Natural products in telomere protection: potential in the prevention of ageing and longevity

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The review project titled "Natural products in telomere protection: potential in the prevention of ageing and longevity" submitted by Mahima Fariha Sharita (20146081), of Spring 2026 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.).

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Ethics Statement

This study did not conduct any animal study.

Abstract

A fundamental biological phenomenon is aging and the hallmarks for this are ceullular degradation, unexpected genetics, persistent chronic health condition. An enzyme called telomerase is responsible for creating the particular DNA sequence found at telomeres, or the terminal DNA at the ends of every chromosome. Chromosome ends are shielded from being identified as damaged DNA by telomeres, which are crucial genetic components. During fetal development, telomerase is activated, preventing telomeres from being significantly lost during this time of tremendous cell expansion. In order to support healthy ageing, the main goal of this thesis is to investigate the function of telomere biology in connection to the ageing process as well as the effects of naturally occurring bioactive compounds on the ageing process. Additionally, this thesis seeks to investigate the underlying molecular mechanisms of telomere shortening and their connections to oxidative stress, inflammation, mitochondrial damage, and defective DNA repair, all of which are crucial factors in the decline of physiological functions with ageing. In a translational manner there is an establishment of connection between the importance of natural object with the telomere bindings property along with the experimental data. It emphasizes the importance of dosage, effectiveness, reliability of translational relevance but points out that clinical trials, which need to be planned carefully, are required to demonstrate their role in extending lives and preventing age-associated diseases.

Keywords: Telomere, telomerase, oxidative stress, aging, natural products.

Dedication

It is my pleasure to dedicate this work to my research supervisor whose guidance and uncompromising support has formed a major pillar of this process; and to my beloved parents, as an expression of the limitless love, sacrifices, and their prayers; to Almighty Allah, who has blessed me with strength and patience, and wisdom; and lastly, to myself for bearing it all and struggling till this came to pass.

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List of Acronyms

CMV	Cytomegalovirus
AIDS	Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic acid
HIV	Human Immunodeficiency Virus
ECM	Extracellular Matrix
TA	Telomerase Activator

Chapter 1

Introduction

1.1 Background Overview

The goal of using dietary supplements is to maintain mental, physical, and emotional well-being and vitality into old life. Measures to maintain health may be a better way to extend our healthy life duration, even while medications and surgical procedures that target diseases of the elderly would presumably stop or partially cure tissue damage caused by ageing and chronic stress. Combinations of vitamins, antioxidants, and other ingredients are found in the majority of dietary supplement programs; some of these have been demonstrated in controlled clinical trials to have major health benefits, while others may have negative effects, highlighting the necessity of evaluating the functional effects of combination products.

The particular DNA sequence at telomeres, or the terminal DNA at the ends of every chromosome, is created by the enzyme telomerase. The vital genetic components known as telomeres are in charge of preventing chromosome ends from being identified as "broken DNA." Telomeres will progressively shorten with time and cell division unless there is enough telomerase activity to maintain telomere length because telomeric DNA cannot be completely replicated by conventional DNA polymerases and because telomeres undergo degradative processing and are a "hotspot" for oxidative damage.

During foetal development, telomerase is activated, preventing telomeres from being significantly lost during this time of rapid cell growth. However, telomerase is repressed before to birth in the majority of somatic tissues, and hence, telomere degradation in most tissues starts at birth and continues throughout life. Because they promote telomerase during the early stages of progenitor expansion, tissues with constant cell turnover or times of fast proliferation are referred to as "telomerase competent." During tissue regeneration, all adult stem cells within the body seem to be able to activate telomerase. Nevertheless, a diminished capacity to activate

telomerase with ageing and stress exacerbates the fact that these activation times are insufficient to stop telomere degradation.

Humans lose telomeric genetic material at a relatively slow rate of 15–60 BP annually in cross-sectional studies. This is probably due to the quiescent condition of cells in other organs and the tiny amount of stem cells that continue to divide in proliferative tissues relative to the total stem cell reserve. Shortening of has been studied in animal instances of telomerase insufficiency, human genetic illnesses involving telomerase mutations, and human cells in culture. According to these findings, telomere shortening, cell ageing, decreased repair of tissue, and loss of tissue form and function are all causally related. Human immunodeficiency virus (HIV) and cytomegalovirus (CMV) are examples of chronic viral infections that hasten telomere loss and early immune system ageing, particularly the infection-specific cytotoxic T cells that destroy infected cells. Along with telomere loss, these cells frequently do not express the complementary receptor CD28 and exhibit decreased proliferative capability, decreased secretion of antiviral chemokines and cytokines, increased susceptibility to apoptosis, and impaired lysing of infected cells. According to circulating CMV-specific antibodies, about 50% of Americans are infected with CMV. However, after a 30% seropositivity rate by age 10, there is a 1% annual seroconversion rate throughout life, which results in a 90% seropositivity by the ninth decade. Here, it is provided preliminary results from a dietary supplement regimen that contains TA-65®, a refined small-molecule telomerase activator made from a plant extract commonly employed in traditional Chinese medicine. Human epidermal keratinocytes and immune cells in cell culture have been the subject of telomerase activation and functional investigations on a related chemical (TAT2) from the same plant. greater replicative capacity, enhanced cytokine and chemokine responses to antigens, and greater death of autologous HIV-infected CD4+ cells were among the effects of TAT2 in tissue culture studies using CD8+ T cells from HIV/acquired immunodeficiency syndrome (AIDS) individuals.

1.2 Importance of Telomere Preservation in Aging

The enzyme telomerase, which is essential for tumor cells' lifespan, has lately come to light as a potential target for cancer therapy. While telomerase activity is absent in most normal cells, it has been detected in 80–85% of tumor cell lines in almost every kind of malignancy. Twenty years ago, it was identified as a viable target for cancer treatment. Since then, a great deal of research has been conducted in this area, and the field is still expanding quickly. In contrast to conventional anti-cancer drugs that interact with targets like tubulin and topoisomerases I and II, telomere maintenance is a fresh and interesting approach that is expected to have wide anti-cancer effectiveness along with reduced unwanted effects. Although some promising compounds are presently undergoing clinical studies, there are currently no medications on the market that target telomeres or telomerase (e.g. GRN163L).

The DNA-protein complexes known as telomeres, which cover the ends of human chromosomes, are crucial for maintaining chromosomal integrity. These structures are made up of a non-coding DNA overhang that allows genetic material to be lost after several DNA replications. DNA polymerase's incapacity to completely replicate all the material up to the end of duplex DNA is the cause of this telomere length reduction. Because of this "end-replication problem," normal somatic cells can only replicate a limited number of times before their telomeres drastically shorten and they stop dividing. The enzyme telomerase helps cancer cells avoid this replicative catastrophe and attain cell immortality by maintaining telomere length. Given that telomerase activity is present in all forms of cancer and that most normal cells do not produce it, selective telomerase inhibitors may be reasonably safe, broad-spectrum anti-cancer drugs. Age-related phenotypes, which include involutive processes like tissue degeneration, telomers shortening, dementia and cognitive deficiencies, functional impairments, and chronic diseases, are the result of aging, which is a normal and evolutionarily planned phenomenon. As a result, aging is a degenerative process that has been extensively

studied recently and for which a number of theories regarding its programmed or non-programmed nature have been developed.

Telomere destruction, mitochondrial and epigenetic malfunction, and overall damage to DNA are the main markers of aging. Importantly, stress can hasten this process, which results in damage accumulation and ultimately mitotic crisis or the death of cells. Ionizing radiation, radiomimetic medications, reactive oxygen species, metabolic mistakes during transcription and replication, and inadequate DNA repair are only a few of the many substances that can cause DNA damage. While some of those causes can be eliminated to slow down aging and premature death, others are just a byproduct of cells' metabolic activity and cannot be removed.

Characterization of skin aging has identified the main functions of changes in fibroblast metabolism. Fibroblasts stick to the intact extracellular matrix (ECM), that is mostly made up of type I collagen, in young skin. Fibroblast size loss, diminished elongation, and collapsed shape are the results of fibroblast attachment being compromised by increasing ECM degradation in old skin. Its regenerative potential is also markedly diminished at the same time, which hinders skin regeneration and accelerates aging. Reduced dermal fibroblast cell size and spreading can also lead to an increase in mitochondrial ROS production, which triggers senescence.

1.3 Role of Natural Products in Telomere Care

The synthesis presented here is framed by three mechanisms that are common to all the compound classes covered in this review: enhancing mitochondrial bioenergetics and redox homeostasis through pathways like SIRT1 or SIRT3 and AMPK; suppressing pro-inflammatory signaling, including NF-κB and related cytokine cascades; and supporting telomere integrity and telomerase regulation. Subsections concentrate on the subtleties unique to a compound. Together, these processes reduce oxidative damage, enhance mitochondrial

efficiency, and alter the inflammatory environment, all of which are common characteristics of natural compound classes.

TA-65® is a >95% pure single chemical entity that was separated from an unique extraction of the dried root of Astragalus membrane and compressed into 5–10 mg capsules with inert excipients. It is only licensed to TA Sciences from Geron Corporation. Based on existing extract usage, starting doses of 5–10 mg/day were deemed safe. After using the product for a few months, some participants upped their dosage to 25–50 mg daily. Each subject's cumulative dose throughout the course of the year was noted and used for an initial dose-response analysis.

Blood samples were taken at baseline and every visit, and they were sent to analytical labs that same day at room temperature. Quest Diagnostics or Bio-Reference Laboratory performed assays for standard blood counts, blood chemical composition, specific immunological subsets, CMV anti-body titer, and inflammatory indicators. UCLA Clinical Laboratories and Pathology Services performed specialized immune subset analyses.

Ageing and disease result from these genetic components shortening over time and under stress since most human cells lack enough telomerase to maintain their telomeres. The PattonProtocol-1 commercial maintenance of health program was launched in January 2007 and included the natural product-derived telomerase activator (TA-65®, 10–50 mg daily), an entire nutritional container, doctor counseling, and laboratory testing at baseline and every three to six months thereafter. Here, we offer a study of the first year's immune system-related data. Low nanomolar concentrations of TA-65® weakly activated telomerase in human keratinocytes, fibroblasts, and immune cells in culture; similar plasma levels of TA-65® were obtained in pilot human pharmacokinetic studies utilizing single 10- to 50-mg doses.

People who tested positive for the cytomegalovirus (CMV) showed the greatest number of these reductions. In a subset of participants, the distribution of telomere lengths in leukocytes at baseline and over a year was determined. The mean telomere length did not increase, but the

percentage of short (<4 kbp) telomeres dramatically dropped (p = 0.037). Negative results did not correlate with PattonProtocol-1. I infer that the approach remodels the relative amount of circulating leukocytes of CMV+ participants towards the more youthful appearance of CMV subjects and lengthens critically short telomeres. Human TA-65®-specific effects will be evaluated through controlled randomized trials. The telomere repeat amplification procedure (TRAP) assay was used to evaluate telomerase activity in human newborn keratinocytes (Cascade Biologics, Portland, OR) and MRC5 fetal human fibroblasts (ATCC# CCL-171) both before and after treatment in culture with TA-65®, largely as previously described.39, In summary, telomerase activity was assessed in actively developing cells that were treated with TA-65® in the vehicle (dimethylsulfoxide [DMSO] at 1% vol/vol [keratinocyte culture] or 0.5% [fibroblasts]) for 24–48 hours as opposed to the vehicle alone. Usually, measurements were taken at either 30–40 population doublings (PD) for fibroblasts or 5–10 PD for keratinocytes. Electrophoresis on nondenaturing polyacrylamide gels was used to separate the telomerase reaction products, and Phosphor screens and PhosphoImager SL (Molecular Dynamics) imaging were used to quantify the results. FlowFISH was used at Repeat Diagnostics (Vancouver, Canada) to measure the median telomere length in granulocytes and peripheral lymphocytes, essentially as previously reported. In Dr. Richard Cawthon's lab at the University of Utah in Salt Lake City, UT, mean telomere length was measured using qPCR. At CNIO, Madrid, high-throughput quantitative fluorescence in situ hybridization was used to measure the intranuclear and internuclear telomere length distributions.

Telomere length and stability are impacted by naturally occurring substances' direct and indirect effects on telomerase activity. The majority of them exhibit antioxidant qualities that indirectly shield telomeres from the damaging effects of ROS through reduced hydrogen peroxide, induced SOD activity (steroidal glycoside or PUFA), and effects on other free radical levels (polysaccharide from Cistanche deserticola). Some of them influence the expression of telomerase by either raising (ginsenoside Rg1) or lowering (epigallocatechin gallate) hTERT.

The fact that the drugs' final effects are dose-dependent is notable.

Genistein is a prime illustration of this action; at high doses, it inhibits telomerase activity, whereas at low concentrations, it increases it. It should be mentioned that goods from various groups and with multidirectional effects are part of a properly balanced diet. Because the Mediterranean diet reduces oxidative stress, it has been shown to be one of the healthiest diets in the world. The two primary antioxidants found in the Mediterranean diet are resveratrol and omega-3. Studies conducted by the Nurses' Health Study have demonstrated that the Mediterranean diet is efficient in maintaining telomere length and increasing telomerase activity in peripheral blood mononuclear cells. Though some data indicate that resveratrol can both boost hTERT expression in the human keratinocyte cell line and limit the proliferation of regular human keratinocytes in vitro, nothing is known about its effects on normal skin cells.

1.4 Thesis Objectives

The foremost objective of this thesis is to explore the role of telomere biology in relation to the aging process, as well as the impact of natural bioactive molecules on the aging process in order to promote healthy aging. Moreover, this thesis aims to explore the underlying molecular mechanisms of telomere shortening and their links with oxidative stress, inflammation, mitochondrial damage, and defective DNA repair, which play pivotal roles in the deterioration of physiological functions with aging. By merging information gathered from molecular studies, cellular as well as animal studies, this thesis focuses on explaining the mechanisms underlying these processes in relation to aging as well as the development of age-related disorders.

Chapter 2

Methodology

The review project is based on a literature review of the extensively written narrative review that is expected to conduct a methodical study of the relationship between aging and telomere biology and the potential protective role played by naturally occurring bioactive compounds in facilitating longevity and telomere repair. The methodological framework was developed to ensure scientific rigor, openness, and rational integration of multidisciplinary evidence consisting of molecular biology, cellular studies, animal experiment, and clinical and observational studies in human beings. The primary objective of this methodology was to find, evaluate, and combine the available scientific evidence on the role of telomere shortening, biological markers of aging, and the capacity of natural substances to manipulate telomerase activity, oxidative stress, inflammation, mitochondrial activity, and DNA repair mechanisms. In order to attain this objective, a systematic search of the scientific literature was conducted using major electronic databases such as PubMed, MEDLINE, ScienceDirect, Nature, and Google Scholar.

These databases were selected to ensure that users could be able to access high impact, peer-reviewed, and scientifically sound sources. Articles that passed the initial inclusion criteria were reviewed in their entirety having been initially filtered on the basis of title and abstract relevance. Review papers and peer-reviewed original research articles that were written in excellent English language were considered to be included. Articles that examined the biological action of natural compounds on telomere length, telomerase activity, genomic stability, oxidative damage, inflammatory signaling pathway, or mitochondrial homeostasis were selected, as well as articles that tested telomere biology in relation to aging or age-related disorders. In order to provide a comprehensive picture, the research that includes human populations, in vivo animal models, in vitro cellular systems such as observational cohorts and

clinical trials were considered.

To maintain methodological coherence and scientific validity, conference abstracts, opinion-based articles, and publications without full text accessibility were disqualified. Only complete studies were included for data extraction, and institutional access was used whenever possible to obtain complete articles in situations where full texts were not directly available. Since this review project is based solely on previously published scientific data, ethical approval was not necessary because the author did not conduct any direct experiments with human subjects or animal models. However, as indicated in their individual publications, it was assumed that all included studies had complied with the relevant institutional and international ethical standards. The thesis wants to offer a logical, mechanistically based, and translationally relevant summary of the state of knowledge about natural products and their possible contributions to longevity promotion, telomere protection, and healthy aging through this methodologically organized framework.

Chapter 3

Telomeres and Aging

3.1 Telomere Definition and Composition

Without a mechanism to lengthen them, continually shortened telomeres limit the ability of cells to proliferate, which contributes to the aging process in organisms. However, in order to preserve their ability to divide, cells with limitless proliferation potential, including cancer and stem cells, must initiate a telomere lengthening process. Cells can preserve telomere length through several pathways: reactivation of telomerase, engagement of recombination-based mechanisms termed alternative lengthening of telomeres (ALT), or more recently described processes such as intercellular telomere transfer in immune interactions. Most malignant cells (estimated 85–95%) rely on telomerase reactivation to sustain unlimited division, whereas a smaller fraction (5– 15%) maintains telomeres through ALT-mediated recombination. Hence, the development of therapeutic strategies targeting telomere maintenance, such as telomerase inhibitors, is of great importance. The third mechanism has recently been discovered. When an antigen-presenting cell interacts with a T-lymphocyte, it degrades the shelterin complex. It severs the telomeres with the help of the telomeric zinc-finger associated protein (TZAP) factor. The telomeres, along with Rad51, which is crucial for recombination, are then packaged into vesicles and transferred to the T-lymphocyte via the immunological synapse. In comparison, unhealthy behaviors are associated with shorter telomeres and accelerated aging. Importantly, there is a direct connection between telomere status and the activation of immune antiviral defenses. Telomere shortening does, therefore, not only reflect the proliferative status of the cell, but constitutes a part of a complex mechanism that plays a crucial role in determining overall health, with its significance increasing with age.

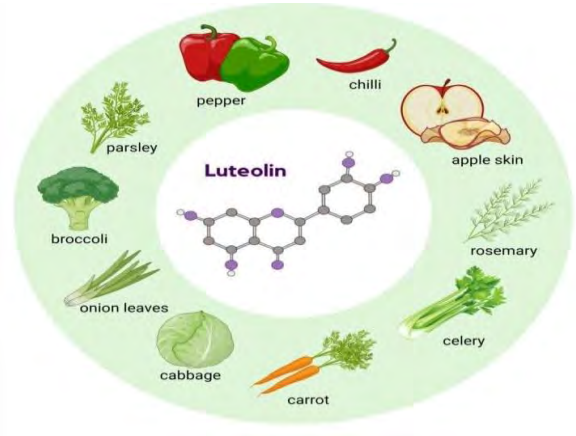

Figure 1. Chemical structure of luteolin. Created in BioRender. (Kulbacka, 2025)

Most of the telomerase inhibitors that are currently recognized come from plants. For ages, traditional Chinese or ayurvedic medicine has utilized many of these substances, including berberine and gambogic acid. Others, such flavonoids from a range of fruits and vegetables, allicin from garlic, and epigallocatechin gallate from green tea, are derived from well-known foods that many people consume on a daily basis. These plant-derived telomerase inhibitors include terpenoids, alkaloids, xanthones, sesquiterpene lactones, and different polyphenols, among other chemical structures. Although some plant metabolites have anti-telomerase activity, it's crucial to remember that several of these substances are also known to interact with a variety of other biological targets. As a result, mechanisms other than their anti-telomerase activity may be responsible for their cytotoxic effect.

3.2 Telomere Shortening and Aging Dynamics:

Telomere attrition was identified as one of the main indicators of ageing in 2013 (López-Otín et al., 2013), and its study has received more attention lately. But the concept of telomeres first surfaced in the 1930s when Creighton and McClintock investigated Zea mays and postulated the existence of a unique structure at telomere that was essential for avoiding chromosomal end fusion (Creighton and McClintock, 1931). As a result, telomeres gradually shorten with each

cell division cycle (Allsopp et al., 1992; Rhodes et al., 2002). Critical telomere shortening results in genomic instability, which prevents additional replication and ultimately causes cell death (Blackburn, 2001). The "end-replication problem" is the inability of DNA polymerase to fully replicate the 3′ ends of the chromosome, but it requires a temporary primer to initiate unidirectional replication from the 5′ to the 3′ end (Levy et al., 1992).

The discovery of telomerase by Greider and Blackburn in 1985 marked a turning point in telomere research since some mechanisms are needed to get around this end-replication issue. By adding DNA sequence repeats at the end of chromosomes, the ribonucleoprotein enzyme telomerase facilitates the expansion of telomere (Greider and Blackburn, 1985). Lee et al. demonstrated that in subsequent mice generation, tissues revealed decreased proliferative capability in the spleen and bone marrow as well as poor spermatogenesis.

3.3 Correlation Between Telomere Length and Age-Linked Ailments:

Scientific studies also indicate that higher blood levels of alpha-carotene, beta- carotene, and beta-cryptoxanthin are associated with telomere lengths up to 5–8% longer. Interestingly, in individuals who are overweight or obese, an increase in beta-carotene levels is also correlated with an increase in telomere length. We can therefore infer that higher carotenoid intake is associated with longer telomere length.

Telomere shortening is a hallmark of cellular aging and a common feature of age-related diseases. It can be stated that shorter telomere length triggers a mechanism that drives replicative aging by limiting the mitotic potential of cells. Several hundred nucleotide repeats at the end of each chromosome are required to prevent the activation of DNA repair pathways. Therefore, we should consume foods that ensure a high level of carotenoids in order to help prevent age- related diseases. A high dietary intake of zeaxanthin and lutein is likely to offer protection against age-related conditions, such as age-related macular degeneration.

Altered telomere length disrupts chromosomal integrity and has been implicated in

carcinogenesis. Both very short and abnormally long telomeres can promote tumorigenesis, depending on context. In fact, telomere abnormalities have been reported in the vast majority of early epithelial cancers, with shortening as the most common alteration. Diet is a major modifiable lifestyle factor that may contribute to the regulation of cancer risk by as much as 40%. Data suggest that several carotenoids may prove beneficial in reducing carcinogenesis. There is evidence that various carotenoids, such as β-carotene, α-carotene, lycopene, lutein, zeaxanthin, β-cryptoxanthin, fucoxanthin, canthaxanthin, and astaxanthin, exhibit anticancer properties in certain tissues. There are indications that carotenoids, in combination with other antioxidants, could potentially be used as a preventive measure against cancer . However, this topic requires further investigation, as there are reports of interactions between β-carotene and substances such as cigarette smoke and alcohol, which may lead to effects that differ from the intended therapeutic outcomes. It has been demonstrated that carotenoids exhibit pro-oxidant activity in cancer cells and antioxidant activity in healthy cells, which presents significant potential for their application, considering the critical role of oxidative stress in carcinogenesis. Carotenoids are undoubtedly promising compounds in the context of cancer prevention; however, their application still requires further research.

Carotenoids such as β-carotene and lutein have been associated with longer telomere length in buccal cells and peripheral leukocytes. The mechanisms are mostly ascribed to the modulation of redox-sensitive transcription factors that control the expression of telomerase and the antioxidant protection of telomeric DNA. Tissue-level evidence supports roles in retinal protection, cardiovascular function, and cognitive preservation, despite the lack of binding affinity data for telomerase . Carotenoids have been shown to have health benefits, but a number of issues limit their practical use. Because of their lipophilic nature, reliance on dietary fat for absorption, and inter-individual metabolic variability, poor bioavailability is still a major concern. What’s important is that clinical results vary, with some research showing no discernible impact on disease biomarkers or oxidative stress. Furthermore, high-dose

supplementation, especially in synthetic forms, has been linked to possible negative effects, such as a higher risk of some types of cancer in smokers. Differences in carotenoid type, dosage, source, and study design make comparisons even more difficult and prevent the development of standardized recommendations.

Proteins and peptides affect cell cycle regulation and particular age-related signaling pathways in addition to the well-known anti-oxidative and mitochondrial- supportive mechanisms. Recent studies emphasize the roles of mitochondrial-derived peptides and regulatory proteins such as p53 and p21 in maintaining homeostasis and delaying age-associated decline (Fig. 2).

Chapter 4

Mechanisms of Telomere Protection

4.1 Enzymatic Strategies for Telomere Maintenance

Telomere function is central to the ability of cells to maintain genomic integrity, which is mediated by the activities of a distinct group of enzymes that are responsible for the regulation of telomeres. Since the shortening of telomeres occurs with each division of the cell due to the replication problem or due to oxidative damage, the process of shortening is mitigated in cells by enzymatic mechanisms. The main enzyme catalyzing telomere extension is telomerase, an RNP enzyme composed of the catalytic subunit telomerase reverse transcriptase (TERT) and an RNP template protein called TERC. The mechanism of telomerase involves adding repeated nucleotide patterns to the ends of chromosomes, thereby offsetting losses incurred during DNA replication. In germline cells, stem cells, and immune cells,telomerase activity is carefully regulated to ensure that the length of chromosomes is maintained for sustained cellular division. Indeed, in most other cells, telomerase expression is minimal or absent; hence, gradual shortening of chromosomes and replicative cellular senescence occur, resulting in cellular and subsequently tissue aging.

In addition to telomerase, the functional integrity of the telomere is maintained by a complex of specialized proteins termed the ‘shelterin complex’, which consists of the proteins TRF1, TRF2, POT1, TIN2, TPP1, and RAP1. These proteins do not add to the telomere but play a crucial enzymatic function in ensuring that the ends of the chromosomes are protected from the cellular DNA damage response. The shelterin proteins modulate telomerase binding to telomeres, suppression of inappropriate DNA repair at the telomere, and the conformational structure of the telomere DNA. Other enzymes such as DNA-dependent protein kinases and exonucleases engage with the shelterin proteins.

Another crucial biological process involved in telomere length upkeep is the alternative lengthening of telomeres (ALT) mechanism, which is an alternative to the action of telomerase.

These enzymatic approaches to maintaining telomere integrity provide important building blocks towards developing complementary approaches to promote telomere homeostasis.

4.2 Non-Enzymatic Mechanisms for Telomere Safeguarding:

Although the role of enzyme systems, including telomerase and DNA repair enzymes, is critical in maintaining the integrity of the telomeres, the integrity of the telomeres is also critically impacted by several other non-enzyme mechanisms that play a crucial role in regulating the cellular context in which the stability of the ends of chromosomes is established. These mechanisms function by modifying the levels of oxidation, an inflammatory response, and metabolism of the cell.

Among the critical non-enzymatic pathways for protecting the cell is redox homeostasis. Telomeric DNA is highly enriched in guanines, the bases of which are highly susceptible to damage triggered by ROS exposure. An imbalance of ROS due to mitochondrial damage, stress, and various environmental factors leads to direct telomeric damage and further results in telomere shortening. Non-enzymatic antioxidants like vitamin C, vitamin E, carotenoids, flavonoids, and polyphenols have been shown to limit the impact of ROS and, in the process, protect telomeres against early shortening. They ensure the maintenance of redox homeostasis and establish a cellular context favorable to telomere longevity and resistance to stress-induced degradation.

A further important epidemiologic component is the presence of low-grade chronic inflammation, which is sometimes called “inflammaging.” “Chronically elevated levels of inflammatory signals lead to increased oxidative stress and cellular turnover, both of which accelerate telomere breakdown.” Cytokines like TNF-alpha, IL-6, and CRP induce stress responses and “DNA and telomere damaging mechanisms” to occur. What can be done to reduce the impact of inflammation on the cell, and therefore decrease telomere breakdown? “Dietary bioactive compounds like omega-3 fatty acids and plant polyphenols,” which are

postbiotics. The maintenance of mitochondria is a non-enzymatic contributor to telomere protection. Mitochondria are a significant source of intracellular ROS, but dysfunctional mitochondria hyperproduce oxidative stress, resulting in telomere deterioration. With mitochondrial efficiency protected by a healthy supply of nutrients, energy maintenance, and the use of antioxidants, intracellular ROS is decreased, which is an indirect form of telomere protection. This is a kind of feedback mechanism because healthy telomeres help maintain mitochondrial efficiency.

In addition to that, epigenetics and chromatin structure also ensure the stability of telomeres. Telomeres are packaged within a unique type of chromatin, which determines the accessibility and vulnerability of telomeres to degradation. Non-enzymatic factors such as nutritional and stress levels, and exposure to the external environment, can affect epigenetics at the DNA methylation levels of the histones around the telomere regions. An ideal chromatin structure prevents the telomeres from deteriorating and entering inappropriate DNA damage responses. When the lifestyle is not healthy or the individual experiences chronic stress, it leads to increased levels of cortisol. These combined mechanisms help provide the biological milieu under which telomeres operate. They help reduce the impact of oxidative damage, inflammatory responses, the activities of the mitochondria, the organization of chromatin, and lifestyle-related stresses in promoting the maintenance of telomere health and arresting the clock of biological aging.

4.3. Natural Products' Role in Augmenting Telomere Stability:

Natural products have shown great potential as biological modulators of telomere function since they can exert effects on most of the cellular mechanisms that contribute to the rate of telomere shortening and degradation as an individual ages. Instead of targeting a specific pathway, natural products in the form of bioactive compounds sourced from plants, bacteria, and other natural materials have been shown to use mechanisms that promote telomere

maintenance through mechanisms such as the reduction of oxidative stress and suppression of inflammation.

One of the significant mechanisms whereby natural products work in protecting telomeres is by virtue of their underlying antioxidant properties. The telomeric DNA is very vulnerable to oxidative damage that invariably contributes to telomere shortening. Flavonoids, carotenoids, polyphenols, and vitamins in fruits, vegetables, and herbs work to reduce oxidative damage to chromosomes by scavenging ROS. This helps to reduce the rate of telomere shortening. Besides, natural products also play a role in telomere support as anti-inflammatory agents. Chronic-low-grade inflammation contributes to elevated cellular turn-over, as well as a higher level of DNA damage, which are mediators for telomere shortening. Curcumin, resveratrol, omega-3 fatty acids, as well as postbiotics, are bioactive molecules that inhibit pro-inflammatory mediators, thus providing an anti-inflammatory condition that diminishes stress on dividing cells, including telomeres. The other mechanism is support for mitochondria function. In fact, mitochondria are large producers of free radicals; in other words, their dysfunction causes increased oxidative stress and damage to telomeres. Natural compounds like carotenoids, polyphenols, and peptides improve the efficiency of mitochondria so that lower amounts of damaging free radicals are produced, thereby indirectly protecting the DNA of telomeres. Some natural agents also affect the activity of telomerase or proteins related to telomeres. Some natural agents have been found in experimental systems to induce an overexpression of telomerase or stabilize the proteins binding to the telomere, hence promoting the maintenance of telomeres. Even if these phenomena have to be precisely controlled in order not to induce an unwanted cell proliferation, they show the interest of natural agents in the systems controlling the telomeres.

In addition to that, the role of natural polysaccharides and postbiotics is to maintain the stability of telomeres through the improvement of the balance of the gut microbiota, which ultimately results in the reduction of systemic inflammation and oxidative stress. This makes the overall

environment optimal for the maintenance of telomeres and tissue regeneration. In sum, natural products are multi-target modulators of telomere stability. Through mechanisms of reduced oxidative stress, improved mitochondrial function, and promotion of telomere-related biological pathways, they provide biologically compatible strategy to target cellular aging.

Chapter 5

Natural Substances with Prolonging and Anti-Aging Telomere Factors

5.1 Overview of Natural Compounds and Their Origins

Angelica sinensis

Angelica sinensis (ASP), a major bioactive component of dong quai, has been reported to exert antioxidant, immunomodulatory, and neuroprotective effects. Marine-derived fucoidan and Polygala tenuifolia polysaccharide blunt telomerase (hTERT) signaling, down-regulate oncogenic drivers (c-Myc, Sp1) and PI3K/Akt activity, thereby enforcing cell-cycle arrest and senescence in rapidly dividing cells. The fungal β-glucan from *Tremella fuciformis* shields dermal fibroblasts by scavenging ROS and activating the SIRT1 stress-response pathway. Angelica sinensis polysaccharide protects haematopoietic, neural, and endocrine tissues by limiting oxidative DNA damage, maintaining testosterone levels, and preserving telomere length and telomerase competence following radiation or D-galactose challenge.

1. **Polysaccharides in the modulation of telomerase activity**

Fucoidan, a polysaccharide from brown algae, has been shown to suppress telomerase by downregulating hTERT and transcription factors such as c-myc and Sp1. The results indicated that fucoidan induces apoptosis and inhibits telomerase in a ROS-dependent manner through inactivation of the PI3K/Akt pathway. In contrast, another polysaccharide, PTP isolated from the roots of Polygala tenuifolia, leads to a decrease in telomerase activity in cancer cells, which may contribute to a reduction in their proliferative potential and ability to grow uncontrollably. X-ray was also found to significantly increase the number of cells in the G1 phase of the cell cycle, increase aging-associated β- galactosidase (SA-beta-Gal) levels and p53 protein expression, while shortening telomere length and decreasing telomerase activity. ASP administration during radiation exposure resulted in the inhibition of these changes, reducing

the number of cells in the G1 phase, decreasing p53 expression, and the number of SA- beta-Gal-positive cells, as well as lengthening telomeres and increasing telomerase activity. This suggests that ASP may have a protective effect on HSCs by delaying the aging process, which may be due to its effects on telomere stability and the regulation of molecular mechanisms related to the cell cycle and apoptosis. Thus, ASP may represent a promising means to protect stem cells and potentially slow down the body's aging process .

Fucoidan is one of the polysaccharides that directly suppresses hTERT expression and inhibits telomerase by suppressing the PI3K/Akt pathway. On the other hand, polysaccharides from Angelica sinensis have been demonstrated to increase telomerase activity and maintain telomere length in hematopoietic stem cell. Neuroprotection, testicular preservation, and bone marrow function support are examples of tissue-specific effects. The lack of binding site mapping at this time indicates a knowledge gap. The majority of evidence supporting polysaccharides' broad pharmacological potential comes from in vitro tests or animal models, which restricts the direct application of these findings in clinical settings, despite multiple studies confirming this. Their intricate molecular makeup and source-dependent composition make standardization extremely difficult, which in turn makes it difficult to compare study findings. Only a small amount of the underlying molecular mechanisms are known, especially those pertaining to telomerase modulation and effects on cellular senescence. The lack of extensive clinical trials confirming these compounds' long-term safety and effectiveness is another major disadvantage.

Essential Oils components

The International Organization for Standardization (ISO) defines an essential oil as a product manufactured by either water or vapor distillation, by mechanical processing of citrus rinds, or by dry distillation, which are commonly used in cosmetic products. Specific constituents such as linalool, β-caryophyllene, and limonene have been shown in experimental models to exert anticancer, antimicrobial, antioxidant, anti- inflammatory, or neuroprotective effects, though

the strength of evidence varies depending on compound and study design. Due to anti-inflammatory properties relevant to various inflammatory conditions such as respiratory inflammation, atopic dermatitis, and arthritis, specific compounds have shown potential in alleviating symptoms and targeting disease-specific pathways, suggesting their therapeutic potential.

Diterpenes and other components of essential oils work through compound-specific mechanisms in addition to the general antioxidant effects that have already been discussed. Diterpenes raise the amounts of endogenous antioxidant enzymes and prevent the synthesis of pro- inflammatory mediators. Diterpenes are used in skin care products to postpone aging [240] and have been shown to have neuroprotective properties. Some of the triterpenoids, isolated from the dried fruiting bodies of *Ganoderma lucidum*, had Brain- Derived Neurotrophic Factor-like neuronal-survival- promoting activities. Some monoterpenoids show beneficial effects on the cardiovascular system. Hemiterpenoids exhibit, among other activities, hepatoprotective effects. Carotenoids, which are also triterpenoids and have already been discussed in this article, exhibit several significant protective effects on human health, such as the induction of apoptosis, anti-aging, anti-atherosclerosis, anti-inflammatory, and anti-cancer properties, as well as the inhibition of the growth of malignant tumors.

Several essential oil compounds exhibit antioxidant activity. For instance, chamazulene from *Matricaria chamomilla* reduced ROS in endothelial cells, while terpenoids such as α-pinene, limonene, and linalool demonstrated radical scavenging effects, with α-pinene showing particularly strong activity. Limonene, the main component of *C. sinensis* essential oil, exhibits moderate antioxidant and significant anti-inflammatory effects by scavenging free radicals and inhibiting pro-inflammatory responses in cells. Additionally, limonene and the essential oil show selective anticancer potential. It also exhibits promising antityrosinase and antielastase properties, suggesting benefits for skin health by potentially reducing hyperpigmentation.

Coriander essential oil demonstrates neuroprotective benefits by exhibiting *in vitro* antioxidant activity through scavenging hydrogen peroxide and reducing SOD activity. This could potentially prevent DNA cleavage induced by amyloid-beta oligomers. Lavender essential oil also shows neuroprotective effects against amyloid beta-induced neurotoxicity. It reduces the activation of caspase-3 and the production of intracellular ROS. Linalool is a major component of both coriander and lavender essential oils. It has been shown that linalool can counteract mitochondrial dysfunction, reducing ROS levels. It has also been proven that, possibly through interaction with NMDA receptors and modulation of calcium homeostasis, linalool can inhibit caspase-3 activation. Linalool prevents oxidative stress, inflammation, and photoaging in adult human dermal fibroblast cells. Linalool is a viable therapeutic option for the management of inflammatory disorders since it reduces inflammation both in vivo and in vitro.

β-Caryophyllene (BCP), a major sesquiterpene, has been reported to reduce neuroinflammation in models of Parkinson's and Alzheimer's disease by inhibiting inflammatory mediators and microglial activation. In PD models, BCP has shown neuroprotective effects. It reduces oxidative stress, restores mitochondrial function, and protects dopaminergic neurons. In the case of another age-related disease- osteoporosis, BCP also promotes bone formation by stimulating osteoblast differentiation and inhibiting bone resorption by suppressing osteoclastogenesis. BCP's ability to combat oxidative stress and inflammation, key drivers of aging and various diseases, suggests a potential role in promoting healthier aging. Among other essential oil components, myrcene, alpha-bisabolol, α-pinene, and β-cyclocitral are worth mentioning. It has been reported that myrcene may protect against UVB-induced skin photo-aging by acting as an effective antioxidant, decreasing ROS and MMP production, reducing IL-6, and increasing TGF-1 and procollagen secretion in UVB- irradiated skin cells. Myrcene also exhibits anti- inflammatory activity. Alpha-bisabolol combats aging and degenerative diseases through its potent antioxidant and anti-inflammatory actions, which protect the nervous and cardiovascular systems. In NDs like PD and AD, alpha-bisabolol demonstrates neuroprotective

effects by reducing oxidative stress, inhibiting neuroinflammation, preventing neuronal degradation, and interfering with amyloid-beta aggregation and acetylcholinesterase activity. α-pinene, on the other hand, demonstrates anti-inflammatory effects by attenuating inflammatory marker expression in myocardial infarction, reducing neuroinflammation in ischemic stroke, and inhibiting inflammatory pathways in macrophages. Furthermore, α-pinene exhibits antioxidant properties by restoring antioxidant enzyme activity, reducing lipid peroxidation in ischemic brains, and preventing UVA-induced lipid peroxidation in skin. This telomere protection and the anti- inflammatory activities of monoterpenes such as thymol and p-cymene suggest that dietary TEO supplementation can promote healthy aging. The possible impacts of TEO on telomere attrition and age-related brain inflammation were investigated in a study by Warman et al. In the hippocampus and cerebellum of chronologically aged male mice, TEO, which has been shown to be effective against neuroinflammation in previous studies, has also shown a significant effect. Previous research has shown that, due to genetic variables, the rate of decreasing telomere length may change not only between animals but also between individuals.

It has been reported that some components of essential oils, like β-cyclocitral, activate telomerase and lengthen telomeres in mammalian cells. Autophagy-enhancing and antioxidant pathways may be involved in this effect. Neuroprotection in Parkinson's and Alzheimer's disease models, bone preservation through β- caryophyllene, and skin photoprotection through linalool and myrcene are examples of tissue-specific evidence. But there is currently no data on direct binding to telomerase. Although several essential oil components show anti-aging potential and some have been studied in relation to telomere maintenance, most act indirectly by reducing oxidative stress. For many compounds, the precise mechanisms remain unclear, effects may vary between individuals, and effective concentrations or dosages have not been well established.

Bioactive postbiotics

Postbiotics have been defined by the International Scientific Association of Probiotics and Prebiotics (ISAPP, 2021) as ‘a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host,’ a definition now widely adopted in the field . Postbiotics are functional foods that may have promising health effects. Direct studies on the impact of defined postbiotics on telomere length remain scarce; however, available evidence suggests they may indirectly influence telomere dynamics through modulation of oxidative stress and inflammation. Postbiotics may have a special effect on gut-organ axes and particular senescence pathways in addition to the general oxidative stress-reducing and inflammation- modulating effects previously mentioned. They also hinder cellular aging by influencing pathways such as mTOR signaling and impaired autophagy. Future research specifically designed to investigate this connection would be valuable.

Several postbiotic metabolites have been shown to alleviate senescence-associated phenotypes by downregulating cell cycle inhibitors and reducing secretion of senescence-associated inflammatory factors, in addition to their general antioxidant and anti- inflammatory actions. Heat-inactivated postbiotics improved intestinal barrier integrity and stimulated regeneration of intestinal stem cells in animal and in vitro studies, suggesting potential to counteract age-related gut alterations. Recent studies highlight a gut–vessel axis linking microbiota to cardiovascular function. Postbiotics may exert cardioprotective effects via both local intestinal actions and systemic vascular signaling, although human evidence remains limited. Postbiotics demonstrate a wide-ranging impact on the cellular mechanisms underlying NDs. This occurs through direct modulation of central nervous system cell signaling pathways or indirect influence on brain function through the gut-brain axis. Documented tissue-specific effects include improved skin elasticity, cardiovascular support through the gut–vessel axis, and neuroprotection via gut brain interactions. Future research should clarify specific mechanisms and validate anti-aging potential in controlled human studies.

5.2 Instances of Natural Compounds Exhibiting Telomere Protective Effects

A number of experimental studies have identified a variety of natural agents with the capacity to counteract the shortening of telomeres by lowering levels of oxidative stress, inhibiting inflammation, improving aspects of mitochondria repair, or facilitating DNA repair mechanisms. Even if the predominant information has been gleaned from cell cultures, model organisms, and human observational trials, the role of natural agents as telomere biology modifiers has been underscored.

Flavonoids are amongst the best-researched telomere-protecting agents. Quercetin, a flavonoid present in apples, onions, and berries, has been observed to decrease oxidative DNA damage and protect telomere length in human cells by diminishing ROS and intervening in stress-response pathways. Epigallocatechin gallate (EGCG), the predominant tea catechin in green tea, safeguards telomeric DNA from oxidative damage and has been observed to modulate telomerase activity with a cell type-dependent action, leading to enhancement of genomic stability. Polyphenols, which include resveratrol found in grapes and red wine, also have very strong telomere-supportive properties. Activation of sirtuin and AMPK pathways initiated by resveratrol enhances mitochondrial function as an indirect mechanism for slowing down telomere shortening. In experimental research, cells treated with resveratrol have been found to have longer telomeres with delayed senescence.

Carotenoids, such as β-carotene, lycopene, and lutein, help protect telomeres by functioning as lipophilic antioxidants. High dietary carotenoid intake from fruits and vegetables has been shown to be related to leukocyte telomere length in observational studies, primarily because it can help prevent oxidative DNA damage.

Medicinal mushrooms and plants' polysaccharides, including β-glucans and compounds extracted from astragalus, have already shown the ability to stabilize telomeres in experimental models. They increase immune system function, reduce inflammation, and in some instances,

activate telomerase, ensuring the maintenance of telomere length and cell proliferative capacity. Biopeptides derived from fermented food sources and the sea may also demonstrate potential. Some peptides possess antioxidant and DNA protective effects that help to reduce telomere degradation. Others claim to protect mitochondria and reduce the appearance of cellular senescence, which indirectly supports telomere maintenance.

The postbiotics, short-chain fatty acids, and specifically those produced by gut bacteria, such as butyrate, affect telomere biology through the suppression of systemic inflammation and improvement of metabolism. The improved inflammation and metabolism profiles promote a reduced rate of cell turnover and DNA damage, which is reflected in a decelerated rate of telomere shortening within immune and epithelial cells. Collectively, these examples show how natural products exert a multitude of mechanisms to safeguard telomeres. By modulating oxidative stress, inflammation, mitochondrial homeostasis, as well as signaling pathways associated with telomeres, these agents could provide a very promising, non-toxic strategy to promote genomic stability and a healthy process of aging.

5.3 Mechanisms Underlying Natural Products' Effects on Telomeres

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Chapter 6

Possible Insights into the Collapse of Senescence and Lifelong

6.1 Therapeutic Prospects of Telomere Preservation in Age-Related Disorders

Muñoz-Lorente et al. (2019) found that mice with hyper-long telomeres had better metabolic parameters, including reduced LDL levels, increased insulin and glucose resistance, a lower incidence of cancer, and longer lifespans. Due to the challenging delivery method, unclear long-term effects, and safety and ethical concerns, direct telomerase therapy utilizing genes has definitely not been investigated in humans. However, it could be premature to abandon the telomerase gene therapy approach given its potential to revolutionize the treatment of sickness and aging. The challenges in human translation clearly necessitate better methodology and advanced clinical trials to reduce the gap and ensure the approach's safety and efficacy for human medicines.

6.2 Natural Products' Role in Fostering Healthy Aging

Chronic stress and age-related telomere degradation have been linked to declining health and an increased risk of disease and death from a number of reasons. In the current investigation, it is reported that a year-long health maintenance program which involves a dietary supplement pack and a telomerase activator made from a natural product lowers the quantity of short leukocyte telomeres and shifts the overall proportion of circulating leukocytes in CMV+ subjects toward the more "youthful" profile of CMV subjects.

The increased morbidity and mortality associated with the immunological risk profile (IRP) support our theory that the decrease in CD8+CD28-T cells is a positive remodeling of the immune system. In the OCTO/NONA Swedish cohort, longitudinal studies of individuals in their 80s and 90s have identified this profile as a CD4/CD8 ratio of less than 1 in relation to

CMV seropositivity.53 years. Like our cohort, the decreased CD4/CD8 among CMV+ individuals in this group is most likely due to an increase of virus-specific CD8+CD28—T cells.

These studies' 6-year follow-up data illustrate that no individuals who were alive for 100 years, even if they were CMV+, exhibit the IRP. The researchers have concluded that effective immunological aging depends on controlling CMV infection without accumulating senescent cytotoxic T cells. Therefore, we conclude that the 20% reduction in CD8+CD28— T cells is a favorable effect even if we have not yet observed increases in the number of CD8+CD28+ T cells. The decrease of CD28 expression and CD8+ T cell tolerance to apoptosis are likely caused by telomere shortening linked to replicative senescence. The most plausible mechanism for this beneficial effect is the activation of telomerase by TA-65, as indicated by the decrease in the percentage of short telomeres we observed. Age-related changes in the innate immune system have not been as well defined as those in the adaptive immune system, despite the growing recognition of the importance of these changes. People's per-cell neutrophil activity, as measured by oxidative burst, phagocytosis, and chemotaxis, is known to decrease with age. The impact of aging on neutrophil count, which has been found to be either preserved, decreased, or increased with age, is a topic of less agreement. The increase in neutrophil counts in the last research from the previously described NONA cohort is based on a comparison between 120 extremely old people (92–100 years old) with an 87% CMV+ prevalence rate and 18 middle-aged (55 years old) participants with a 55% CMV+ prevalence rate.

However, CMV status is not reported in the first two studies. Only a 52-cell rise occurred between the ages of 55 and 92, with the majority of the cross-sectional increase of 960 neutrophils occurring between the 92–100 age range. Additionally, there is a notable longitudinal increase in the extremely old group during a 6-year period.

The lack of a cross-sectional increase in neutrophil count with age in CMV+ individuals implies that compensatory compensation is inhibited in these individuals, possibly as a result of the

senescent T cells' inhibitory cytokine release. By lowering the quantity of senescent T cells, the protocol's effect on raising neutrophil counts in CMV+ individuals might be seen as a beneficial removal of this obstruction. NK cells proliferate after activation and undergo additional telomere shortening after being discharged from the bone marrow, in contrast to other innate immune system cells.

Scientists discovered a drop in the percentage of short telomeres, which may lead to better signal transmission as a mechanism for the decline in the quantity of NK cells. When combined, these three protocol-induced changes in leukocyte counts show that CMV+ subjects' immune systems have been remodelled to resemble those of CMV— subjects and successfully ageing CMV+ centenarians. No adverse events that were probably connected to the protocol were recorded by doctors who kept an eye on the current trial participants' health for a year while they were using the product. Nevertheless, two individuals who recently increased their daily dosage reported feeling "anxious" when taking 100 mg, but not when switching back to 50 mg. Assuming earlier age-specific risks in our population were comparable to those in the United States, no new cases of cancer or cardiovascular disease have been identified during the total 260 person-years of dosing with Patton-Protocol-1 through June, 2010. This is statistically significant ($p < 0.05$, cancer; $p < 0.02$, CVD).

Telomerase was triggered in cultured human cells by TA-65® at levels observed in the plasma of protocol participants. Ironically, the mean telomere length decreased nonsignificantly on average across all patients, despite the fact that 40% of subjects demonstrated an increase over time. However, we hypothesise that telomerase preferentially lengthens the shortest telomeres, which explains this effect in terms of cell dynamics. Preliminary dose-response analyses revealed an increase in beneficial effects with TA-65® doses up to 20–30 mg per day average compared to the initial 5–10 mg, and studies using oral TA-65® in aged mice demonstrated similar reductions in the percentage of cells with short telomeres and positive functional effects on tissues (Blasco et al., submitted). Lastly, advantages in the cardiovascular system, metabolic

rate, and bone mineral density are suggested by study of additional indicators of ageing in PattonProtocol-1 patients; these findings will be investigated further and reported elsewhere. There are plans for independent randomised controlled trials using TA-65® exclusively.

6.3 Ramifications for Longevity Approaches and Anti-Aging Tactics

Advances in the scientific comprehension of telomere function and the regulatory function of natural compounds have profound implications for approaches designed to enhance longevity potential and reduce the effects of age-related morbidity. The preservation of telomeres has been argued to be a factor of primary concern in determining the life span of cells, the ability for tissue regeneration, and healthspan—the length of life spent in good physiological health. Through the targeting of the biological mechanisms leading to accelerated telomere shortening, it may be possible to retard the process of cellular senescence.

1. Integration of Natural Compounds into Diet-Based Therapies:

Evidence for the antioxidant, anti-inflammatory, mitoprotective, and telomere-stabilizing effects of bioactive compounds indicates the potential role of diet in anti-aging interventions. Addition of fruits with high content of flavonoids, vegetables with high content of carotenoids, bioactive peptides, polysaccharides, essential oils, or foods that promote the production of postbiotics may help in the alleviation of cellular stress, protection of telomeres, or both. Unintended effects, cost, and easy usage make these modalities particularly attractive for long-term use.

2. Development of Targeted Nutraceutical:

Knowledge about the mechanisms of natural compounds' effects on telomere biology creates opportunities to develop targeted supplements or functional foods aiming to provide optimal telomere protection. Mixing a set of bioactive compounds with a range of effects—e.g., antioxidants with anti-inflammatory and mitoprotective agents—might also ensure a synergistic positive effect in a nutraceutical treatment.

3.Lifestyle Anti-Aging Methods:

“Non-enzymatic modulation of telomeres reinforces the role of lifestyle modifications, such as stress management, exercise, sleep, and mental health, in aging interventions.” When these alternative therapies are supplemented with dietary nutrients in the form of natural agents proven to promote telomeres, these interventions can have an amplified effect in the prevention of both systemic inflammation and oxidative stress as well as in maintaining homeostasis.

Chapter 7

Challenges and Future Trajectories

7.1 Emerging Trends and Prospects in the Field:

Although mechanistic findings are promising, clinical practice has yet to fully adopt them. Large-scale, closely watched human trials with clinically significant objectives and standardised formulations are still lacking. Future studies should focus on formulation, bioavailability, and long-term safety before recommending these chemicals for usage in therapy or prevention.

7.2. Recommendations for Future Endeavours and Clinical Deployments

"The emerging evidence regarding telomere biology and the modulatory effects of natural compounds has identified the challenges and opportunities associated with translation of scientific findings into efficient anti-aging and longevity therapies. In order to further develop the field and translate achievements into safe and efficient approaches, the following points deserve consideration:"

1. Stringent Human Clinical Trials:

Although compelling in vitro and animal data exist for the protective role of telomeres, human trials are required to verify their efficacy. The future of research would be best spent on clinical trials designed to measure the dosage, bioavailability, pharmacokinetics, and safety of these natural agents. Various populations would be needed to study different genetic, metabolic, and lifestyle factors that might affect levels of responsiveness to telomeres.

2. **Standardization and Quality Control of Natural Products:**

Natural compound variations in terms of sources, modes of extraction, as well as formulation may have significant implications for their biological activities.

Chapter 8

Conclusion

Aging constitutes a complex biological phenomenon that is shaped and modulated by a wide range of genetic, metabolic, and environmental factors. The increasing awareness of telomere functions and the potential of natural molecules to modulate this knowledge has a profoundly positive impact on both scientific research and medical use. Telomere degradation is a characteristic feature of aging at the cellular level and is a contributing cause of many age-related diseases; hence, telomere stabilizing molecules may hold immense future promise in not only increasing longevity but also enhancing health span. By taking a genetic, epigenetic, metabolomics, or advanced imaging approach, much more information can possibly come to light regarding the interaction between oxidative stress, inflammation, the mitochondria, or telomeres. Mechanistic studies can help determine the best way in which these natural compounds can best protect telomeres. Telomere length, telomerase expression, and redox system balance are some of the essential components shielding cells from the unavoidable aging process. Using natural molecules to modify these parameters is an appealing substitute for the still-commonly-used synthetic chemicals.These data may also contribute to the development of more effective anti-aging strategies, which are also important for the prevention of age-related diseases that are closely related to cellular aging. The option of using naturally derived telomerase and telomere modulators gives a comprehensive perspective in the context of improved quality and length of human life.

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