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Literature Review

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THE ROLE OF TELOMERASE IN CELULLAR SENESCENCE AND ITS IMPLICATIONS FOR ANTI-AGING THERAPY

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Abstract
Aging is a complex biological process influenced by genetic, environmental, and lifestyle factors. One of the primary mechanisms contributing to aging is telomere shortening, which plays a crucial role in genome stability and cellular regeneration. As individuals age, progressive telomere shortening can trigger cellular apoptosis and tissue dysfunction, impacting health and skin aesthetics. Consequently, telomere-based anti-aging therapies have become a significant focus of strategies aimed at slowing the aging process and improving quality of life. Several studies have explored various therapeutic approaches, including telomerase activation, bioactive compounds, and genetic engineering technologies to maintain telomere length and enhance cellular function. This literature review aims to analyze recent developments in telomere-based anti-aging therapies, evaluate their effectiveness, and discuss their potential applications in health and aesthetic medicine. A deeper understanding of telomere mechanisms and their therapies is expected to facilitate the development of more effective and sustainable anti-aging strategies.

INTRODUCTION

Aging is a complex biological process influenced by genetic, environmental, and lifestyle factors. As individuals age, cellular function declines, contributing to various degenerative conditions, including reduced skin elasticity, impaired tissue regeneration, and an increased risk of chronic diseases. The aging process is generally divided into intrinsic (or chronological) and extrinsic processes. The inherent process relates to internal factors, such as telomere shortening, DNA damage, inflammation, etc. On the other hand, the extrinsic aging process is directly influenced by environmental factors, such as exposure to UV radiation (Samuel et al., 2022). One of the central theories in the aging mechanism is telomere shortening, a DNA-protein structure at the ends of chromosomes that plays a critical role in maintaining genomic stability during cell division (Karimian *et al*., 2024). Aging is a change that every individual will experience, and it is an inevitable process. Aging has become a significant issue in both healthcare and aesthetics. Aging-related problems, such as decreased skin elasticity, roughness, uneven tone, and wrinkles, are common symptoms experienced by most individuals (Z. Li *et al*., 2021).

Telomeres progressively shorten each time a cell undergoes replication. When they reach a critical point, the cell enters senescence or apoptosis, leading to tissue and organ function decline. The activity of the enzyme telomerase, which extends telomeres, has become a focal point in anti-aging strategies due to its potential to slow or reverse aging effects at the cellular level (Tenchov *et al*., 2024). Telomere length indicates cellular aging: the shorter the telomere, the older the cell. Several factors contribute to telomere shortening, one of which is oxidative stress. Oxidative stress is produced by exposure to free radicals, which can accelerate telomere shortening. High levels of oxidative stress can lead to single-strand DNA breaks at telomeres, disrupting chromosome stability and accelerating cellular aging.

Cellular aging impacts not only overall health but also aesthetics. Numerous diseases are associated with cellular aging, such as cardiovascular diseases and cancer. Furthermore, cellular aging affects skin health, which can interfere with an individual's aesthetic appearance (Samuel *et al*., 2022). In aesthetic medicine, telomere-based therapies have begun to attract attention as an innovative approach to maintaining skin health and youthfulness. Various interventions, including telomerase activation through lifestyle modifications, nutritional supplements, gene therapy, and pharmacological approaches, have been developed to optimize cellular regeneration and improve the quality of life for individuals seeking to preserve a youthful appearance for longer (Sohn *et al*., 2023).

This literature review explores telomere therapy's emerging role in extending cellular lifespan and its applications in aesthetic medicine. By analyzing recent studies on the biological mechanisms of telomeres, the therapeutic potential of various phases, and their implications in anti-aging treatments, this review seeks to provide deeper insights into the prospects of telomere-based therapies for improving health and aesthetics holistically. Additionally, the review examines various factors influencing the effectiveness of telomere therapies, including epigenetic regulation, inflammation, and oxidative stress. Various therapeutic approaches, such as telomerase activators, gene therapy, and senolytics, are highlighted as key innovations in telomere-based anti-aging treatments. The clinical implications of these therapies are not limited to skin rejuvenation but also extend to improving organ function and increasing healthy life expectancy. Thus, further exploration of telomere therapies' safety, effectiveness, and regulation is critical for in-depth investigation. Continued research in this field will open new opportunities for regenerative therapy and cell-based aesthetic medicine.

RESEARCH METHODS

Time and Location

This literature study was conducted in Soegijapranata Catholic University in Semarang, located at Rm. Hadisoebeno Sosro Wardoyo, Jatibarang street, Mijen district, Semarang City, Central Java. The study was conducted between October and December 2024.

Study Design

This research employs a literature review method using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) approach. The process involves searching and collecting literature from databases, followed by analysis to draw a conclusion. The databases used include PubMed, ScienceDirect, and Google Scholar. The literature reviewed encompasses various articles analyzing the application of telomere-based anti-aging therapies, particularly in aging and aesthetics (Haddaway *et al*., 2022).

The inclusion criteria for the literature were research articles with open access published between 2019 and 2024. Exclusion criteria included studies not involving humans, those that did not discuss the role of telomeres in aging, those that did not address telomere-based anti-aging therapies in aging and aesthetics, and studies not available in full text. The keywords used for the article search included "telomere," "anti-aging therapy," "aging," and "aesthetic."

Research Procedure

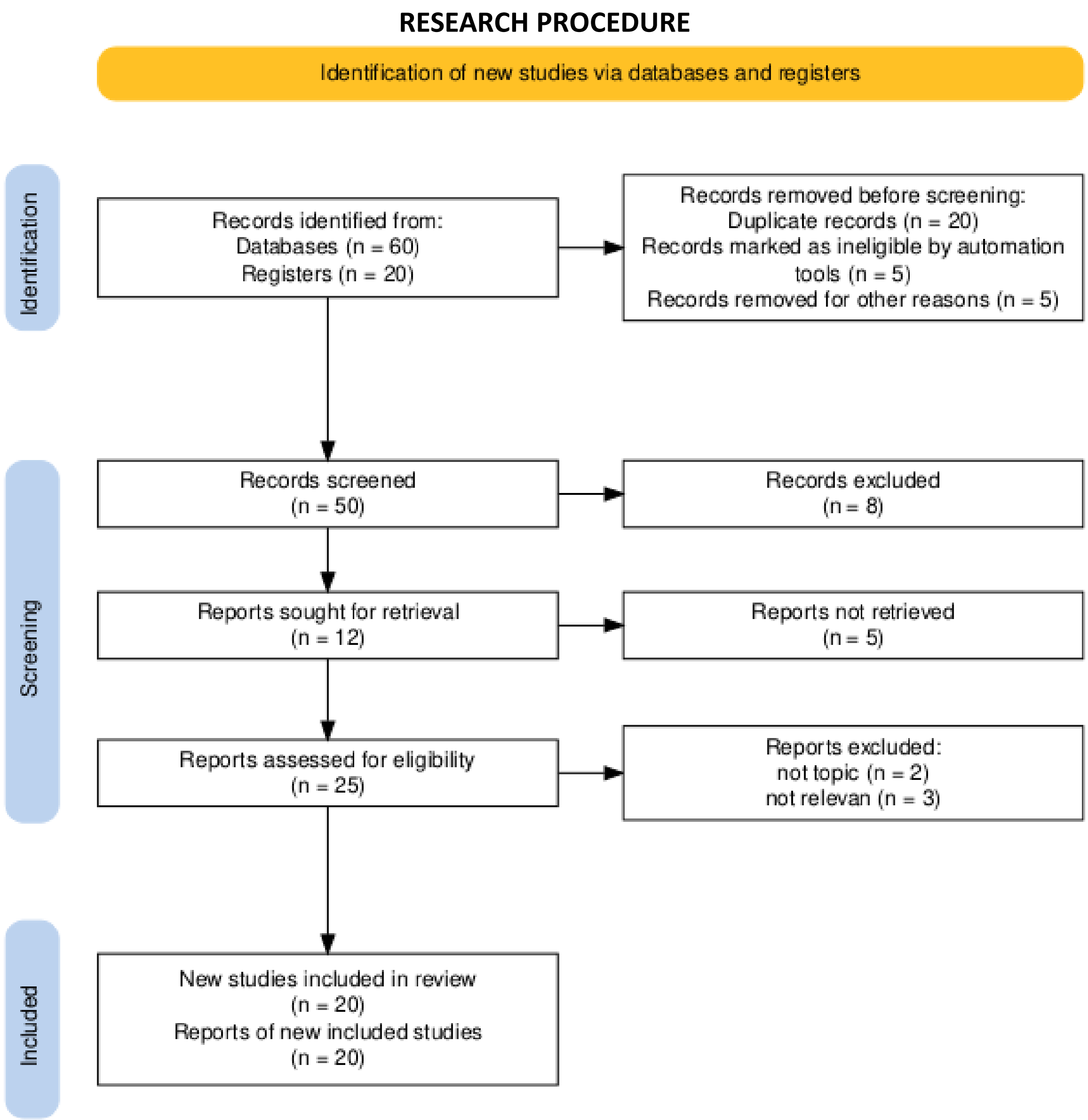

Figure1. Diagram PRISMA (Haddaway *et al*., 2022)

Data Analysis

This literature review used a descriptive approach to data analysis, presenting the findings from various literature collected and selected based on inclusion and exclusion criteria.

RESULTS AND DISCUSSION

The primary intrinsic factor of the aging process is telomere shortening (Samuel *et al*., 2022). According to research by Zhan and Hägg (2021), telomere shortening can lead to visible signs of facial aging. Furthermore, telomere dysfunction may also trigger the aging process, as evidenced by the study of Victorelli *et al*. (2020). Telomere shortening can trigger the progression of various pathological conditions. Studies by Son *et al*. (2022) and Sohn et al. (2023) suggest that telomere shortening may lead to melanoma and non-melanoma conditions.

Schneider *et al*. (2022) examined the relationship between leukocyte telomere length (LTL) and disease-related mortality risk. Their research showed that declines in the cardiovascular, respiratory, digestive, and musculoskeletal systems can trigger LTL shortening. The disease most strongly correlated with LTL shortening is cardiovascular disease. In addition to declines in body system health, the oxidative balance score (OBS) can contribute to LTL shortening. This was confirmed by studies from Zhang *et al*. (2022) and Casagrande *et al*. (2020). Samuel *et al*. (2020) also demonstrated that ergothioneine-induced oxidative stress can trigger LTL shortening.

In the fight against aging and the progression of pathological conditions, scientists worldwide continue to develop therapies based on the principles of anti-aging medicine. Preclinical studies by Piñeiro-Hermida *et al*. (2020) showed that the therapeutic agent AAV9-Tert can trigger telomere elongation through telomerase activation. AAV9-Tert has been shown to reduce the progression of idiopathic pulmonary fibrosis (IPF). Another therapeutic agent researched by Ningarhari *et al*. (2021) targets the inhibition of TERT gene expression. The therapeutic agent used in this study, Anti-TERT Antisense Oligonucleotide (ASO), inhibited TERT gene expression, which could otherwise trigger malignant cell proliferation. Sechium edule is also an antioxidant agent that can inhibit telomere shortening, as demonstrated by the research of Gavia-García *et al*. (2020).

Telomerase is a process that elongates telomere chains. As such, this process has become a primary target for anti-aging therapy. Research by Tsoukalas *et al*. (2019) demonstrated that a therapeutic agent capable of activating telomerase, namely telomerase activator 08AGTL, can prevent the aging process. When combined with *Centella asiatica* extract, 08AGTL inhibited telomere shortening by activating telomerase (Tsoukalas *et al*., 2019). Besides *Centella asiatica* extract, carrot juice (*Daucus carota* L.) has also been shown to address early signs of facial aging. This was supported by the study of Shufyani *et al*. (2023), which demonstrated that carrot juice can improve skin hydration, smooth skin texture, reduce pore size, eliminate dark spots, and reduce wrinkles. Similarly, aloe vera has been shown to have comparable effects, as evidenced by research from Iskandar (2021). Polyphenols have also been proven to have antioxidant properties that can prevent aging (Jacczak *et al*., 2021; Maleki *et al*., 2020).

Several medical drugs have also been shown to inhibit the aging process. Research by Li Z *et al*. (2021) confirmed that metformin and rapamycin can prevent aging by inhibiting telomere shortening (Zhang *et al*., 2021; Zheng *et al*., 2024). Additionally, Tsoukalas *et al*. (2019) supported the use of nutraceutical supplements for preventing aging, their findings showed that these supplements can extend telomeres (Tsatsakis *et al*., 2023).

Research by Schellnegger *et al*. (2024) showed that telomeres act as protectors of chromosomes; however, they tend to shorten with each cell division, contributing to the aging process. Antioxidants and anti-inflammatory agents can be utilized to maintain telomere length and protect cells from damage. Telomeres indicate cellular aging, so it is crucial to maintain them through proper nutrition, lifestyle, and physical activity, as women tend to live longer than men (Boccardi & Polom, 2024).

Both intrinsic and extrinsic factors can trigger cellular aging. The primary intrinsic factor driving the aging process is telomere shortening, which has become the target of anti-aging therapies. Telomere shortening can be induced by the inhibition of telomerase, which elongates the telomere chains. Consequently, many anti-aging therapies target the telomerase process (Samuel *et al*., 2022).

Scientists worldwide continue to develop therapies based on anti-aging medicine principles to halt aging and the progression of pathological conditions (Y. Li *et al*., 2024). The development of telomere-based anti-aging therapies has led to innovative approaches, such as telomerase activators, with one of the primary focuses being the activation of the telomerase enzyme to extend telomeres. Agents such as ASO (Anti-TERT Antisense Oligonucleotide), 08AGTL, and AAV9-Tert have been investigated. AAV9-Tert has shown preclinical potential to trigger telomere elongation through telomerase activation and can reduce the progression of IPF. 08AGTL, when combined with *Centella asiatica* extract, has been shown to prevent aging by activating telomerase. Nutraceutical supplements have also been found to support aging prevention by extending telomeres (Piñeiro-Hermida *et al*., 2020).

Natural bioactive compounds from various plant sources show promise as anti-aging agents. Sechium edule is an antioxidant that can inhibit telomere shortening. Polyphenols, vitamins, unsaturated fatty acids, and polysaccharides can support telomerase activity and maintain telomere stability (Natasya *et al*., 2023). Compounds such as resveratrol and epigallocatechin gallate have significant antioxidant and anti-inflammatory effects that protect skin cells from oxidative stress and inflammation (Hussein *et al*., 2025). The extracts of *Daucus carota* L. (carrot juice) and *Aloe vera* have also been proven effective in addressing early signs of facial aging, such as improving hydration and smoothing skin texture (Iskandar *et al*., 2021).

Pharmacological therapies with metformin and rapamycin can prevent aging by inhibiting telomere shortening (Blagosklonny, 2021; Sirtori *et al*., 2024). Gene therapy is currently a focal point in telomere-based anti-aging innovations. However, it remains in the research and development stages and requires further exploration regarding its safety and effectiveness (Schellnegger *et al*., 2024). Using both antioxidants and anti-inflammatory agents, a combination approach is important for maintaining telomere length and protecting cells from damage (D'Angelo, 2023).

Women tend to live longer than men but often face challenges such as physical frailty and chronic diseases, especially as they age (Shi *et al*., 2021). Telomeres, as biological markers of cellular aging, play an essential role in the aging process and can serve as targets for interventions to slow aging and enhance quality of life (Boccardi & Polom, 2024). A gender-specific approach to healthcare is needed, as women exhibit different biological responses to aging (Nair *et al*., 2021). The correlation between predicted genetic telomere length and facial skin aging suggests that longer telomeres are associated with a lower likelihood of facial aging ($\beta = -0.02$, CI 95%: -0.04, -0.002) (Zhan *et al*., 2021).

Oxidative stress is a key cause of telomere shortening and activation of telomere. Sechium edule acts as an antioxidant that does not directly alter telomerase levels but can protect against telomere shortening (Gavia-García *et al*., 2020). Natural compounds, including polyphenols, vitamins, unsaturated fatty acids, and polysaccharides, support telomerase activity and slow aging (Pointner *et al*., 2021). Compounds such as resveratrol and epigallocatechin gallate have significant antioxidant and anti-inflammatory effects that help protect skin cells from oxidative stress and inflammation (Ali & Walter, 2023; Gutlapalli *et al*., 2020). Furthermore, modulation of telomerase by these compounds could prevent skin aging and reduce the risk of age-related diseases. Stress-induced glucocorticoid increases can reduce telomere length (Shen *et al*., 2017), and excessively shortened telomeres lead to cellular apoptosis (Casagrande et al., 2020).

Telomeres serve as protectors for chromosomes; however, their length tends to shorten with each cell division, contributing to aging. Therapies targeting telomeres, such as telomerase activators and tankyrase inhibitors, show potential in extending telomeres and slowing down aging (Tsoukalas *et al*., 2019). Furthermore, antioxidants and anti-inflammatory agents are critical in maintaining telomere length and protecting cells from damage. Although promising progress has been made, further research is necessary to develop more effective and safe therapies that harness the potential of telomere-based treatments in supporting healthier aging (Samuel *et al*., 2020).

CONCLUSION

Telomeres are protective structures at the ends of chromosomes that play a crucial role in genomic stability and cell regeneration. Their shortening is a key intrinsic factor in cellular aging, contributing to tissue dysfunction and visible signs of aging. Telomere-based anti-aging therapies have become a primary focus in strategies to slow the aging process and enhance the quality of life, extend telomeres through telomerase activation, and protect telomeres from damage.

Recent developments in this field encompass a variety of approaches, ranging from telomerase activators such as AAV9-Tert and 08AGTL to the use of bioactive natural compounds like *Centella Asiatica*, *Aloe vera*, *Sechium edule*, polyphenols, resveratrol, and epigallocatechin gallate, all of which exhibit antioxidant and anti-inflammatory effects. Additionally, pharmacological therapies such as metformin, rapamycin, and gene therapies also show potential in inhibiting telomere shortening.

Evaluations of therapy effectiveness suggest that direct intervention with telomerase can extend telomeres, while antioxidants and anti-inflammatory agents help protect telomeres from oxidative stress-induced damage. A comprehensive approach that combines these various strategies is expected to yield optimal results. Telomere-based therapies have vast potential for skin rejuvenation, organ function, and extending a healthy lifespan. However, further research is still required to develop more effective, safe, and sustainable therapies in health and aesthetic medicine.

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