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Life Span and Healthspan Extension Strategies

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ABSTRACT
This review synthesizes insights from the studies investigating mechanisms and strategies for extending lifespan and healthspan. Telomere shortening is key to cellular aging, as evidenced by the fact that activation of telomerasein normal human cells prolongs their replicative lifespan by preserving telomere length and young cell phenotypes. Through the modulation of pathways such as sirtuins and caloric restriction mimetics, the polyphenolic molecule **r**esveratrol improves age-related illnesses and increases longevity and healthspan in model species. Nevertheless, there are difficulties in applying these advantages to people.Reactive oxygen species (ROS) produce cumulative oxidative damage to cellular macromolecules, including as proteins, lipids, and nucleic acids, which is closely associated with aging. An enzyme called peptide methionine sulfoxide reductase A (MSRA) fixes oxidized methionine residues in proteins. It has been linked to reducing oxidative damage and affecting longevity. With a primary focus on neural tissues, this study investigates the effects of MSRA overexpression in Drosophila melanogaster. The results show that transgenic flies that overexpress MSRA have noticeably longer lifespans, improved tolerance to oxidative stress caused by paraquat, and postponed reductions in physical and reproductive activity that are linked with senescence. MSRA's strong antioxidative mechanism is demonstrated by the lifespan extension attained with MSRA overexpression, which surpasses previous oxidative damage mitigation techniques.Finally, invertebrate models emphasize pharmacological methods to aging intervention, particularly high-throughput screening to uncover drugs that reduce aging.

Key words: Telomeres, Calorie restriction(CR) Diet, Resveratrol, MSRA peptidyl enzyme, C.elegans & D.melanogaster, IGF signalling, DAF-2 receptor.

I. INTRODUCTION

Senescence often known as aging, is the gradual deterioration of cellular integrity and physiological processes over time, which reduces resilience and raises the risk of illness and death. The accumulation of molecular damage, telomere shortening, genomic instability, epigenetic changes, and oxidative stress are the hallmarks of aging at the cellular level. One of the most important aspects of aging is cellular senescence, a condition in which cells irreversibly lose their capacity to divide. Telomere attrition and the initiation of DNA damage responses are frequently connected to thisphenomenon. The senescence-associated secretory phenotype (SASP), which is caused by pro-inflammatory substances secreted by senescent cells, is linked to age-related illnesses and tissue failure.This condition made the researchers to work on the delay of senescence,which in other terms known as Extension of Lifespan.

Several mechanisms and interventions for lifespan extension was evolved in the research scale. The goal of lifetime extension initiatives is to improve healthspan, or the percentage of life spent in good health, and postpone the onset of aging-related deterioration. Numerous molecular processes and therapies that impact lifespan have been identified by aging research:

1.Telomere Maintenance:

Normal human diploid cells in culture have a limited lifespan for proliferating and go into a nondividing condition known as Senescence, which is marked by changes in gene expression. [1,2].The fact that replicative senescence depends on cumulative cell divisions rather than chronological or metabolic time suggests that a "mitotic clock" controls proliferation[3]. It is believed that telomere loss regulates the onset of senescence[4-7]. The ribonucleoprotein enzyme telomerase synthesizes the repeats of the sequence TTAGGG/CCCTAA at the chromosome ends that make up human telomeres[8,9]. In human germline

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cells, telomerase is active, and the telomeres in these cells are kept at roughly 15 kilobase pairs (kbp). On the other hand, telomere length is significantly shorter[10]and telomerase is not expressed in the majority of human somatic tissues[11,12]. According to the telomere hypothesis of cellular aging[13], cells undergo senescence when a threshold telomere length is reached as a result of increasing telomere shortening during each division.It has been possible to clone the human telomerase reverse transcriptase component (hTRT)[14]. In normal human diploid cells, which produce low quantities of the template RNA component of telomerase (hTR) but not hTRT, we have recently shown that telomerase activity can be restored by transient production of hTRT[15]. This gave researchers the chance to experiment with telomere length and test the theory that cellular senescence is caused by telomere shortening.

2. Mimetic Compounds and Caloric Restriction:

It has been demonstrated that CR increases lifespan in a variety of animals, most likely as a result of metabolic reprogramming and decreased oxidative damage. By triggering the proteins like sirtuinswhich involved in many biological processes that control metabolism, stress reactions, and DNA repair, substances such as resveratrol imitate CR.It has been shown that modifying the Sir2 gene [16],AMPK signaling[17], TOR signaling[18],and insulin signaling[19] experimentally can alter lifespan in a variety of organisms. The prospect that it would one day be feasible to prolong human longevity has been strengthened by the recent descriptions of several nutritional and pharmaceutical therapies that can increase lifespan and avoid age-related disorders. For instance, the lifespan of yeast [20], worms[21],flies [22],and rodents [23] is increased by caloric restriction (CR), a dietary regimen that involves a reduction in calorie intake. Furthermore, a number of more recent research have shown that CR can lower age-related and all-cause mortality in rhesus monkeys [24–26]despite one study finding that CR had no effect on monkey lifespan [27].It has also been demonstrated that nutritional supplementation with a small chemical, such as rapamycin [28],metformin [29],spermidine [30], or resveratrol [31], can prolong the lifespan of several model organisms as an alternative to CR. Resveratrol has been the most extensively researched molecule among these in the context of aging research, not only because of its apparent lack of toxicity [32],but also because of its exceptional capacity to treat and prevent a variety of age-related diseases in mammals, such as diabetes, cancer, Alzheimer's disease, and heart disease [32,33].In addition to discussing resveratrol's capacity to prolong the healthspan of mammals, we also give an overview of how it extends longevity in a variety of animals and offer insight into the myriad debates, difficulties, and potential applications of these discoveries in the clinic.

3.Extension of High-quality life using peptide MSRA:

An organism's lifespan is determined by the complex process of aging, which is impacted by both environmental and genetic variables. Reactive oxygen species (ROS) generated during regular metabolism are thought to cause cumulative oxidative damage to cellular macromolecules, including proteins, lipids, and nucleic acids, which shortens lifespan and speeds up aging[34,35]. The oxidative damage theory of aging is supported by multiple lines of evidence, with oxidative protein changes potentially being of particular significance. According to one study, an 80-year-old person may have up to 50% of their proteins oxidized [36]. In the fruit fly Drosophila, the amount of oxidized protein likewise rises with age [37], and animals that live longer are more resilient to ROS [38,39,40,41].Drosophila's lifespan is increased by overexpressing superoxide dismutase and catalase, two enzymatic components of the cellular antioxidant system[42].while its lifespan is shortened by genetic disruption of the superoxide dismutase–catalase antioxidant system[43]. Other lifespan-extending measures like cutting calories and modifying genes related to growth-factor signaling cascades and cell metabolism may also have an indirect effect by lowering ROS generation or raising antioxidant levels[44].Methionine (met) makes up around 2% of amino acid residues in proteins[45] and physiological oxidants easily convert it to methionine sulfoxide [met(O)] [46].The enzyme peptide methionine sulfoxide reductase A (MSRA) [47]catalyzes the reduction of met(O) back to methionine. The biological activity of several proteins is impacted by the presence of oxidized met residues[48], and MSRA has been proposed to function as a regulator of cellular excitability. Additionally, there is growing evidence that met-MSRA may be a significant antioxidant system in cells. Yeast and human T lymphocyte cells that overexpress the MSRA gene are protected against oxidative stress[49]while strains of Escherichia coli and yeast that lack the gene are

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more vulnerable to it [50].In rats, MSRA expression and activity decline with age[51], and Alzheimer's disease patients' brains likewise exhibit down-regulated enzyme activity[52]. Calmodulin's amount of oxidized met, which is crucial for cellular Ca2- Rats' homeostasis has been demonstrated to rise dramatically with age [53]. Met residues may potentially contribute to longevity, according to a mitochondrial genotyping study of Japanese centenarians[54]. According to a recent study by Moskovitz et al[55] mice with lower levels of MSRA activity live shorter lives. Therefore, we postulated that overexpressing MSRA to aid in the repair of oxidized methionine residues in proteins could prolong life and reduce the harmful age-related consequences of ROS.

4.Invertebrates' Pharmacological Lifespan Extension:

The potential for treating age-related disorders makes novel chemicals that slow down aging very desirable. Here, is the case that the discovery of potential compounds and mechanistic insights will result from the recent development of a new subfield called the chemical biology of aging, which will eventually advance the treatment of age-related illnesses.In addition to offering the ability to efficiently screen hundreds of thousands of chemical compounds, cell culture and invertebrate model organisms also enable the quick elucidation of the genetic pathways that these compounds are targeting due to their strengths in molecular genetics.The contribution of invertebrate models to the comprehension of the pharmacology of aging is compiled in this review, along with predictions for the future of the area. Since the majority of the chemical biology of aging research to far has been done on nematodes, we shall almost entirely concentrate on studies on C. elegans. Nevertheless, we will also talk about a small number of pharmacological aging investigations that were conducted on the fruit fly Drosophila melanogaster (D. melanogaster).

PHARMACOLOGICAL STATEGIES FOR LIFE SPAN EXPANSION

1.Telomerase Shortening:

The process of maintaining telomeres in human cells relies on the enzyme telomerase, which is a specialized ribonucleoprotein reverse transcriptase. This enzyme extends the ends of chromosomes by synthesizing telomeric simple sequence repeats using a segment of its RNA component. In certain conditions, human cells can also lengthen telomeres through a different mechanism that involves homologous recombination, which has been observed in some transformed fibroblast cultures and a small number of cancers. The composition of telomerase ribonucleoproteins is only partially understood. Our understanding of the proteins associated with human telomerase has been developed through various candidate approaches. The RNA component of telomerase is widely transcribed and forms a stable, yet catalytically inactive, ribonucleoprotein. The processing and stability of human telomerase RNA (hTR) depend on the binding of small nucleolar ribonucleoproteins like dyskerin, NHP2, NOP10, and GAR1 to the H/ACA motif of hTR. The catalytic function is achieved through the binding of the telomerase reverse transcriptase subunit (TERT) and is influenced by other factors, including chaperones and nucleic acid-binding proteins. Additionally, certain unknown conformational changes or interactions are required to recruit telomerase to telomeres during the DNA synthesis phase of the cell cycle. Most human somatic cells lose telomerase activity after early fetal development, while telomerase-positive cells are more commonly found in mouse tissues. The inactivation of telomerase in human somatic cells primarily results from the transcriptional repression of TERT, which can be countered by the constant expression of a human TERT (hTERT) transgene. This continuous expression of hTERT in pre-senescent fibroblasts, lymphocytes, epithelial cells, and other cell types can prolong their replicative lifespan. Other forms of telomerase inactivation, such as alternative mRNA splicing that produces a catalytically inactive version of hTERT, have been observed during early development. The general suppression of telomerase activity in somatic cells may serve as a tumor-suppressing mechanism, particularly in long-lived organisms. Since telomere shortening in telomerase-negative cells restricts their ability to proliferate, the chances of accumulating the numerous spontaneous DNA mutations necessary for cancer development are likely reduced. This theory aligns with findings from certain mouse models, although the short telomeres resulting from telomerase disruption can also increase the risk of tumorigenesis by causing genomic instability.In human somatic tissues, telomerase inactivation has some exceptions, particularly in a limited number of adult tissues that are rapidly proliferating. Telomerase is active in certain germline, epithelial, and hematopoietic cells. In the stages of these cell lineages where telomerase is present, its activation is associated with the transcription of the hTERT

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gene. Sometimes, this activation is further enhanced by an increase in ribonucleoprotein levels, posttranslational modifications of hTERT, or the movement of catalytically active ribonucleoprotein within the nucleus. In somatic stem cells, telomerase does not compensate for the loss of telomeres due to proliferation; it only functions during a specific phase of progenitor cell proliferation and is later downregulated during terminal differentiation. While one might expect telomerase activation to restore every telomeric repeat lost during previous DNA replication cycles, this telomere length maintenance has been well-studied in single-celled organisms like yeasts and is currently being researched in long-term cultures of mammalian cells. In cancer cells, the equilibrium between telomere loss and addition can sustain stable telomere lengths over prolonged periods of division. However, in normal human somatic tissues, telomerase activation does not lead to the establishment or maintenance of stable telomere lengths. The temporary nature of telomerase activation in normal somatic cell lineages is in stark contrast to the continuous activation seen in tumor cells. The extent of telomere shortening that somatic cell telomerase activation can counteract is influenced by the initial telomere length, the rate of telomere shortening with each cell division, the level of telomerase activity, and the cellular regulation of telomere-telomerase interactions. There is still much to learn about the mechanisms that determine telomere length, especially in light of observations like the proliferation-linked activation of telomerase in cells that experience rapid telomere erosion[69].

2.Hypotheses of anti-aging effect by Caloric restriction:

The specific mechanisms by which caloric restriction influences longevity have not been conclusively established. There are numerous hypotheses that require further testing to fully comprehend how reduced food intake leads to an extended lifespan. Early studies on caloric restriction proposed several theories, such as the developmental delay hypothesis by McCay et al., which suggested that slowing growth through caloric restriction could increase lifespan. Pearl's reduced metabolic rate hypothesis posited that caloric restriction lowers metabolic rates, thereby extending lifespan. Additionally, the laboratory gluttons hypothesis examined whether the overeating of lab animals compared to their wild counterparts negatively impacted their health, suggesting that the benefits of caloric restriction might simply be a result of excessive eating. However, most of these early theories have been largely dismissed due to conflicting findings from various studies.

The most credible explanation for the anti-aging effects of caloric restriction relates to the reduction of oxidative stress. When oxygen is metabolized in the body, it is converted into reactive oxygen species (ROS), which can damage cellular macromolecules and contribute to age-related changes. It is believed that caloric restriction lowers ROS production, thereby slowing the aging process. This hypothesis has been supported by numerous studies, although it is not without controversy. For instance, mice lacking the antioxidant superoxide dismutase did not exhibit accelerated aging despite increased oxidative damage, and reducing ROS production did not prolong the lifespan of Drosophila. Therefore, further research is needed to clarify the connections between ROS, lifespan, and caloric restriction.

Moreover, caloric restriction has been shown to lower body temperature, which is considered one of the mechanisms that contribute to increased lifespan. Specifically, the benefits of caloric restriction were negated when animals on a restricted diet were kept at higher temperatures. Overall, current evidence suggests that a complex interplay of various mechanisms may underlie the positive effects of caloric restriction on longevity[70].

3.Extension of High-quality life using peptide MSRA:

It is now well established that the peptide methionine sulfoxide reductase system plays a role in aging and the lifespan of Escherichia coli, yeast, Drosophila, and mammals, although the underlying molecular mechanisms are still unclear . Research conducted by Stadtman and Hoshi's laboratories utilizing knock-out mice and transgenic Drosophila, respectively, examined the function of MsrA in lifespan regulation related to the enzyme's antioxidant properties. In transgenic Drosophila, the over expression of Msr A increased the average lifespan by as much as 70%;the flies showed greater resistance to oxidative stress induced by paraquat and maintained excellent health. Conversely, mice that were deficient in the msr A gene exhibited heightened sensitivity to oxidative stress; they exhibited an accumulation of oxidized proteins and experienced a

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40% reduction in lifespan. Furthermore, MsrA animals developed physical and neurological issues. The relationship between thioredoxin/thioredoxin reductase and the peptide methionine sulfoxide reductase system in regulating cellular redox balance was highlighted by the differing levels of thioredoxin reductase expression in MsrA mice compared to wild-type counterparts. The thioredoxin/thioredoxin reductase system is a crucial part of the defense mechanisms utilized against damage caused by reactive oxygen species in both vertebrates and invertebrates, and it also plays an essential role in protein maintenance. It is involved in the thiol-disulfide exchange necessary for the regeneration of catalytic sites in various enzymes such as peroxiredoxin, along with MsrA and MsrB. The thioredoxin/thioredoxin reductase system was initially found to remain unchanged during aging . However, more recent research appears to indicate that the thioredoxin/thioredoxin reductase system participates in aging and specifically in controlling lifespan . A decline in the system's efficiency was noted in older rats, which was compensated in animals that underwent caloric restrictions, known to slow the aging process. Loss-of-function mutations in the Drosophila thioredoxin reductase 1 gene were found to significantly decrease adult lifespan, while the disruption of this gene in both Drosophila and mice leads to embryonic de ath. In contrast, the overexpression of human thioredoxin in mice improves resistance to oxidative stress and extends lifespan .

We have demonstrated that, in rat organs where MsrA is particularly abundant—namely the liver, kidney, and brain—the activity of peptide methionine sulfoxide reductase is significantly diminished with aging . This decline correlates with a reduction in MsrA gene expression in the liver and kidney. In contrast, in the brain, the differences we observed in gene expression were not statistically significant, and the MsrA protein level was only reduced in 26-month-old rats at the very end of their lifespan. This fascinating observation may now be understood better in light of the discovery of multiple MsrB genes that encode at least four distinct proteins in mammalian cells, in addition to MsrA. Although MsrB2 (Cbs-1) is not abundant in the brain, the other MsrB proteins could account for the observed changes in peptide methionine sulfoxide reductase activities during brain aging. Dysfunctional expression and/or activity of the peptide methionine sulfoxide reductases system may clarify the accumulation of faulty repair within proteins and could potentially therefore add to the age-related buildup of oxidized proteins, assessed by measuring protein carbonyl levels. Indeed, MsrA has been referred to as an antioxidant system that can operate catalytically because, in proteins, the methionine residues that are on the surface can serve as scavengers for various oxidants . A reduction in MsrA activity could thus induce an imbalance in cellular redox homeostasis, a rise in the level of reactive oxygen species, and as a result an accumulation of oxidative protein damage.

Using replicative senescence as a model for cellular aging, we have examined the function and regulation of the peptide methionine sulfoxide reductase system in both young and aged WI-38 fibroblasts . Following a finite number of divisions, primary human cells enter a phase of replicative senescence characterized by growth arrest and resistance to mitogenic stimuli. At this point, cells display numerous morphological and biochemical alterations linked to aging; specifically, they accumulate altered macromolecules, including damaged DNA and oxidized proteins . There is currently evidence indicating that the enzymatic systems responsible for protein maintenance are influenced during replicative senescence. In fact, the degradation activities of the proteasome have been demonstrated to be significantly diminished in fibroblast cells experiencing replicative senescence; this reduction is correlated with a decrease in proteasome levels . The condition of the peptide methionine sulfoxide reductases system was evaluated in WI-38 fibroblasts as they undergo cellular senescence. Total peptide methionine sulfoxide reductaseActivity was evaluated by observing the decrease of the synthetic substrate N-acetyl(3 H)MetR,S(O) to N-acetyl(3 H) MetR,S, which can be reduced by MsrA or MsrB. We demonstrated a decline in peptide methionine sulfoxide reductase activity in senescent cells, associated with a reduction in gene expression for both MsrA and MsrB2 (Cbs-1). In contrast, in Saccharomyces cerevisiae, no changes in the expression of the peptide methionine sulfoxide reductase genes were noted between young and old yeast cells during replicative senescence . However,

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in that research, no alterations were found in the oxidative stress response genes during senescence, suggesting the presence of potential oxygen-independent factors of aging. In that same research, the impact of MsrB on the replicative lifespan of yeast cells was also examined. The deletion of the msrA gene resulted in a lifespan reduction of 26%, while overexpression led to a 25% increase in lifespan. Little to no impact of MsrB (SelR) was observed, yet the lifespan of the double mutant DmsrA/msrB was shortened compared to the msrA mutant, indicating the involvement of both proteins in yeast longevity. The influence of MsrA and MsrB on lifespan is no longer noticeable when yeasts are cultivated under anaerobic conditions. Nonetheless, MsrA overexpressing yeast cells showed improved survival rates and no buildup of protein oxidative damage when subjected to H2O2, paraquat, or 2-amidinopropane dihydrochloride treatment[71].

4.Invertebrates' Pharmacological Lifespan Extension:

4.1 Selecting a suitable model to find substances that prolong lifespan:

a) Caenorhabditis elegans:

C. elegans is quickly taking the lead as the preferred invertebrate model for chemical studies on aging and age-related traits because of its short lifetime and ease of cultivation. In fact, C. elegans is a potent system for figuring out the mode of action of well-known pharmaceutical therapies due to its abundance of genetic tools, which also serve as a model for evaluating the biological effects of several chemicals.These various investigations have shown how adaptable the approach is for chemical testing and screening. In light of this, worm peculiarities should be kept to a minimum when evaluating how drugs affect lifespan. This subject has already been discussed previously [56]for their justifications of consistency in the lifetime assays.

b)Drosophila melanogaster:

It is more difficult to screen a large number of compounds in D. melanogaster than in C. elegans, but the existence of complex behavioural traits and a variety of reliable models of age-related disorders in humans make these tough tasks important.Drosophila have long been utilized to investigate for aging-related chemical effects.In 1948, the fruit fly was employed to ascertain the biological impacts of the chemical components of royal jelly; thus, pantothenic acid was proposed as a means of prolonging the fly's lifespan[57].

4.2 List of Aging Pathways that Lifespan can use as Targets:

a) Oxidative stress and its impact on lifespan:

Age-related diseases are evidently largely caused by macromolecular oxidative damage, which is a characteristic of aging[58]. The modulation of mitochondrial activity has been the subject of numerous investigations because mitochondria are a major generator of oxygen radicals, including diffusible hydrogen peroxide (H2O2). Mn superoxide dismutase (MnSOD), an enzyme that catalyzes the conversion of superoxide anion (O2 • −) to H2O2, is the main enzyme in mammals that guards against oxidative damage in the mitochondria. Although lowering MnSOD in mice models does not cause accelerated aging, knocking out the gene encoding MnSOD is developmentally fatal, demonstrating the significance of this function[59]. Exercise can decrease the accelerated aging disease caused by limiting mitochondrial function by lowering the mitochondrial specific RNA polymerase[60].

b) Role of protein homeostasis in promoting longevity:

A well-researched phenomena that is common to many human disorders is the creation of molecular aggregates. It is particularly well-researched in neurodegenerative diseases, where abnormal protein types like huntingtin (in Huntington's disease), β-synuclein (in Parkinson's disease), and β-amyloid (in Alzheimer's disease) may accelerate the course of the illness[61]. Non-neurological systemic illnesses such as type II diabetes and a number of myopathies also exhibit aggregate formation. In fact, during the past few decades, it has become evident that one morphological characteristic of aging is the creation of protein aggregates. Protein homeostasis networks deteriorate with age; this decline in fidelity has been documented in numerous systems and is probably a significant factor in organism aging.Therefore, pharmacologically addressing the age-related loss of protein homeostasis may help to prolong life and lessen or delay the pathogenesis of age-related diseases.

c) Dietary restriction pathway and its effect on lifespan:

One reliable strategy for increasing the longevity of model organisms is dietary restriction (DR). The positive effects of DR in invertebrates

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extend their lifespan and also mitigate many age-related declines in stress resistance, motor function, and protein homeostasis [62]. Research on flies, worms, and yeast has focused on signaling components that initiate the DR response by adjusting nutritional circumstances[63].Although it is well established that DR increases the longevity of lab animals and is reliable in invertebrate models, it is unclear if this is true for populations with specific genetic backgrounds, such as wild populations.

d) Insulin/IGF like signaling and its effects on lifespan:

It has been demonstrated that insulin/IGF like signaling (IIS) plays a significant role in regulating lifespan. Indeed, the earliest evidence of a significant impact on metazoan lifespan was found in C. elegans genes involved in this pathway[64]. In vertebrates, including humans, homologous pathways have been demonstrated to affect lifespan [65]. Insulin and insulin-like ligands regulate the activation of the insulin/IGF receptor in C. elegans through the IIS pathway. In C. elegans, the downstream FOXO type transcription factor, DAF-16, is activated when the receptor (DAF-2) is inhibited. Pro-longevity gene transcription is triggered by activated DAF-16 when it translocates into the nucleus [66]. In addition to the induction of stress-resistant genes that confer thermotolerance and increased resistance to oxidative damage[67], this causes significant morphological and metabolic changes, such as an increase in the storage of fat and glycogen in intestinal and hypodermal cells[68].

II. CONCLUSION

The study showed that by inhibiting telomere shortening, which is connected to cellular senescence, telomerase increased the longevity of healthy human cells. The findings suggest that telomere loss plays a significant role in regulating the quantity of cell divisions prior to senescence. While preserving regular cellular processes, the results point to possible medical uses, including preventing age-related illnesses and enhancing cell-based treatments. Beside of that, a variety of compoundssuch as resveratrol and its synthetic counterpartshave demonstrated potential for boosting health and longevity. Regulatory obstacles still exist despite tremendous advancements since aging is not formally recognized as a disease. Future studies must concentrate on determining safe and efficient substances that promote longevity as well as resolving moral dilemmas related to lifespan extension.Therefore, while vertebrate models remain essential for later-stage research, the cost-effectiveness and amenability to genetic manipulation of invertebrate models, coupled with the efficiency of in vitro systems, position them as indispensable tools in the ongoing quest to understand and ultimately manipulate the aging process through chemical interventions.In conclusion, the evidence clearly points to a connection between aging and oxidative damage, specifically protein oxidation. By fixing oxidized methionine residues, the enzyme methionine sulfoxide reductase A (MSRA) seems to be essential in reducing this damage. The concept that increasing MSRA activity could potentially prolong longevity and lessen age-related decline is supported by the observed fall in MSRA activity with age, as well as by the protective effects of MSRA against oxidative stress and the shorter lifespan of species without MSRA. Consequently, more investigation into the therapeutic potential of overexpressing MSRA or other ways to increase its activity is necessary, providing a promising path for therapies meant to support healthy aging.

Declarations:

Ethics approval and consent to participate:‘Not applicable’, as this studyis areview of existing literature and does not involve human participants or animals.

Consent for Publication:‘Not applicable’, as this article does not contain any individual person’s data in any form.

Availability of data and material:Data - All data analyzedin this review are available in publicly accessible databases, Links to each dataset are provided in their respective references.**Materials –** ‘Not applicable’, as no kind of supporting materials such as tables, figures, raw data were used in this manuscript.

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AuthorMs. Sai Sravanthi Padam and Ms. Chandrika Satya Mangadevi Dasari -conducted the literature search and collected relevant articles.
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REFERENCES

[1]. HAYFLICK, L., & MOORHEAD, P. S. (1961). The serial cultivation of human diploid cell strains. Experimental cell research, 25, 585–621. https://doi.org/10.1016/0014-4827(61)90192-6

[2]. Campisi J. (1997). The biology of replicative senescence. European journal of cancer (Oxford, England: 1990), 33(5), 703–709. https://doi.org/10.1016/S0959-8049(96)00058-5

[3]. Bodnar, A. G., Ouellette, M., Lichsteiner, S., & Wright, W. E. (1998). Extension of life-span by introduction of telomerase into normal human cells. Science, 279(5349), 349+. https://link.gale.com/apps/doc/A20183440/AONE?u=anon~43460897&sid=googleScholar&xid=ac1479a5

[4]. Harley, C. B., Futcher, A. B., & Greider, C. W. (1990). Telomeres shorten during ageing of human fibroblasts. Nature, 345(6274), 458–460. https://doi.org/10.1038/345458a0

[5]. Bodnar, A. G. (1998). Extension of Life-Span by Introduction of Telomerase into Normal Human Cells. Science, 279(5349), 349–352. https://doi.org/10.1126/science.279.5349.349

[6]. Chang, E., & Harley, C. B. (1995). Telomere length and replicative aging in human vascular tissues. Proceedings of the National Academy of Sciences of the United States of America, 92(24), 11190–11194. https://doi.org/10.1073/pnas.92.24.11190

[7]. Weng, N., Granger, L., & Hodes, R. J. (1997). Telomere lengthening and telomerase activation during human B cell differentiation. Proceedings of the National Academy of Sciences of the United States of America, 94(20), 10827–10832. https://doi.org/10.1073/pnas.94.20.10827

[8]. Lingner, J., Hughes, T. R., Shevchenko, A., Mann, M., Lundblad, V., & Cech, T. R. (1997). Reverse transcriptase motifs in the catalytic subunit of telomerase. Science (New York, N.Y.), 276(5312), 561–567. https://doi.org/10.1126/science.276.5312.561

[9]. Greider, C. W., & Blackburn, E. H. (1989). A telomeric sequence in the RNA of Tetrahymena telomerase required for telomere repeat synthesis. Nature, 337(6205), 331–337. https://doi.org/10.1038/337331a0

[10]. de Lange, T., Shiue, L., Myers, R. M., Cox, D. R., Naylor, S. L., Killery, A. M., & Varmus, H. E. (1990). Structure and variability of human chromosome ends. Molecular and cellular biology, 10(2), 518–527. https://doi.org/10.1128/mcb.10.2.518-527.1990

[11]. Kim, N. W., Piatyszek, M. A., Prowse, K. R., Harley, C. B., West, M. D., Ho, P. L., Coviello, G. M., Wright, W. E., Weinrich, S. L., & Shay, J. W. (1994). Specific association of human telomerase activity with immortal cells and cancer. Science (New York, N.Y.), 266(5193), 2011–2015. https://doi.org/10.1126/science.7605428

[12]. Shay, J. W., & Bacchetti, S. (1997). A survey of telomerase activity in human cancer. European Journal of Cancer, 33(5), 787–791. https://doi.org/10.1016/s0959-8049(97)00062-2

[13]. Harley C. B. (1991). Telomere loss: mitotic clock or genetic time bomb. Mutation research, 256(2-6), 271–282. https://doi.org/10.1016/0921-8734(91)90018-7

[14]. Nakamura, T. M., Morin, G. B., Chapman, K. B., Weinrich, S. L., Andrews, W. H., Lingner, J., Harley, C. B., & Cech, T. R. (1997). Telomerase catalytic subunit homologs from fission yeast and human. Science (New York, N.Y.), 277(5328), 955–959. https://doi.org/10.1126/science.277.5328.955

[15]. Weinrich, S. L., Pruzan, R., Ma, L., Ouellette, M., Tesmer, V. M., Holt, S. E., Bodnar, A. G., Lichtsteiner, S., Kim, N. W., Trager, J. B., Taylor, R. D., Carlos, R., Andrews, W. H., Wright, W. E., Shay, J. W., Harley, C. B., & Morin, G. B. (1997). Reconstitution of human telomerase with the template RNA component hTR and the catalytic protein subunit hTRT. Nature genetics, 17(4), 498–502. https://doi.org/10.1038/ng1297-498

[16]. Kaeberlein, M., McVey, M., & Guarente, L. (1999). The SIR2/3/4 complex and SIR2 alone promote longevity in Saccharomyces cerevisiae by two different mechanisms. Genes & development, 13(19), 2570–2580. https://doi.org/10.1101/gad.13.19.2570

[17]. Hardie, D. G., Ross, F. A., & Hawley, S. A. (2012). AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nature reviews. Molecular cell biology, 13(4), 251–262. https://doi.org/10.1038/nrm3311

[18]. Hansen, M., Taubert, S., Crawford, D., Libina, N., Lee, S. J., & Kenyon, C. (2007). Lifespan extension by conditions that inhibit translation in Caenorhabditis elegans. Aging cell, 6(1), 95–110. https://doi.org/10.1111/j.1474-9726.2006.00267.x

[19]. Kenyon C. (2011). The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 366(1561), 9–16. https://doi.org/10.1098/rstb.2010.0276

[20]. Anderson, R. M., Bitterman, K. J., Wood, J. G., Medvedik, O., & Sinclair, D. A. (2003). Nicotinamide and PNC1 govern lifespan extension by calorie restriction in Saccharomyces cerevisiae. Nature, 423(6936), 181–185. https://doi.org/10.1038/nature01578

[21]. Lee, G. D., Wilson, M. A., Zhu, M., Wolkow, C. A., de Cabo, R., Ingram, D. K., & Zou, S. (2006). Dietary deprivation extends lifespan in Caenorhabditis elegans. Aging cell, 5(6), 515–524. https://doi.org/10.1111/j.1474-9726.2006.00241.x

[22]. Partridge, L., Piper, M. D., & Mair, W. (2005). Dietary restriction in Drosophila. Mechanisms of ageing and development, 126(9), 938–950. https://doi.org/10.1016/j.mad.2005.03.023

[23]. Weindruch, R., Walford, R. L., Fligiel, S., & Guthrie, D. (1986). The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake. The Journal of nutrition, 116(4), 641–654. https://doi.org/10.1093/jn/116.4.641

[24]. Colman, R. J., Beasley, T. M., Kemnitz, J. W., Johnson, S. C., Weindruch, R., & Anderson, R. M. (2014). Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. Nature communications, 5, 3557. https://doi.org/10.1038/ncomms4557

[25]. Colman, R. J., Anderson, R. M., Johnson, S. C., Kastman, E. K., Kosmatka, K. J., Beasley, T. M., Allison, D. B., Cruzen, C., Simmons, H. A., Kemnitz, J. W., &Weindruch, R. (2009). Caloric restriction delays disease onset and mortality in rhesus monkeys. Science (New York, N.Y.), 325(5937), 201–204. https://doi.org/10.1126/science.1173635

[26]. Bodkin, N. L., Alexander, T. M., Ortmeyer, H. K., Johnson, E., & Hansen, B. C. (2003). Mortality and morbidity in laboratory-maintained Rhesus monkeys and effects of long-term dietary restriction. The journals of gerontology. Series A, Biological sciences and medical sciences, 58(3), 212–219. https://doi.org/10.1093/gerona/58.3.b212

[27]. Mattison, J. A., Roth, G. S., Beasley, T. M., Tilmont, E. M., Handy, A. M., Herbert, R. L., Longo, D. L., Allison, D. B., Young, J. E., Bryant, M., Barnard, D., Ward, W. F., Qi, W., Ingram, D. K., & de Cabo, R. (2012). Impact of caloric restriction on health and survival in rhesus

monkeys from the NIA study. Nature, 489(7415), 318–321. https://doi.org/10.1038/nature11432

[28]. Harrison, D. E., Strong, R., Sharp, Z. D., Nelson, J. F., Astle, C. M., Flurkey, K., Nadon, N. L., Wilkinson, J. E., Frenkel, K., Carter, C. S., Pahor, M., Javors, M. A., Fernandez, E., & Miller, R. A. (2009). Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature, 460(7253), 392–395. https://doi.org/10.1038/nature08221

[29]. Martin-Montalvo, A., Mercken, E. M., Mitchell, S. J., Palacios, H. H., Mote, P. L., ScheibyKnudsen, M., Gomes, A. P., Ward, T. M., Minor, R. K., Blouin, M. J., Schwab, M., Pollak, M., Zhang, Y., Yu, Y., Becker, K. G., Bohr, V. A., Ingram, D. K., Sinclair, D. A., Wolf, N. S., Spindler, S. R., … de Cabo, R. (2013). Metformin improves healthspan and lifespan in mice. Nature communications, 4, 2192. https://doi.org/10.1038/ncomms3192

[30]. Morselli, E., Galluzzi, L., Kepp, O., Criollo, A., Maiuri, M. C., Tavernarakis, N., Madeo, F., & Kroemer, G. (2009). Autophagy mediates pharmacological lifespan extension by spermidine and resveratrol. Aging, 1(12), 961–970. https://doi.org/10.18632/aging.100110

[31]. Wood, J. G., Rogina, B., Lavu, S., Howitz, K., Helfand, S. L., Tatar, M., & Sinclair, D. (2004). Sirtuin activators mimic caloric restriction and delay ageing in metazoans. Nature, 430(7000), 686–689. https://doi.org/10.1038/nature02789

[32]. Baur, J. A., & Sinclair, D. A. (2006). Therapeutic potential of resveratrol: the in vivo evidence. Nature reviews. Drug discovery, 5(6), 493–506. https://doi.org/10.1038/nrd2060

[33]. Hubbard, B. P., & Sinclair, D. A. (2014). Small molecule SIRT1 activators for the treatment of aging and age-related diseases. Trends in pharmacological sciences, 35(3), 146–154. https://doi.org/10.1016/j.tips.2013.12.004

[34]. HARMAN D. (1956). Aging: a theory based on free radical and radiation chemistry. Journal of gerontology, 11(3), 298–300. https://doi.org/10.1093/geronj/11.3.298

[35]. Beckman, K. B., & Ames, B. N. (1998). The free radical theory of aging matures. Physiological reviews, 78(2), 547–581. https://doi.org/10.1152/physrev.1998.78.2.547

[36]. Starke-Reed, P. E., & Oliver, C. N. (1989). Protein oxidation and proteolysis during aging and oxidative stress. Archives of biochemistry and biophysics, 275(2), 559–567. https://doi.org/10.1016/0003-9861(89)90402-5

[37]. Orr, W. C., & Sohal, R. S. (1994). Extension of life-span by overexpression of superoxide dismutase and catalase in Drosophila melanogaster. Science (New York, N.Y.), 263(5150), 1128–1130. https://doi.org/10.1126/science.8108730

[38]. Larsen P. L. (1993). Aging and resistance to oxidative damage in Caenorhabditis elegans. Proceedings of the National Academy of Sciences of the United States of America, 90(19), 8905–8909. https://doi.org/10.1073/pnas.90.19.8905

[39]. Tyler, R. H., Brar, H., Singh, M., Latorre, A., Graves, J. L., Mueller, L. D., Rose, M. R., & Ayala, F. J. (1993). The effect of superoxide dismutase alleles on aging in Drosophila. Genetica, 91(1-3), 143–149. https://doi.org/10.1007/BF01435994

[40]. Leips, J., & Mackay, T. F. (2000). Quantitative trait loci for life span in Drosophila melanogaster: interactions with genetic background and larval density. Genetics, 155(4), 1773–1788. https://doi.org/10.1093/genetics/155.4.1773

[41]. Mockett, R. J., Orr, W. C., Rahmandar, J. J., Sohal, B. H., & Sohal, R. S. (2001). Antioxidant status and stress resistance in long- and short-lived lines of Drosophila melanogaster. Experimental gerontology, 36(3), 441–463. https://doi.org/10.1016/s0531-5565(00)00258-8

[42]. Fleming, J. E., Reveillaud, I., & Niedzwiecki, A. (1992). Role of oxidative stress in Drosophila aging. Mutation Research/DNAging, 275(3), 267–279. https://doi.org/10.1016/0921-8734(92)90031-J

[43]. Phillips, J. P., Campbell, S. D., Michaud, D., Charbonneau, M., & Hilliker, A. J. (1989). Null mutation of copper/zinc superoxide dismutase in Drosophila confers hypersensitivity to paraquat and reduced longevity. Proceedings of the National Academy of Sciences of the United States of America, 86(8), 2761–

2765. https://doi.org/10.1073/pnas.86.8.2761

[44]. Sohal, R. S., &Weindruch, R. (1996). Oxidative stress, caloric restriction, and aging. Science (New York, N.Y.), 273(5271), 59–63. https://doi.org/10.1126/science.273.5271.59

[45]. McCaldon, P., & Argos, P. (1988). Oligopeptide biases in protein sequences and their use in predicting protein coding regions in nucleotide sequences. Proteins, 4(2), 99–122. https://doi.org/10.1002/prot.340040204

[46]. Brot, N., & Weissbach, H. (2000). Peptide methionine sulfoxide reductase: biochemistry and physiological role. Biopolymers, 55(4), 288–296. https://doi.org/10.1002/1097-0282(2000)55:4<288::AID-BIP1002>3.0.CO;2-M

[47]. Brot, N., Weissbach, L., Werth, J., & Weissbach, H. (1981). Enzymatic reduction of protein-bound methionine sulfoxide. Proceedings of the National Academy of Sciences of the United States of America, 78(4), 2155–2158. https://doi.org/10.1073/pnas.78.4.2155

[48]. Yermolaieva, O., Xu, R., Schinstock, C., Brot, N., Weissbach, H., Heinemann, S. H., & Hoshi, T. (2004). Methionine sulfoxide reductase A protects neuronal cells against brief hypoxia/reoxygenation. Proceedings of the National Academy of Sciences of the United States of America, 101(5), 1159–1164. https://doi.org/10.1073/pnas.0308215100

[49]. Moskovitz, J., Flescher, E., Berlett, B. S., Azare, J., Poston, J. M., &Stadtman, E. R. (1998). Overexpression of peptide-methionine sulfoxide reductase in Saccharomyces cerevisiae and human T cells provides them with high resistance to oxidative stress. Proceedings of the National Academy of Sciences, 95(24), 14071–14075. https://doi.org/10.1073/pnas.95.24.14071

[50]. Moskovitz, J., Rahman, M. A., Strassman, J., Yancey, S. O., Kushner, S. R., Brot, N., & Weissbach, H. (1995). Escherichia coli peptide methionine sulfoxide reductase gene: regulation of expression and role in protecting against oxidative damage. Journal of bacteriology, 177(3), 502–507. https://doi.org/10.1128/jb.177.3.502-507.1995

[51]. Petropoulos, I., Mary, J., Perichon, M., &Friguet, B. (2001). Rat peptide methionine sulphoxide reductase: cloning of the cDNA, and down-regulation of gene expression and enzyme activity during aging. The Biochemical journal, 355(Pt 3), 819–825. https://doi.org/10.1042/bj3550819

[52]. Gabbita, S. P., Aksenov, M. Y., Lovell, M. A., &Markesbery, W. R. (2002). Decrease in Peptide Methionine Sulfoxide Reductase in Alzheimer's Disease Brain. Journal of Neurochemistry, 73(4), 1660–1666. https://doi.org/10.1046/j.1471-4159.1999.0731660.x

[53]. Gao, J., Yao, Y., & Squier, T. C. (2001). Oxidatively modified calmodulin binds to the plasma membrane Ca-ATPase in a nonproductive and conformationally disordered complex. Biophysical journal, 80(4), 1791–1801. https://doi.org/10.1016/S0006-3495(01)76149-8

[54]. Tanaka, M., Gong, J., Zhang, J., Yamada, Y., Borgeld, H. J., & Yagi, K. (2000). Mitochondrial genotype associated with longevity and its inhibitory effect on mutagenesis. Mechanisms of ageing and development, 116(2-3), 65–76. https://doi.org/10.1016/s0047-6374(00)00149-4

[55]. Moskovitz, J., Bar-Noy, S., Williams, W. M., Requena, J., Berlett, B. S., &Stadtman, E. R. (2001). Methionine sulfoxide reductase (MsrA) is a regulator of antioxidant defense and lifespan in mammals. Proceedings of the National Academy of Sciences of the United States of America, 98(23), 12920–12925. https://doi.org/10.1073/pnas.231472998

[56]. Gruber, J., Ng, L. F., Poovathingal, S. K., & Halliwell, B. (2009). Deceptively simple but simply deceptive--Caenorhabditis elegans lifespan studies: considerations for aging and antioxidant effects. FEBS letters, 583(21), 3377–3387. https://doi.org/10.1016/j.febslet.2009.09.051

[57]. GARDNER T. S. (1948). The use of Drosophila melanogaster as a screening agent for longevity factors; the effects of biotin, pyridoxine, sodium yeast nucleates, and pantothenic acid on the life span of

the fruit fly. Journal of gerontology, 3(1), 9–13. https://doi.org/10.1093/geronj/3.1.9

[58]. Bailly, C. (2004). Active oxygen species and antioxidants in seed biology. Seed Science Research, 14(2), 93–107. https://doi.org/10.1079/ssr2004159

[59]. Huang, T. T., Carlson, E. J., Raineri, I., Gillespie, A. M., Kozy, H., & Epstein, C. J. (1999). The use of transgenic and mutant mice to study oxygen free radical metabolism. Annals of the New York Academy of Sciences, 893, 95–112. https://doi.org/10.1111/j.1749-6632.1999.tb07820.x

[60]. Kujoth, G. C., Hiona, A., Pugh, T. D., Someya, S., Panzer, K., Wohlgemuth, S. E., Hofer, T., Seo, A. Y., Sullivan, R., Jobling, W. A., Morrow, J. D., Van Remmen, H., Sedivy, J. M., Yamasoba, T., Tanokura, M., Weindruch, R., Leeuwenburgh, C., &Prolla, T. A. (2005). Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. Science (New York, N.Y.), 309(5733), 481–484. https://doi.org/10.1126/science.1112125

[61]. Selkoe D. J. (2003). Folding proteins in fatal ways. Nature, 426(6968), 900–904. https://doi.org/10.1038/nature02264

[62]. Kastman, E. K., Willette, A. A., Coe, C. L., Bendlin, B. B., Kosmatka, K. J., McLaren, D. G., Xu, G., Canu, E., Field, A. S., Alexander, A. L., Voytko, M. L., Beasley, T. M., Colman, R. J., Weindruch, R. H., & Johnson, S. C. (2010). A calorie-restricted diet decreases brain iron accumulation and preserves motor performance in old rhesus monkeys. The Journal of neuroscience : the official journal of the Society for Neuroscience, 30(23), 7940–7947. https://doi.org/10.1523/JNEUROSCI.0835-10.2010

[63]. Katewa, S. D., &Kapahi, P. (2010). Dietary restriction and aging, 2009. Aging cell, 9(2), 105–112. https://doi.org/10.1111/j.1474-9726.2010.00552.x

[64]. Friedman, D. B., & Johnson, T. E. (1988). Three mutants that extend both mean and maximum life span of the nematode, Caenorhabditis elegans, define the age-1 gene. Journal of gerontology, 43(4), B102–B109. https://doi.org/10.1093/geronj/43.4.b102

[65]. Baba, T., Shimizu, T., Suzuki, Y., Ogawara, M., Isono, K., Koseki, H., Kurosawa, H., &Shirasawa, T. (2005). Estrogen, insulin, and dietary signals cooperatively regulate longevity signals to enhance resistance to oxidative stress in mice. The Journal of biological chemistry, 280(16), 16417–16426. https://doi.org/10.1074/jbc.M500924200

[66]. Hsu, A. L., Murphy, C. T., & Kenyon, C. (2003). Regulation of aging and age-related disease by DAF-16 and heat-shock factor. Science (New York, N.Y.), 300(5622), 1142–1145. https://doi.org/10.1126/science.1083701

[67]. Gems, D., Sutton, A. J., Sundermeyer, M. L., Albert, P. S., King, K. V., Edgley, M. L., Larsen, P. L., & Riddle, D. L. (1998). Two pleiotropic classes of daf-2 mutation affect larval arrest, adult behavior, reproduction and longevity in Caenorhabditis elegans. Genetics, 150(1), 129–155. https://doi.org/10.1093/genetics/150.1.129

[68]. Kimura, K. D., Tissenbaum, H. A., Liu, Y., &Ruvkun, G. (1997). daf-2, an insulin receptor-like gene that regulates longevity and diapause in Caenorhabditis elegans. Science (New York, N.Y.), 277(5328), 942–946. https://doi.org/10.1126/science.277.5328.942

[69]. Wong, J. M., & Collins, K. (2003). Telomere maintenance and disease. The Lancet, 362(9388), 983–988. https://doi.org/10.1016/s0140-6736(03)14369-3

[70]. Lee, S.-H., & Min, K.-J. (2013). Caloric restriction and its mimetics. BMB Reports, 46(4), 181–187. https://doi.org/10.5483/bmbrep.2013.46.4.033

[71]. Petropoulos, I., & Bertrand Friguet. (2005). Protein maintenance in aging and replicative senescence: a role for the peptide methionine sulfoxide reductases. 1703(2), 261–266. https://doi.org/10.1016/j.bbapap.2004.08.018