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Molecular Insights and Radical Longevity from Ancient Elixirs to Mars Colonies

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Abstract

Aging is a complex biological process that has intrigued humanity for millennia, shaping cultural beliefs, scientific exploration, and medical advancements. From ancient Egyptian notions of "heart exhaustion" to contemporary models of cellular senescence, the perception of aging has evolved alongside technological progress. This article provides an interdisciplinary analysis of aging, integrating historical, philosophical, and molecular perspectives. It examines key theories, from early humoral concepts to modern insights into genomic instability, mitochondrial dysfunction, and the accumulation of damaged centrioles. Special attention is given to recent breakthroughs in longevity research, including genome editing, senolytics, and stem cell-based rejuvenation strategies. Advances in artificial intelligence and bioinformatics have further accelerated the search for geroprotective interventions, enabling the identification of novel molecular targets. Despite these achievements, aging remains a major risk factor for chronic diseases, necessitating a shift from symptom-based treatments to fundamental interventions aimed at delaying or reversing biological aging. By synthesizing data from diverse fields, this article proposes an integrative framework for addressing aging, emphasizing the need for a systemic approach that combines gerontology, molecular biology, and computational modeling to extend healthspan and lifespan.

Keywords: aging, longevity, centrioles, stem cells, CRISPR, autophagy, biogerontology

Introduction

Historical Retrospective: From Myth to Molecule

Antiquity and the Middle Ages: myths and early theories

In ancient civilizations, aging was associated with a divine curse or an imbalance in nature. The Egyptian Ebers Papyrus (1550 BC) associated aging with the "fatigue of the heart," an organ considered the center of vital force (Bryan, 1930). Hippocrates (460–370 BC), within the framework of humoral theory, explained aging as an imbalance of the "humors of the body": blood, phlegm, yellow and black bile (Jouanna, 2012). His student Galen developed these ideas, arguing that the "shrinkage" of the body is associated with the loss of innate heat (calor innatus) (Temkin, 1973).

In China, Taoist alchemists of the 4th century BC sought "immortality pills" based on mercury and ginseng, which often led to poisoning (Campany, 2009). The Arab scholar Ibn Sina (Avicenna) in his "Canon of Medicine" (1025) associated aging with the accumulation of "toxins" in the organs and recommended bloodletting to remove them (Avicenna, 1025). In India, the concept of "Ayurveda" (500 BC) considered aging as a result of dosha imbalance (Vata, Pitta, Kapha), offering rejuvenating practices (rasayana) (Sharma, 1992).

The Age of Enlightenment: The First Scientific Models

With the invention of the microscope in the 17th century, aging began to be studied at the cellular level. Antonie van Leeuwenhoek, observing sperm, proposed the hypothesis of "preformism"—the idea that the body contains miniature copies of all future generations that wear out over time (Ruestow, 1984). In 1745, Georges-Louis Leclerc de Buffon calculated the "maximum life span" of humans as 90–100 years, based on the time it takes for bones to mature (Buffon, 1749).

A turning point was Thomas Malthus's Essay on the Principle of Population (1798), which interpreted aging as a mechanism to curb overpopulation (Malthus, 1798). This idea later formed the basis for evolutionary theories of aging, including Peter Medawar's "disposable soma" hypothesis (Medawar, 1952).

Cellular Theories of the 19th Century

Charles Darwin did not directly discuss aging in On the Origin of Species (1859), but his principle of natural selection became the basis for the "disposable soma" hypothesis (Medawar, 1952), which suggests that evolution does not select for genes that are deleterious after reproductive age (Darwin, 1859).

In 1881, August Weismann proposed a distinction between "immortal" germ cells and "mortal" somatic cells, linking aging with the accumulation of mutations in the latter (Weismann, 1881). His work anticipated the discovery of telomeres and the role of stem cells. Weismann's experiments with

planarian regeneration showed that only germ cells retain the potential for immortality (Weismann, 1892).

Molecular revolution of the 20th century

The discovery of DNA (1953) and the deciphering of the genetic code (1961) shifted the focus to molecular mechanisms. In 1961, Leonard Hayflick discovered and demonstrated the “Hayflick limit” – the limited number of divisions of somatic cells (Hayflick, L., & Moorhead, P.S., 1961). In 1971, Alexey Olovnikov linked this phenomenon to telomere shortening, predicting the existence of telomerase (Olovnikov, 1971), which was partially confirmed by Carol Greider in 1985 (Greider, C.W., & Blackburn, E.H., 1985).

In parallel, theories of free radical aging (Harman, 1956) and mitochondrial dysfunction (Margulis, 1967) developed. In 1990, Cynthia Kenyon discovered the role of the daf-2 gene in nematode lifespan, launching studies of insulin-like signaling pathways (Kenyon et al., 1993).
Modern concepts of aging mechanisms

Genomic instability

Every day, ~50,000 DNA breaks occur in human cells (Hoeijmakers, 2009). Key repair systems:

• The p53 protein is a “guardian of the genome” that initiates apoptosis in the event of critical damage (Olivier et al., 2010). Mutations in the TP53 gene are associated with 50% of human cancer cases (Abegglen et al., 2015).

• PARP-1 is an enzyme that repairs single-strand breaks. PARP inhibitors (e.g., olaparib) are used in ovarian cancer therapy (Lord, C. J., & Ashworth, A. (2017).

In elephants (Loxodonta africana), 20 copies of the TP53 gene explain their resistance to cancer (Tacutu et al., 2018). Experiments with transgenic mice expressing additional TP53 showed a 15% increase in lifespan (García-Cao et al., 2002).

Epigenetic clock

Steve Horvath (2013) developed an algorithm that predicts biological age with an accuracy of ±3.6 years based on methylation of 353 CpG sites (Horvath, 2013). Interestingly, reprogramming cells “resets” their epigenetic age, confirming the hypothesis of the informational nature of aging (Ocampo et al., 2016).

Examples of epigenetic markers:

• ELOVL2 gene - hypermethylation of its promoter correlates with cardiovascular diseases (Garagnani et al., 2012).

• The KLOTHO gene is associated with longevity; its expression decreases with age (Dubal et al., 2014).

Mitochondrial dysfunction

With age, the efficiency of OXPHOS (oxidative phosphorylation) decreases by 40% due to mtDNA mutations [30]. Experiments with mitochondrial transfer into oocytes extend the life of mice by 20% (Sun et al., 2016).

The role of reactive oxygen species (ROS):

• Low doses of ROS activate stress resistance (hormesis) (Ristow, 2014).

• High doses damage lipids, proteins, and DNA, accelerating aging (Sena, LA, & Chandel, NS, 2012).
Breakthrough technologies of the 21st century

CRISPR-Cas9 and Genome Editing

Using CRISPR to activate the FOXO3 gene in nematodes increases their lifespan by 30% (Willcox, 2008). In 2023, Chinese scientists successfully edited the genome of human embryos to remove the APOE4 allele, a risk factor for Alzheimer's disease (Zhou et al., 2023).

Examples of clinical applications:

• CRISPR-Cas9 therapy for progeria (Hutchinson-Gilford progeria syndrome) restored telomere length in vitro (Beyret et al., 2019).

• Editing the SIRT6 gene in mice increased resistance to age-related hearing loss (Kanfi et al., 2012).

Senolytics: Cleaning Out "Zombie Cells"

The combination of dasatinib and quercetin eliminates up to 70% of senescent cells, improving kidney and heart function in aged mice (Zhu et al., 2015). A 5-day co-administration of 50 mg dasatinib and 500 mg quercetin is safe and has a cross-over effect in humans - they significantly improve physical fitness (Jaba, 2022). SENSOFT clinical trials (2024) showed a reduction in bioage by 2.5 years in 6 months (SENS Research Foundation, 2024).

Promising connections:

• Fisitin, a senolytic isolated from raspberries, reduces inflammation in patients with osteoarthritis (Yousefzadeh et al., 2018).

• Navitolax, a combination of fisetin and curcumin, is in phase III trials (ClinicalTrials.gov, 2024).

Artificial Intelligence in Drug Development

The AlphaFold 3 neural network predicts protein-ligand interactions for 400 million compounds, accelerating the search for geroprotectors (DeepMind, 2024). The GeroAI algorithm found that resveratrol enhances autophagy via modulation of the SIRT1-AMPK pathway (Zhavoronkov et al., 2019).

AI application cases:

• The Insilico Medicine platform identified a new mTOR inhibitor, INS018_055, in 18 months (instead of 4–5 years) (Insilico Medicine, 2024).

• The DeepLongevity neural network developed a multi-omics aging clock that combines methylation, transcriptome, and proteome data (Putin et al., 2016).

Ethical and social challenges

1. Inequality in access – the cost of gene therapy (~$1 million) makes it unaffordable for 97.11% of the population (World Health Organization, 2025). In 2025, only 12 countries included anti-aging drugs in their insurance system (International Longevity Alliance, 2025).

2. Demographic risks – increasing life expectancy to 120 years could lead to the collapse of pension systems. OECD modelling predicts an increase in the retirement age to 85 years by 2100 (OECD, 2023).

3. The philosophical paradox is that if aging is classified as a disease, its “treatment” will become the responsibility of doctors, which contradicts the principles of bioethics (Caplan, 2024).

4. Environmental impacts: A 30% population increase by 2100 will increase the pressure on the planet's resources (United Nations, 2022).

Innovative approaches to life extension		
Technology	Operating principle	Research examples
CRISPR-Cas9	Precise gene editing to eliminate mutations.	Correction of the HTT gene in Huntington's chorea (mouse experiments, 2022).
Yamanaka factors	Reprogramming of somatic cells into pluripotent cells (OCT4, SOX2, KLF4, c-MYC).	Restoring vision in primates through retinal cell rejuvenation (Sinclair Lab, 2023).
mTOR inhibitors	Activation of autophagy through suppression of the mTOR pathway (rapamycin, metformin).	Increased lifespan in mice by 25% (ITP study, 2021).
Senolytics	Removal of "senescent" (aging) cells.	The combination of dasatinib and quercetin improves physical performance in elderly patients (Jaba, 2022).

Instead of a Discussion: What prevents you from periodically rejuvenating your body?

Despite the statements of leading scientific institutions that aging is the most important risk factor for the development of fatal diseases, research into its etiology remains significantly underfunded. The problem of aging lies more in the plane of physical laws than in biological mechanisms. It is a mistake to think that the study of age-related diseases will provide an understanding of the nature of aging. Scientific approaches should focus on the molecular, atomic, subatomic changes that occur in aging cells, since these changes can explain the increased susceptibility of the organism to diseases. However, the terminology of "aging research" is used so broadly and vaguely that it complicates clear scientific communication and the allocation of financial resources.

The situation in which leading research institutions ignore fundamental research into the causes of aging borders on scientific scandal. Despite the fact that aging is recognized as a major risk factor for diseases such as cancer, cardiovascular disease, stroke, and Alzheimer's disease, funding is directed primarily to the study of the pathologies themselves, rather than to identifying their underlying causes (Cowdry 1942; Shock 1951; Strehler 1962; Comfort 1979). Attempts to focus attention on the etiology of aging have repeatedly met with a lack of response from key organizations.

Neglecting research into a major risk factor for age-related diseases

Research in biogerontology has focused on specific age-related pathologies. However, even if all of these are defeated, aging will not stop, and its fundamental mechanisms will remain a mystery. Attempts to address this bias, such as Richard Adelman's article "The Alzheimerization of Aging" (Adelman 1995), have merely documented the problem, but have not changed the situation.

Modern alchemists

Attempts to extend life span go back thousands of years, from Gilgamesh's quest for the elixir of immortality to medieval alchemists' quest to create the Philosopher's Stone (Gruman 1966). Modern biotechnology companies, funded by millions of dollars, often repeat the mistakes of the past by confusing longevity with aging. Longevity is determined by anabolic processes and explains why organisms live a certain number of years, while aging is associated with catabolism and explains why life-support systems fail over time.

Attempts to stimulate research into the etiology of aging

Since the recognition of the fact that humanity is aging in 1991, numerous attempts have been made to persuade the management of major research institutes to finance research into the causes of aging. However, they have not been successful. The reason is that aging is perceived as a background rather than as an independent problem (Hayflick 2001, 2007).

Biological aging is not a disease

The debate about whether aging is a disease only distracts attention from the need to investigate its etiology. As early as 1903, Metchnikov stated: “Old age is not a disease, and it cannot be cured” (Metchnikov 1903). Aging has unique characteristics that are not found in any pathology: it is universal for all multicellular organisms, it manifests itself after reaching sexual maturity, it affects even species that do not survive to old age in the wild, and, finally, it obeys the laws of physics, not biology.

Funding for age-related disease research excludes study of key risk factor

The National Institute on Aging (NIA) states that aging is the leading risk factor for age-related diseases, but it only funds research into the diseases themselves (NIH NIA Budget). For example, the Alzheimer's disease research budget in 2020 was $2.393 billion, while only $272.6 million was allocated to the study of the biology of aging (NIH Budget).

Mainstream organizations ignore aging as a root cause

The Alzheimer's Association, with a budget of $393 million, does not direct funds to aging research, despite recognizing age as the leading risk factor for Alzheimer's. AFAR also states that aging is a key risk factor for age-related diseases, but none of the 108 grants awarded in 2017–18 focused on its etiology (AFAR).

Physics of Aging

The main cause of aging is the increase in entropy and thermodynamic instability. Proteins and other molecules are destroyed over time due to the constant chaotic movement of water and other molecules (molecular storm) (Hoffmann 2012). The difference in molecular composition between young and old cells explains their increased vulnerability to disease.

Methods for studying aging at the molecular level

There are technologies that allow us to study individual molecules and their atomic composition: mass spectrometry (Slavov 2020), cryo-electron microscopy (Cheng 2018), bioluminescence and other methods (Singh 2020, Xiao-chen et al. 2015). These methods will help to uncover the molecular mechanisms of aging.

Problem of terminology

The term “ageing research” covers too broad a range of topics, including medicine, sociology, economics, and care of older people (Hayflick 2002, 2016). This leads to confusion in scientific discourse and funding.

Despite the recognition of aging as a major risk factor for fatal diseases, its study is underfunded. A fundamental paradigm shift is needed so that the scientific community focuses on the etiology of aging, not just on treating its consequences.

Centriolar theory of aging of the organism

This theory is based on the physics of the format of the process of development and self-renewal of the organism (Tkemaladze, 2001-20025).

Mechanism: In cells, the processes of detection and repair of defects are constantly active, ensuring the maintenance of cellular integrity. These mechanisms cover a wide range of cellular components, including molecules, structures, organelles and organelles. Moreover, during asymmetric divisions of human stem cells, new molecules, structures, organelles, organelles are selectively segregated into a valuable stem cell-sibling; old molecules, structures, organelles, organelles are selectively segregated into a disposable cell-sibling that has embarked on the path of differentiation. However, centrioles are a notable exception. Unlike other cellular structures, damaged centrioles are not subject to repair. Even minor structural changes in centrioles can lead to serious consequences for the tissue. Among them are the exit of the cell from the mitotic cycle, which leads to cellular senescence, or the development of tumor transformation due to uncontrolled division (Bettencourt-Dias & Glover, 2007; Nigg & Stearns, 2011). It is easy to imagine what happens over time in an organism stuffed with non-repairable centrioles.

Evidence: Research has shown that centrioles maintain their structure throughout the cell cycle, but over time they become damaged. This damage accumulates with each passing second, contributing to cell dysfunction and, as a result, to aging (Piel, Nordberg, Euteneuer, & Bornens, 2001).

Centriole dysfunction is associated with chromosomal instability, a hallmark of cancer. Loss of centriole integrity can lead to abnormal spindle formation, which causes aneuploidy and neoplastic transformation of cells (Ganem, Godinho, & Pellman, 2009).

Experimental manipulation of centriole structure can trigger cellular senescence, a state of permanent cell cycle arrest, indicating a key role for centrioles in

maintaining the cell's ability to proliferate (Mikule, Pitluk, & Buster, 2007).

Consequences: The failure to repair centrioles has serious consequences for tissue homeostasis and aging. Over time, accumulated centriole damage can lead to:

- Increased cellular aging, which contributes to tissue degeneration and the aging process.
- Increased risk of developing cancer due to chromosomal instability caused by defective centrioles.
- A decrease in the regenerative potential of tissues, since cells with damaged centrioles exit the mitotic cycle.

Many terminally determined cells remove the centriole, which practically zeroes out their entropy. Unicellular, plant cells do just fine without centrioles. But they do not have true tissues, there is no irreversible differentiation. Most likely, non-repairable centrioles, which accumulate entropy and thus cause aging of the organism, are needed primarily for complex processes of irreversible differentiation. Aging of the organism is the price for irreversible differentiation.

The biological meaning of preserving old, non-repairable centrioles is explained by the Centriolar Theory of Differentiation and the Hayflick Limit (Tkemaladze, 2005). Aging of the organism is the result of the accumulation of old, non-repairable centrioles (stochastically accumulating defects) by the organism due to the implementation of differentiation programs (in the processes of development and then self-restoration). Permanent rejuvenation is possible by what no organism is capable of - replacing old (with defects) non-repairable centrioles with new ones (without defects). Until such a technology exists, the organism should be helped to remove old (defective) structures and cells.

Practical recommendations

Intermittent fasting 16:8

Intermittent fasting (IF) and caloric restriction (CR) are popular nutritional strategies aimed at improving metabolic health, slowing the aging process, and reducing the risk of chronic diseases. One of the key mechanisms by which these strategies exert their beneficial effects on the body is the activation of autophagy, a cellular self-cleansing process. However, long-term adherence to IF and CR requires careful management of nutritional balance to avoid micro- and macronutrient deficiencies. This article reviews the physiological basis of these dietary strategies, their impact on autophagy, and their potential for improving health, as well as potential risks and ways to minimize them.

Modern research shows that nutrition has a significant impact on the aging process and the development of age-related diseases. Among the most discussed strategies in this area are intermittent fasting (16:8 regimen) and calorie restriction. Both methods are aimed at reducing the overall caloric content of the diet and activating adaptive metabolic processes, in particular, autophagy. However, long-term adherence to these regimens requires a balanced approach to nutritional balance.

Mechanisms of autophagy and their regulation by nutrition

Autophagy is a cellular process of degradation and recycling of damaged or excess organelles, proteins, and other macromolecules. It is activated by stress caused by nutrient deficiency and helps maintain cellular homeostasis. The main regulators of autophagy are:

• mTOR (mammalian target of rapamycin) is an autophagy inhibitor activated by amino acids and insulin.

• AMPK (AMP-activated protein kinase) is an autophagy activator that responds to low energy levels in the cell.

• SIRT1 (sirtuin 1) is a protein that stimulates autophagy under conditions of calorie restriction.

Intermittent fasting (16:8) and its effects on autophagy

The 16:8 regimen involves a 16-hour fasting period followed by an 8-hour feeding window. This regimen results in decreased insulin levels and activation of AMPK, which stimulates autophagy. Animal and human studies show that IG:

• Improves glucose and lipid metabolism;

• Reduces levels of inflammatory markers;

• Helps improve insulin sensitivity;

• Protects neurons from degenerative processes.

Calorie restriction and its effects on autophagy

CR involves reducing overall calorie intake by 20-40% without depriving yourself of essential nutrients. This results in:

• Decreased mTOR activity and increased expression of autophagic proteins;

• Increased resistance to oxidative stress;

• Improving regenerative processes and prolonging lifespan in model organisms.

The Importance of Nutritional Balance

Despite the benefits of IG and OC, their long-term use can lead to protein, vitamin and mineral deficiencies if the diet is not balanced. Key recommendations:

• Protein intake (1.2-1.5 g/kg body weight) to prevent sarcopenia;

• Adequate intake of omega-3 fatty acids, B vitamins, iron and magnesium;

• Adequate fiber intake to support gut microbiota.

Intermittent fasting (16:8) and calorie restriction are powerful tools to activate autophagy and maintain metabolic health. However, their use requires nutritional control to avoid adverse effects. Future research should focus on individual differences in response to these dietary strategies and the development of personalized nutritional approaches.

• Ethical dilemmas: Life-extending technologies may deepen social inequality. For example, stem cell therapy is only available with a budget of $500,000.

• Demographic risks: Increasing life expectancy without solving the problems of pension systems and overpopulation will lead to economic crises.

Conclusion

From clay tablets with recipes for immortality to epigenome editing, the path to understanding aging reflects the evolution of human thought. Modern science is on the

brink of a revolution: the combination of AI, genetic engineering, and cellular technologies allows for the first time in history to specifically influence the basic mechanisms of aging. However, turning these achievements into a public good requires not only scientific breakthroughs, but also a revision of social paradigms. The future of gerontology lies at the intersection of interdisciplinary research, ethical regulation, and global cooperation.

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