ISSN: 2322 - 0902 (P)
ISSN: 2322 - 0910 (O)

International Journal of Ayurveda and Pharma Research

Review Article

RASAYANA THERAPY: A MOLECULAR PERSPECTIVE ON LONGEVITY AND TELOMERE BIOLOGY-A NARRATIVE REVIEW

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Article info

Article History:
Received: 19-05-2026
Accepted: 16-06-2026
Published: 19-07-2026

KEYWORDS:
Rasayana, Telomere Biology, Cellular Aging, Longevity, Ayurveda, Telomerase.

ABSTRACT

Rasayana therapy, a distinctive rejuvenative branch of Ayurveda detailed in classical texts such as the Charaka Samhita, is designed to promote longevity, enhance immunity, improve cognitive function, and delay the aging process. In recent years, there has been a surge in scientific interest aimed at elucidating the molecular mechanisms underlying the anti-aging effects of *Rasayana* drugs. Contemporary biomedical research indicates that many traditional benefits attributed to *Rasayana* therapy can be explained through mechanisms involving oxidative stress reduction, epigenetic modulation, immune regulation, and telomere preservation. Telomeres are protective nucleotide sequences located at the ends of chromosomes, playing a crucial role in maintaining genomic stability during cell division. The progressive shortening of telomeres is recognized as a key biomarker of cellular aging and is linked to several age-related diseases, including cardiovascular disorders, neurodegenerative conditions, and metabolic syndromes. *Rasayana* herbs, rich in bioactive phytochemicals, exhibit potent antioxidant, adaptogenic, and immunomodulatory properties, which may mitigate the factors contributing to telomere shortening. By reducing oxidative damage, modulating inflammatory pathways, and enhancing cellular repair mechanisms, *Rasayana* therapy may support the preservation of telomere length and the maintenance of genomic integrity. Furthermore, emerging evidence suggests that *Rasayana* compounds may influence epigenetic processes, thereby regulating gene expression associated with longevity and cellular resilience. These mechanisms collectively contribute to healthy aging and disease prevention. By integrating traditional Ayurvedic principles with contemporary molecular biology, we can gain novel insights into the scientific foundation of *Rasayana* therapy and its potential role in promoting longevity and preventing age-related disorders.

INTRODUCTION

In Ayurveda, *Rasayana* therapy is esteemed as a crucial strategy for enhancing longevity, immunity, and rejuvenation by improving the quality of the body's *Dhatus* (tissues). By enhancing digestion, metabolism, and tissue nourishment, this therapy functions as a mechanism to cultivate superior-quality *Dhatus*, which, when well-nourished and balanced, contribute to a prolonged lifespan, a robust immune system capable of resisting diseases, optimal growth and development, and the preservation of youthfulness. *Rasayana* supports the maintenance of physical strength, mental clarity, and overall vitality, thereby augmenting both lifespan and quality of life in both healthy and diseased individuals[1].

Telomeres are repetitive sequences of deoxyribonucleic acid (DNA) that cap the ends of chromosomes, serving to protect them from degradation. Unlike other regions of DNA, telomeres do not encode the information necessary for protein synthesis. Telomerase is an enzyme that plays a critical role in maintaining telomere length by repairing these structures, thereby preventing their progressive shortening during successive rounds of chromosome replication[2].

As a science of nutrition, *Rasayana* provides nourishment to all seven *Dhatus*, thereby slowing the

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Quick Response Code
https://doi.org/10.47070/ijapr.v14i7.4044

degradation of these tissues and enhancing their essence. This practice has historically been a key specialty focused on rejuvenation, geriatric care, mental acuity, and increased immunity, contributing to a long and healthy life. When examined through a scientific lens, *Rasayana* is recognized for its roles as a nutraceutical, antioxidant, and immunomodulator. The present study shows the understanding of *Rasayana* and its role in epigenetics and telomere which acts as the hidden reason for the development of diseases and aging[3].

Review of Literature

Rasayana is instrumental in enhancing life span and strength, described as *"Maha Phalam"* by Chakrapanidatta, the esteemed commentator of the Charaka Samhita. Caraka asserts that *Rasayana* is a promotive treatment designed to enhance the quality of *Rasa* and other *Dhatus*, effectively serving as an accelerated and optimized form of nutrition that enhances the body's biological competence. Chakrapani, in his interpretation of this concept, emphasizes that *Rasadi* encompasses not only physical attributes but also mental qualities such as memory. Therefore, according to him, *Rasayana* is a rejuvenative therapy aimed at achieving vigor and health, accompanied by superior mental competence. Building on Charaka's definition, Gangadhar comments that *Rasayana* is a treatment that produces excellent dhatus, thereby promoting longevity, memory, and other benefits [4].

According to Dalhana, the concept of *Vyasthapan* can be interpreted as the ability to live up to 100 years, while *Ayushkara* refers to living beyond 100 years. Dalhana also notes that some scholars equate *Vyasthapan* with *Jarapaharana*, which signifies the maintenance of a longer youthful life. A review of Chakrapani's commentary on *Vayasthapan* reveals that it pertains to age sustainability, effectively stabilizing youthful vitality and preventing senility. In his commentary on Sushruta, Dalhana interprets the term "*Rasayana*" in two distinct ways: first, as a nourishment for *Rasa* and other *Dhatus*, and second, as a therapeutic approach that enhances the compatibility of *Bheshaja* (medicinal substances) with the body's *Rasa* (taste), *Guna* (properties), *Veerya* (potency), *Vipak* (post-digestive taste), and *Prabhava* (specific effects). This comprehensive compatibility is believed to confer longevity, strength, and a delay in the aging process, while also promoting the production of superior *Rasadi dhatus* and bolstering immunity against diseases [5].

Telomeres are specialized nucleotide sequences located at the termini of linear chromosomes, serving to safeguard genetic information. With each cell division, telomeres undergo progressive shortening; once a critical length is reached, cellular replication ceases, leading to a state known as senescence. To mitigate this shortening, the enzyme telomerase plays a pivotal role. Telomerase functions to extend and repair telomeres, thereby preventing their gradual reduction during successive rounds of chromosome replication [6].

OBSERVATION

Oxidative stress and *Rasayana* Intervention

Rasayana therapy, a rejuvenative aspect of Ayurveda detailed in classical texts such as the Charaka Samhita, is traditionally believed to enhance longevity, vitality, and disease resistance. From a contemporary biomedical standpoint, these assertions can be analyzed through the framework of telomere biology. *Rasayana* herbs are abundant in bioactive phytochemicals, including polyphenols, flavonoids, alkaloids, and withanolides, which are known for their significant antioxidant and anti-inflammatory properties. Botanicals typically classified as *Rasayana,* such as Withania somnifera, Emblica officinalis, and Tinospora cordifolia, have been demonstrated in experimental studies to enhance the activity of endogenous antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, while also reducing lipid peroxidation [7]. Given that telomeric DNA is particularly susceptible to damage from reactive oxygen species (ROS), mitigating oxidative stress may contribute to slowing the rate of telomere shortening.

Inflammation, stress and Telomere Erosion

In addition to their antioxidant effects, *Rasayana* therapy may also impact telomere dynamics through immunomodulatory and stress-reducing mechanisms[8]. Chronic systemic inflammation is known to increase cellular turnover and oxidative damage, both of which can accelerate telomere erosion. Research has shown that *Rasayana* herbs can downregulate pro-inflammatory cytokines, such as TNF-α and IL-6, in preclinical models. Moreover, adaptogenic *Rasayana* plants may help lower cortisol levels and alleviate psychological stress, another factor linked to telomere shortening. Despite these mechanistic insights, direct clinical evidence supporting the preservation of telomere length through *Rasayana* interventions in humans remains limited. Most existing data are derived from in vitro studies, animal models, or indirect clinical markers of oxidative stress and inflammation. Therefore, large-scale, controlled human trials that measure telomere length and telomerase activity before and after *Rasayana* interventions are essential to establish a causal relationship [9].

Cellular ageing and telomere shortening

Aging is a continuous and irreversible biological process that significantly contributes to the onset of various age-related disorders, including

cancer, cataracts, osteoporosis, hypertension, cardiovascular and metabolic diseases, as well as neurodegenerative conditions[10]. A central mechanism underlying cellular aging is telomere shortening. Telomeres, which are repetitive DNA sequences (TTAGGG repeats in humans) located at the ends of chromosomes, serve to protect genetic material during cell division. With each cycle of DNA replication, telomeres progressively shorten. Once they reach a critically short length, cells either enter a state of senescence or undergo apoptosis, leading to tissue degeneration and the aging process. To mitigate telomere shortening, telomerase plays a crucial role. Telomerase is an enzyme that repairs telomeres, preventing them from becoming progressively shorter during successive rounds of chromosome replication. Additionally, telomeres enable cells to differentiate between natural chromosomal termini and double-strand breaks in the DNA[11]. The telomeres themselves are safeguarded by protein complexes known as "shelterins." These shelterins regulate telomerase activity at the telomere and prevent excessive telomerase activity, thereby avoiding undue telomere elongation. Telomerase plays a crucial role in maintaining chromosome integrity by adding TTAGGG repeats to the ends of chromosomes, thereby safeguarding them from excessive shortening and preventing significant DNA loss. This enzymatic activity is essential for preserving genomic stability and ensuring optimal cellular function. However, in the majority of human somatic cells, telomerase activity is either very low or completely absent [12]. Consequently, telomeres progressively shorten over time, leading to a decline in DNA repair capacity and an acceleration of the aging process.

Lifestyle Factors Affecting Telomere Health

Telomere shortening and DNA damage are influenced by both exogenous and endogenous factors. Exogenous factors encompass radiation exposure, poor dietary and lifestyle choices, psychological stress, and environmental toxins. In contrast, endogenous contributors include chronic inflammation, oxidative stress, spontaneous replication errors, and the intrinsic chemical instability of DNA.

Telomerase Activity and Cellular Longevity

The limited effectiveness of many conventional pharmacological approaches in modulating aging has led to an increasing interest in natural products and traditional medicinal systems as potential anti-aging strategies. These approaches focus on reducing oxidative stress and inflammation, enhancing DNA repair mechanisms, and potentially supporting telomere maintenance, thereby decelerating the biological processes associated with aging. A healthy diet, characterized by high dietary fiber and unsaturated fats, plays a protective role in telomere health. In contrast, excessive consumption of sugar and saturated fats is linked to accelerated telomere attrition, as exemplified by the differences between the Mediterranean diet and the modern Western diet. These effects are likely related to oxidative stress and inflammation, as the antioxidant and anti-inflammatory properties of certain nutrients are associated with longer telomeres [13]. Physical activity is believed to have a protective effect on telomeres; however, there is no consensus on the optimal exercise dosage. The beneficial impact of physical activity on telomere length may be attributed to an increase in telomerase activity following acute exercise, which could mitigate oxidative stress and positively influence skeletal muscle health. Regular physical activity is thought to contribute to telomere length preservation, thereby extending human lifespan. A systematic review indicates that exercise positively influences telomere length compared to inactivity, with moderate-intensity aerobic exercise over six months being the most effective in slowing the rate of telomere shortening. Shorter telomere length is associated with advanced age and increased morbidity and mortality. Emerging studies suggest that stress may accelerate telomere erosion from early life and could even influence the initial setting of telomere length in newborns [14].

Telomere Dysfunction, Cancer and Genomic Instability

Smoking and excess weight accelerate telomere shortening and contribute to the aging process. Telomere shortening is not solely associated with aging; it is also linked to various chronic, preventable diseases. Research indicates that shorter telomeres and reduced telomerase activity are correlated with conditions such as hypertension, cardiovascular disease, insulin resistance, type 2 diabetes, depression, osteoporosis, and obesity. In normal tissues, telomere shortening and the absence of telomerase serve as a tumor-suppression mechanism[15]. Conversely, tumors often aberrantly upregulate telomerase, which elongates short telomeres and facilitates continuous cellular growth. Maintaining telomere integrity is essential for stem cell function and normal tissue homeostasis; however, this mechanism can be exploited by cancer cells to achieve cellular immortality. Telomeres can be restored by the enzyme telomerase, which extends their length. Telomerase activity is typically observed in cells that undergo regular division, such as stem cells and lymphocytes within the immune system[16]. Additionally, telomeres can be elongated through the Alternative Lengthening of Telomeres (ALT) pathway. In this process, telomeres are exchanged between chromosomes via homologous recombination, resulting in one set of daughter cells with shorter

telomeres and another set with longer telomeres. Although the ALT pathway is not yet fully understood, it has been the subject of ongoing research. However, the extension of telomeres carries potential risks, including the possibility of uncontrolled cell division and cancer. Elevated telomerase activity is commonly found in the majority of cancer cells, while non-telomerase tumors frequently exhibit activation of the ALT pathway. Furthermore, cells with short telomeres face a heightened risk of improper chromosome recombination, which can lead to genetic instability and aneuploidy, characterized by an abnormal number of chromosomes. Cellular geometry significantly influences nuclear architecture and chromosome dynamics, particularly concerning telomeres.

Emerging Concepts: Mechanical Forces and Telomere Biology

Recent studies have demonstrated that mechanical forces can modulate pathways critical for maintaining genome integrity[17]. ATR, a nuclear protein, functions as a sensor for DNA damage. Under conditions of osmotic stress or mechanical stretching, ATR relocates to the nuclear membrane, indicating its mechano sensitivity, which plays a crucial role in safeguarding DNA from mechanical stresses. Additionally, experiments utilizing magnetic tweezers to stretch the telomere tetraplex structure have revealed the existence of three distinct folded states, each characterized by varying lifetimes and mechanical stability. These findings underscore the impact of mechanical forces on the protective functions of telomeres in genome integrity and their potential involvement in tumorigenesis [18].

Evidence-Based Studies on *Rasayana* and Longevity

Amalaki (*Phyllanthus emblica*) and its Action on Telomere Biology

Amalaki Rasayana, prepared from the fruits of Phyllanthus emblica, is a classical Ayurvedic formulation widely used to prevent and treat age-related health conditions, with telomerase activity playing a central role in its anti-aging mechanism[19]. The fruit is characterized by the presence of vitamin C, alkaloids, ellagitannins, gallic acid, emblicanin A and emblicanin B, and flavonoids- particularly rutin and quercetin- which collectively confer potent antioxidant, anti-inflammatory, and anti-aging pharmacological properties[20]. Oxidative stress and free radicals play an indispensable role in telomere shortening by reducing the action of telomerase and telomeric repeat-binding factor 2 (TRF-2), and through their antioxidant and anti-inflammatory actions, the polyphenolic constituents of *Amalaki* can slow telomere shortening and support telomerase enzyme function [21]. At the molecular level, these polyphenols support telomerase activity via the PI3K/Akt and ERK signaling pathways, wherein AKT stabilizes telomeres by phosphorylating TRF1, and the MAPK/ETS pathway drives hTERT gene expression [22].

Brahmi (*Bacopa monnieri*) and its Action on Telomere Biology

Brahmi (Bacopa monnieri L. Wettst.), a revered Ayurvedic *Rasayana*, possesses well-documented antioxidant, anti-inflammatory, anti-stress, immunomodulatory, and anti-aging pharmacological properties, with its principal bioactive constituents being triterpenoid saponins known as bacosides- comprising 12 known analogs- along with alkaloids such as brahmine, herpestine, and apigenin[23]. The methanolic extract of B. monnieri possesses radical scavenging properties that exert a defensive effect against DNA cleavage, and its anti-lipid peroxidation property plays a critical role in protecting genomic and telomeric DNA from oxidative degradation[24]. Studies on *Brahmi* extracts have reported an extraordinary adaptogenic potential, including the scavenging of superoxide anions and hydroxyl radicals and the reduction of H_2O_2-induced cytotoxicity and DNA damage in human fibroblast cells- with the methanol extract demonstrating marked protective activity against oxidative genotoxicity, directly relevant to the preservation of telomere integrity[25]. Bacosides, the key active constituents of *Brahmi*, enhance critical antioxidant enzymes- including superoxide dismutase (SOD) and catalase- through probable NRF2 pathway activation, and have been shown to confer a protective effect against DNA damage in human fibroblasts and brain cells including astrocytes, both of which are susceptible to telomere-shortening oxidative stress [26].

A current double-blind, placebo-controlled randomized clinical trial is investigating the effects of Bacopa monnieri freeze-dried herbal decoction (BMFD) in elderly participants, with primary outcomes measuring telomerase activity and telomere length in peripheral blood mononuclear cells by qPCR at baseline, 45 days, and 90 days, aimed at establishing definitive clinical evidence for *Brahmi's* role in preserving telomere length and supporting cellular longevity[27]. (Biomedres) Collectively, the pharmacological evidence positions *Brahmi* as a potent genoprotective and anti-aging *Rasayana* whose bacoside-rich phytochemical profile safeguards telomeres from oxidative erosion while supporting the cellular antioxidant machinery that preserves telomerase activity and chromosome stability.

Guduchi (*Tinospora cordifolia*) and its Action on Telomere Biology

Guduchi (Tinospora cordifolia) is a classical Ayurvedic *Tridosha-shamaka* and *Ojovardhaka* herb, categorized as a *Naimittika Rasayana* for its utility in chronic illness, and is known to promote *Rasa* and *Rakta dhatu* regeneration while modulating *Agni* to

optimize *Srotas* (channels)[28]. Pharmacologically, *Guduchi* exhibits a pleiotropic profile characterized by potent immunostimulatory and anti-inflammatory actions, with the ability to increase IL-10 and suppress pro-inflammatory cytokines such as TNF-α, making it directly relevant in mitigating inflammaging- the chronic, low-grade inflammation that underlies many age-related pathologies including telomere shortening[29]. Network pharmacology, molecular docking, and molecular dynamics simulation studies on T. cordifolia have identified key phytochemicals- notably berberine, amritoside, and piperine- that demonstrate strong binding affinity with AKT1, a kinase critically involved in telomere stabilization through phosphorylation of telomeric repeat-binding factor 1 (TRF1), with KEGG pathway analysis confirming involvement in cellular aging, lipid metabolism, and cAMP signaling pathways[30]. Berberine, the principal alkaloid of *Guduchi*, specifically suppresses replicative senescence driven by progressive telomere erosion following each cell division, and prevents premature senescence induced by oxidative DNA damage- the primary molecular event accelerating telomere attrition[31]. Berberine has further been shown to reduce constitutive DNA damage signaling, suppress γH2AX and ATM activation, decrease intracellular ROS, and lower mitochondrial transmembrane potential, collectively attenuating the oxidative mechanisms that damage telomeric DNA and drive the aging phenotype[32]. Thus, through its rich phytochemical arsenal- particularly Berberine and its genoprotective polyphenols- *Guduchi* preserves telomere integrity by combating oxidative stress, suppressing inflammaging, and modulating AKT1-mediated telomere stabilization, substantiating its classical Ayurvedic role as a potent anti-aging *Rasayana*.

Ashwagandha (Withania somnifera) and its Action on Telomere Biology

Ashwagandha (*Withania somnifera* Dunal) has been used for millennia as a *Rasayana* or "life extender" in Ayurveda[33]. Its principal bioactive constituents are steroidal lactones known as withanolides- particularly Withaferin A, Withanolide, and Withanone- which confer potent antioxidant and immunomodulatory properties and are believed to modulate RNA-level changes associated with aging[34]. Withanolide, an active constituent of Withania somnifera, demonstrated a 29.7% extension in the lifespan of C. elegans via regulation of the insulin/IGF-1 signaling pathway, while dysregulation of metabolic and physiological stress has been shown to affect telomere length and maintenance, accelerating aging [35]. In a key experimental study, HeLa cells treated with various concentrations of *Ashwagandha* root extract showed a significant increase in telomerase activity, measured using the established Telomerase Rapid Amplification Protocol (TRAP) assay, with the highest enhancement of approximately 45% observed at a concentration of 10–50µg The mechanisms underpinning these effects include enhancing telomerase activity to support cellular longevity, combating systemic oxidative stress, and powerfully countering inflammaging by modulating immune responses and lowering inflammatory markers such as C-reactive protein [36]. Thus, through its withanolide-rich phytochemical profile, *Ashwagandha* acts as a potent telomerase activator and telomere protector, supporting healthy cellular aging.

DISCUSSION

Rasayana and Cellular Longevity

The classical portrayal of *Rasayana* in the Charaka Samhita emphasizes its effects on sustaining youth, enhancing vitality, and promoting longevity. From a contemporary molecular perspective, these attributes can be elucidated through the lens of telomere biology. Telomeres, the repetitive nucleotide sequences that protect chromosomal ends, progressively shorten with each cell division and are especially susceptible to oxidative stress and chronic inflammation- primary contributors to biological aging. Although direct clinical studies evaluating the effect of *Rasayana* therapy on telomere length are currently limited, available experimental and clinical evidence suggests a plausible molecular basis for the rejuvenative and longevity-promoting actions described in classical Ayurvedic texts. Further well-designed clinical trials are required to establish a direct relationship between *Rasayana* interventions and telomere biology.

Clinical and Experimental Evidences

Numerous *Rasayana* formulations, including *Withania somnifera, Emblica officinalis*, and *Centella asiatica*, demonstrate substantial antioxidant, anti-inflammatory, and adaptogenic properties in experimental studies. These pharmacological effects may indirectly alleviate telomeric DNA damage by reducing reactive oxygen species and systemic inflammatory burden. Furthermore, the documented influence of *Rasayana* on stress modulation suggests a potential psychoneuroimmunological pathway affecting telomerase activity, particularly through the regulation of TERT expression and epigenetic mechanisms that control cellular senescence. *Guduchi* (*Tinospora cordifolia*) has been reported to possess immunomodulatory and anti-inflammatory properties that may help reduce chronic inflammatory states associated with accelerated aging [37].

Recent findings in molecular biology indicate that oxidative stress, chronic inflammation, and psychological stress play a substantial role in telomere shortening. Given that many *Rasayana* drugs possess

antioxidant, anti-inflammatory, and adaptogenic properties, they may indirectly aid in maintaining telomere integrity and genomic stability. Furthermore, research on lifestyle interventions such as yoga, meditation, and stress reduction has shown positive effects on telomerase activity and telomere preservation. These findings lend additional support to the Ayurvedic concept of *Rasayana* in promoting healthy aging and longevity.

While direct clinical studies assessing the impact of *Rasayana* therapy on telomere length remain limited, existing experimental and clinical evidence indicates a credible molecular foundation for the rejuvenative and longevity-enhancing effects detailed in classical Ayurvedic literature. To substantiate a direct correlation between *Rasayana* interventions and telomere biology, further rigorously designed clinical trials are necessary.

The Ayurvedic concept of *Ojas*, representing systemic resilience and vitality, may align with genomic stability and telomere integrity at the cellular level. While direct clinical evidence linking *Rasayana* therapy to telomere length preservation remains limited, the therapy's focus on antioxidant defense, immunomodulation, metabolic optimization, and stress reduction provides a biologically plausible framework that connects traditional Ayurvedic rejuvenation principles with modern models of cellular longevity. Rigorous longitudinal and molecular studies are essential to substantiate this integrative hypothesis.

Action of *Rasayana* in Telomere

Rasayana drugs exert their effects on telomeres primarily through their antioxidant properties. Oxidative stress is a significant factor that accelerates telomere shortening by causing DNA damage at chromosome ends. Many *Rasayana* herbs are rich in potent antioxidants that neutralize reactive oxygen species (ROS), thereby safeguarding telomeric DNA from oxidative harm. For instance, *Phyllanthus emblica* is abundant in vitamin C and polyphenols, which help mitigate oxidative stress and support genomic stability[38].

Additionally, *Rasayana* drugs may influence telomerase activity, the enzyme responsible for maintaining telomere length. Certain phytochemicals in *Rasayana* herbs are suggested to enhance cellular repair mechanisms and support telomerase function. Adaptogenic herbs such as *Withania somnifera* may bolster cellular resilience and reduce stress-induced telomere attrition by regulating stress hormones and inflammatory mediators. Another critical mechanism is the anti-inflammatory effect of *Rasayana* medicines. Chronic inflammation accelerates telomere shortening and cellular aging. Immunomodulatory *Rasayana* herbs like *Tinospora cordifolia* help regulate inflammatory pathways, thereby reducing cellular damage and slowing telomere shortening [39].

CONCLUSION

Rasayana is a promotive treatment designed to enhance the quality of *Rasa* and other *Dhatus,* effectively serving as an accelerated and optimized form of nutrition that enhances the body's biological competence. Telomeres, which are repetitive DNA sequences, with each cycle of DNA replication, progressively shorten. Numerous *Rasayana* formulations with their phytochemical property shows effective pharmacological actions that may indirectly alleviate telomeric DNA damage by reducing reactive oxygen species and systemic inflammatory burden[40]. These actions promote cellular regeneration and maintain tissue integrity, potentially correlating with the preservation of telomere length and improved cellular longevity. This study helps in understanding the importance of *Rasayana* therapy and *Rasayana* drugs that support telomere maintenance through multiple mechanisms, including the reduction of oxidative stress, modulation of inflammation, enhancement of cellular repair processes, and potential stimulation of telomerase activity. These effects provide a molecular basis for the classical Ayurvedic claim that *Rasayana* therapy promotes longevity and delays the aging process.

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Cite this article as:
Asha Yesudas. Rasayana Therapy: A Molecular Perspective on Longevity and Telomere Biology-A Narrative Review. International Journal of Ayurveda and Pharma Research. 2026;14(7):49-56.
https://doi.org/10.47070/ijapr.v14i7.4044
Source of support: Nil, Conflict of interest: None Declared

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