$) and 24 mg ($p = 0.011$) astaxanthin treatments and with the control group ($p = 0.001$), but did not differ significantly from the 48 mg dose ($p = 0.220$). Conversely, the control group did not differ significantly from the 12 mg ($p = 0.984$) or 24 mg ($p = 0.273$) treatments. This pattern indicates that increasing astaxanthin dosage consistently enhances its protective effect against oxidative telomere damage. The results confirm that higher astaxanthin doses provide greater protection against smoke-induced telomere shortening.

The protective effects of astaxanthin can be explained by its strong antioxidant capacity in neutralizing ROS. At low doses, astaxanthin's ability to eliminate ROS is limited, allowing oxidative processes to dominate and cause telomere damage. However, increased dosage strengthens its antioxidant activity, enabling more effective suppression of oxidative stress (Suryadinata, 2018). Several studies also report that astaxanthin can activate the Nrf2/ARE pathway (Nuclear factor erythroid 2–related factor 2/Antioxidant Response Element), which stimulates the production of endogenous antioxidant enzymes such as SOD, Catalase (CAT), and Glutathione Peroxidase (GPx) (Chen et al., 2020; Kubo & Kazuhisa, 2019). Activation of this pathway is crucial in reducing intracellular ROS accumulation, the primary trigger for DNA damage, including at telomeric ends.

The optimal effect was observed at the 48 mg dose. The telomere length ratio in this group reached 0.80 ± 0.02 and was statistically indistinguishable from the normal group ($p = 0.220$). This indicates that at higher doses, astaxanthin can maintain telomere length near normal levels while also demonstrating significant improvement compared to the control group ($p = 0.014$). The effectiveness of high-dose astaxanthin may be attributed to its unique molecular properties. As a xanthophyll carotenoid with a long polyene structure, astaxanthin has strong free radical scavenging ability, protects cellular membranes, and stabilizes DNA structures. Liu et al. (2016) reported that high-dose astaxanthin improves mitochondrial function, reduces MDA, and enhances cellular redox capacity, ultimately slowing telomere shortening.

Beyond its antioxidant activity, astaxanthin's protective mechanism may also involve increasing telomerase activity, the enzyme responsible for adding telomeric sequences (TTAGGG)n to chromosome ends. A recent study by Boniewska-Bernacka et al. (2020) suggests that Nrf2 activation by astaxanthin can upregulate telomerase expression, thereby not only reducing the rate of telomere shortening but also potentially restoring lost telomeric length. This aligns with the present study, in which the highest astaxanthin dose produced telomere lengths nearly equivalent to normal, supporting the compound's potential regenerative effect on genomic stability.

Biologically, telomere shortening in cardiac tissue has major implications for cardiovascular health. It induces cellular senescence, a condition in which cells lose the ability to divide and repair themselves. In the heart, this condition can affect cardiomyocytes and progenitor cells, reducing regenerative capacity and increasing the risk of fibrosis, heart failure, and degenerative cardiovascular disease (Moslehi et al., 2012; Mourkioti et al., 2013). Thus, the finding that high-dose astaxanthin can protect telomeres from smoke-induced damage highlights its considerable potential as a natural cardioprotective agent acting through antioxidant mechanisms and telomerase enhancement.

Nevertheless, this study has limitations. The analysis focused solely on cardiac tissue, leaving uncertainty about whether astaxanthin's protective effects are specific to the heart or systemic across other organs. To strengthen these findings, future studies should include analyses across multiple target organs, more comprehensive oxidative stress biomarkers, and direct observations of telomerase activity and gene expression related to cellular protection.

Overall, the study shows that cigarette smoke exposure significantly accelerates telomere shortening in rat cardiac tissue through oxidative stress mechanisms. Significant telomere shortening in cardiac cells has serious implications for cardiovascular function, as shortened telomeres trigger cellular senescence, reducing the regenerative capacity of cardiomyocytes and progenitor cells. This makes cardiac tissue more vulnerable to fibrosis, contractile dysfunction, and the development of ischemic or degenerative heart disease (Moslehi et al., 2012; Mourkioti et al., 2013). Therefore, telomere shortening may be considered one of the molecular mechanisms underlying premature aging and structural cardiac damage caused by chronic cigarette smoke exposure.

Conversely, astaxanthin intervention demonstrated protective effects against such damage in a dose-responsive manner. The most optimal effect was observed at 48 mg/kgBW, which preserved telomere length near normal levels and significantly reduced shortening compared with the positive control group. This protective mechanism is likely related to astaxanthin's ability to suppress ROS formation, enhance endogenous antioxidant enzyme activity, and stabilize telomeric DNA through Nrf2/ARE activation and increased telomerase expression.

These findings confirm that astaxanthin has strong potential as a natural cardioprotective agent for preventing oxidative DNA damage and slowing cellular aging processes in the heart, particularly those induced by chronic cigarette smoke exposure.

4. CONCLUSION

Exposure to cigarette smoke was shown to accelerate telomere shortening in the cardiac tissue of Wistar rats. Administration of astaxanthin, particularly at a dose of 48 mg per kg body weight, effectively inhibited this process and maintained telomere length close to normal levels. These findings indicate that astaxanthin has strong potential as a natural antioxidant for protecting telomere integrity from oxidative stress–induced damage.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

MANDATORY DISCLOSURE ON USE OF ARTIFICIAL INTELLIGENCE

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AUTHORS' DECLARATION

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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None.

AUTHOR CONTRIBUTIONS

Putu Andita Ratnata: Research concept and design, Collection and/or assembly of data, Writing the article. Arif Santoso: Research concept and design, Collection and/or assembly of data, and data analysis and interpretation. Firdaus Hamid & Aminuddin Aminuddin: Data analysis and interpretation, Critical revision of the article. Husni Cangara: Data analysis and interpretation, Final approval of the article.

ORCID

Putu Andita Ratnata 0009-0006-2352-3359
Arif Santoso 0000-0003-4125-005X
Firdaus Hamid 0000-0003-1788-0836
Aminuddin Aminuddin 0000-0001-8564-7847
Husni Cangara 0000-0002-5160-8265

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