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Advancements and Challenges in Anti-aging Research: Exploring Anti-aging Pathways to Longevity and Disease Prevention

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ABSTRACT

Anti-aging research has become central to understanding the biological processes that regulate aging and affect the health span and lifespan. This narrative review summarizes the evolution of anti-aging research from early theories to major 20th-century breakthroughs, which established a foundation for this research, particularly in cellular senescence and antioxidant mechanisms. Now, contemporary research defines aging as the complex interplay shaped by genetic, molecular, and environmental factors. Revolutionary concepts such as caloric restriction, oxidative stress, telomere biology and cellular aging explained the basic mechanisms of aging. Current genetic and molecular approaches, regenerative medicine, and elaboration of anti-aging compounds such as NAD^+ enhancers, metformin, and rapamycin push the range of therapeutic strategies for aging diseases. Moreover, genetic findings of longevity, such as SIRT1 and FOXO3, with their genome-editing technologies like CRISPR, opened new directions for interventions into aging. Advancements in stem cell therapies, tissue engineering, and personalized medicine aim to extend healthy longevity. Despite these advances, anti-aging research has many difficulties, such as ethical, scientific, and regulatory ones. However, anti-aging research may help to prevent chronic diseases, improving the quality of life, and socioeconomic and psychological outcomes. Future directions point toward emerging technologies, interdisciplinary collaborations, and global contributions of researchers to extend human health and improve lifespan.

1. INTRODUCTION

Ever since the dawn of civilization, humans have been exploring methods for their fascination with longer and healthy lives. The scientific study focused on this purpose of extending healthy span and slowing down the effects of aging is today best known as anti-aging research. This multi-disciplinary research is focused on understanding the biological mechanisms to stop the aging process or at least halt it. A wide range of interventions, ranging from lifestyle changes to pharmacological approaches, regenerative medicines, and genetic engineering, have been explored for this purpose. According to UN research, in 2050, the population of people above 60 is over 2 billion [1]. With the increase in the elderly population, the prevalence of aging-related diseases has shot up, leading to more pressure on already strained healthcare systems and anti-aging management and the cost associated with these. Thus, this research holds great potential in solving this problem, contributing to economic stability, and managing health problems [2]. This review aims to provide a comprehensive outlook on the evolution of anti-aging research, highlighting historical milestones, current innovations and interventions, and possible future directions. Most of the early theories on fighting off aging and their practice were related to mystic remedies and traditional medicine. In the 20th century, important developments included the discovery of antioxidants and further developments in cellular biology, which reshaped

understandings of aging [3].

The pioneering work of a few researchers, such as Leonard Hayflick and his theory of cellular senescence, set the stage for the modern era of anti-aging research. The scientific thought about aging evolved from a very simple, straightforward concept to complex biological processes, to genetics, epigenetics, and cellular repair mechanisms [4]. Anti-aging research has made tremendous progress in recent years, in parallel with the advancements in molecular biology and genetic engineering, which have enhanced our knowledge of the molecular processes of aging. Research on longevity genes such as SIRT1 and *FOXO3* has also improved our understanding of aging [5]. Nowadays, the most sought-after interventions, i.e., regenerative medicines and stem cell-based therapies, have great potential in this regard. Pharmacological interventions such as rapamycin and metformin have also attracted a lot of scientific and public interest [6]. Anti-aging research has great potential in improving healthy span, overall life span, quality of life, relieving burden on healthcare systems, as well as psychological and cultural implications. However, there are many barriers to this research, ranging from negative public perception to misinformation and ethical dilemmas to regulatory challenges. In this review, we have discussed all of these aspects in detail.

2. Historical Milestones in Anti-Aging Research

Anti-aging practices have evolved significantly over the years, from simple milk baths in ancient Egypt and Ayurvedic herbal products to hormonal therapies and the use of retinoids in the previous century. In the modern era, Botox, stem cell therapies, and gene editing technologies have taken over the reins of anti-aging interventions. As of today, anti-aging research is a consortium of ancient wisdom as well as practices and advancements in science.

2.1 Humoral Theory

The Humoral Theory was pioneered by Hippocrates (370 BCE) and, later, Galen (200 CE) in ancient Greece [7]. According to this theory, the human body is composed of four humors (bodily fluids) named as blood, phlegm, black bile, and yellow bile, each of which is synonymous with air, water, earth, and fire, respectively. This theory postulates that these humors determine the health, aging, and temperament of each individual [8]. Imbalances in humors were thought to lead to aging and diseases. This states that humors are balanced at birth, and as a person ages, the balance of humors in the body changes depending on the lifestyle and diet of a person. For example, excessive black bile in the body was expected to lead to aging and melancholy [9]. During that era, physicians used to counteract the effects of aging with prescriptions aimed at restoring the balance of humors. The prescriptions included a change in diet, bloodletting, and herbal remedies. Although these early understandings lacked a scientific or biological basis, they provided an initial framework that pioneered research in this area [10].

2.2 Elixirs and Alchemy: From the Medieval Era to the Renaissance

Throughout the Middle Ages and during the Renaissance, the art of alchemy was used in search of longevity and often immortality. The alchemist, part philosopher, part proto-scientific experimenter, searched for an "Elixir of Life," a mythical substance said to bestow on those who consumed it eternal youth or possibly even immortality. This was also closely associated with the often major, related quest for what was called the “Philosopher's Stone”, supposedly capable of changing the base metals into gold and also enabling the prolongation of life indefinitely [11]. Alchemists like Paracelsus started preaching that substances could restore the body. Often termed the father of toxicology, Paracelsus concluded that aging was a natural order of things; it was undoubtedly possible, if not to eliminate aging, then to postpone or significantly decrease its effects using defined minerals, chemicals, and a cocktail of herbs. The logic he applied was that a long life relied on mastery of understanding the body's chemistry [12]. While alchemy was practically mystical and speculative, it contributed something to early pharmacology. Alchemists experimented with various mixtures of substances that led to the discovery of their use, later influencing medical practices, including the use of minerals and compounds in contemporary medicine [13].

2.3 Vitalism and the Vital Force

Simultaneously with the mechanical explanation, in the 17th and 18th centuries, the theory of Vitalism was taking center stage against the conceived explanation for life and aging. According to the vitalism theory, living organisms are controlled by a "vital force" or "life force" independent of those physical and chemical systems characterizing all non-living matter. This was supposedly in charge of the development, metabolism, and maturation or aging of living things [14]. This vital force is diminished with time, allowing aging to set in. They also believed that such a gradual depletion of the force may bring a decline in physical and mental aspects. Unlike earlier humoral theories, vitalism attempted an explanation for aging on a more abstract metaphysical level. Although the ritualistic view eventually was discredited by advances in biology and chemistry, it nevertheless played a crucial role in early scientific thought by encouraging the study of the processes of living organisms beyond mechanistic explanations and hence laid a limited foundation for the later cellular and molecular biology-based understanding of aging [15].

2.4 Key Breakthroughs in the 20th Century

In the 1930s, Clive McKay and his colleagues at Cornell University discovered that limiting the caloric intake of rats significantly extended their lifespan. The process, now termed caloric restriction (CR), would later be studied in great detail using a variety of organisms such as yeast, worms, flies, and mammals [16]. Although details of the exact mechanisms of CR are still under investigation, it is believed to extend lifespan by reducing metabolic rates, diminishing oxidative stress, and altering signaling pathways such as insulin/IGF-1 that are involved in growth and aging. The finding of CR-induced longevity promoted a whole new era in aging research,

inclusive of the pursuit of CR mimetics, namely. These drugs could mimic the effects of CR without drastic dietary restrictions. Denham Harman proposed this phenomenon in 1956. Free radical theory of aging suggests that highly reactive molecules with unpaired electrons, called free radicals, cause cell damage like DNA, Proteins and Lipids. This oxidative damage was considered a major factor in aging and developing age-related diseases [17]. In the early 1960s, Leonard Hayflick and his coworker Paul Moorhead discovered that human cells have a finite capacity to divide. This phenomenon, later called the "Hayflick limit", demonstrates that cells can only divide 40-60 times before going to a state of senescence where cell division stops, but cells remain metabolically active [18]. There are repetitive DNA sequences at the ends of chromosomes to save them from degeneration due to cell divisions, called telomeres. Elizabeth Blackburn, along with her colleagues, discovered an enzyme known as telomerase. The enzyme rebuilds telomeres, allowing the cells to divide beyond their capacity. This enzyme is highly active in cancerous cells. In the 1990s, specific genes controlling longevity began to be identified. The age-1 gene was identified, among others, by Cynthia Kenyon in the nematode worm Caenorhabditis elegans and shown to double the life span of the worm when mutated. Other key genes and pathways controlling life span were, and continue to be, rapidly identified, including the insulin/IGF signaling pathway [19].

3. Current Innovations in Anti-Aging Research

3.1 Genetic and Molecular Approaches

Bio-gerontology is the subfield of gerontology that focuses on biological mechanisms involved in the process of aging and the relevant diseases [20]. Biogerontology is a multidisciplinary research field on comprehending biological aging's effects, causes, and mechanisms. Of special significance is that bio-gerontologist Leonard Hayflick has calculated that human life expectancy is around 92 years. He thinks that in the absence of innovative ways to combat aging, humanity is going to be constrained by this life expectancy [21]. These genetic factors are linked to stress response, DNA repair, cellular maintenance, and longevity. As the organisms age, their cells also acquire damage from environmental stress, like ultraviolet light toxins, as well as internal processes, including oxidative stress. Cells sustain a continuous rate of DNA damage. The capability of efficient repair of DNA damage through genes such as ATM, BRCA1, and TP53 maintains DNA in a non-damaged state. An impaired capacity for DNA repair has been associated with both aging and age-related diseases, including cancer [22]. Aging has been characterized as a chronic low-grade inflammation state, and is thus sometimes referred to as Inflammaging [23]. Candidate genes include those responsible for regulating inflammatory responses, such as NF-KB. A decrease in chronic inflammation promotes longevity by reducing the incidence of age-related diseases such as cardiovascular disease and diabetes [24]. Impairment of the insulin/IGF-1 signaling pathway (IIS) has been variously associated with the extension of life span in organisms ranging from nematode worms to mammals. It represents one of the most important mechanistic pathways in nutrient sensing and energy metabolism. Reduced insulin signaling is characterized by more stress resistance, retarded cellular growth, and enhanced cellular repair processes. These factors are of paramount importance in the quest for longevity and to delay age-related diseases. IIS-reducing mutations orchestrate longevity in animal models by triggering pathways that enable cells to cope more effectively with stress and nutrient availability [25].

3.1.1 Senolytics

Senolytics are agents (small molecules, peptides) that remove senescent cells by targeting their dependence on anti-apoptotic, pro-survival pathways (e.g., BCL-2 family, PI3K/AKT, HSP90, ephrins), thereby lowering the senescence-associated secretory phenotype (SASP) and the downstream pro-inflammatory and tissue-remodelling damage [26]. Representative compounds include dasatinib + quercetin (D+Q), navitoclax (BCL-2/BCL-xL inhibitor), fisetin, and newer peptide or conjugate senolytics aiming for cell-type specificity. In preclinical mouse studies, intermittent or late-life treatment with D+Q has improved physical function (walking speed, endurance, grip strength), reduced frailty, preserved tissue structure (intervertebral discs), lowered markers such as p16, p21 and SASP cytokines, improved metabolic function, and in some cases extended median and maximal lifespan [26]. For example, fisetin given in old or progeroid mice reduced markers of senescence across tissues and extended lifespan. However, human evidence is still sparse: small pilot studies of D+Q show reductions in senescence biomarkers in patients with diabetic kidney disease or pulmonary fibrosis, but robust clinical endpoints remain to be established [27].

3.1.2 Caloric-restriction (CR) Mimetics

Caloric-restriction (CR) mimetics are designed to reproduce the metabolic benefits of CR by modulating nutrient-sensing pathways such as mTOR, AMPK, sirtuins and insulin/IGF-1 signaling [28]. Thereby enhancing stress resistance, autophagy and metabolic efficiency mechanisms consistently linked to lifespan extension in model organisms [29]. Prototypical agents include rapamycin and its analogues, which inhibit mTORC1, stimulate autophagy and robustly extend median and maximal lifespan in multiple mouse strains (with short or intermittent dosing lessening immunosuppression); metformin, which activates AMPK and exerts pleiotropic effects on mitochondrial function, inflammation and insulin signaling (epidemiology and rodent studies support metabolic and health span benefits, and the large TAME trial aims to test age-related endpoints); and sirtuin activators such as resveratrol, which show SIRT1-linked benefits in preclinical models but have mixed translational evidence. In humans, data are still limited: low-dose or intermittent rapamycin regimens are being explored with small trials suggesting improved immune markers, and metformin is widely prescribed for diabetes. Still, it is only now being evaluated formally as a seroprotective, and evidence for resveratrol and newer

sirtuin activators remains inconsistent [30].

3.1.3 Gene Editing

Gene therapies prevent aging by targeting the genetic effects of aging cells. Gene therapy targets telomere attrition, repairing poor DNA, and oxidative stress pathways. Regenerative medicine uses stem cell transplantation to reprogram or replace old cells. Key approaches include AAV-mediated gene delivery, CRISPR/Cas-based genome editing to correct or regulate genes, and in vivo or ex vivo cellular therapies. Representative examples include telomerase (TERT) gene therapy, in which systemic AAV-TERT delivery in mice increased median lifespan by approximately 13-24% and improved tissue features, and partial cell reprogramming, which uses temporary expression of Yamanaka factors (OCT4, SOX2, KLF4) to rejuvenate tissues and increase lifespan in preclinical studies while being carefully controlled to avoid tumorigenesis. CRISPR-based editing of DNA repair, senescence, or metabolic genes also holds promise for gene correction and epigenetic manipulation in animal models [26]. The need for safe and tissue-specific delivery in humans (due to AAV immunity and tropism concerns), the possibility of off-target or on-goal mutations with CRISPR, the oncogenic risks of telomerase activation or mis-regulated reprogramming, species differences in telomere biology and the susceptibility of most cancers, the difficulty of extrapolating from mice to humans, and significant regulatory and financial barriers are some of the significant translational obstacles that these successful proofs of concept must overcome [31].

3.1.4 Key Discoveries in Gene Longevity

Sirtuins are a family of nicotinamide adenine dinucleotide (NAD+)- dependent deacetylases implicated in the regulation of important cellular processes, including DNA repair, metabolism, gene expression, and cellular stress responses. Of these, SIRT1 has been the most studied with aging and longevity [25]. SIRT1 is becoming increasingly recognized as a key regulator of the integrity of the genome, either directly through commanding DNA repair pathways for the restoration of double-strand breaks or indirectly by preventing their accumulation with aging. SIRT1 delays cellular aging by regulating chromatin structure and modifying gene expression. SIRT1 allows mitochondrial biogenesis and enhances mitochondrial function through the activation of PGC-1α, enabling cells to meet their energetic needs more efficiently, especially under calorie-restricted conditions. Improved mitochondrial function has been related to longevity enhancement in animal models [32]. SIRT1 overexpression contributes to longevity in animal models like mice by protecting them against age-related metabolic diseases. Resveratrol is a polyphenol from red wine, now shown to give CR-like effects by activating SIRT1, thereby improving mitochondrial function and oxidative stress responses [33].

The *FOXO* family of transcription factors is one of the central regulators of longevity and controls the expression of genes related to cellular responses to stresses, antioxidant defense, metabolism, and apoptosis. Of these, *FOXO3* is an important member, associated with human longevity and protection against age-related diseases [34]. *FOXO3* regulates the transcription of genes that counteract oxidative stress, including superoxide dismutase and catalase, neutralizing ROS. High levels of ROS lead to cell damage, inflammation, and aging. *FOXO3* protects cells from this oxidative damage, hence promoting longevity. The centenarian populations have been studied to find out special variants of the *FOXO3* gene responsible for extended human life with protection from age-related diseases of cardiovascular nature and cancer [35]. These genetic variants increase *FOXO3*'s ability to modulate stress response pathways, hence promoting the longevity of these people. *FOXO3* also has a crucial function in maintaining stem cell functionality. With the progress of aging, the efficiency of stem cells that regenerate tissues declines. *FOXO3* maintains the stem cell pools by preventing DNA damage and fostering mechanisms of cellular repair, another important aspect of healthful aging [36]. In the case of the latter, targeting longevity genes, CRISPR modifies genes such as SIRT1, *FOXO3*, and other longevity candidate genes in animal models. Overexpression or suppression enables the study of new means of extending the life span and protecting against age-related diseases. Such that, for instance, in mice, CRISPR-mediated upregulation of SIRT1 improves mitochondrial function and resists age-related decline [37].

Scientists are trying to use CRISPR technology to reverse certain aspects of aging in the cells. One promising area involves the modification of telomerase, an enzyme that elongates telomeres, the protective caps on the ends of chromosomes; their shrinkage is a general feature of aging. The results of one such study, which reactivated human telomerase using CRISPR, indeed showed elongated telomere length and reduced markers of cellular aging [38]. Recently, CRISPR has begun to be applied to mutation correction that is associated with aging, with the hope of improving DNA repair mechanisms. The first example includes the use of CRISPR technology to repair age-related mutations in mitochondrial DNA, one of the key sites of damage. CRISPR-based therapies in the near future may be employed in treating diseases of aging anchored on sequential accumulation of specific genetic mutations [39]. Most of the life-threatening diseases, such as Alzheimer's and Parkinson's, do have a genetic predisposition; fortunately, CRISPR does have the ability to correct such mutations and may slow down neurodegenerative progression. Klotho protein protects the neurons, enhances antioxidant defenses, and repairs the injured nerve fibers [40]. These results suggested that approaches aimed at increasing the Klotho expression could represent a potentially promising strategy for gene therapy in the context of neurodegenerative disease, kidney disorders, and even certain cancers associated with cognitive decline [41].

3.2 Advancements in Regenerative Medicine

3.2.1 Stem Cell Research and Therapies

It has emerged as one cornerstone in regenerative medicine for anti-aging, and the great potential therein is

not only for the treatment of conditions associated with aging but even for reversing the age of tissues and organs within the body. Uniqueness relates to stem cells in their proficiency to self-renew and give rise to other cell types, thus permitting tissue regeneration and repair [42]. The kinds of stem cells utilized in anti-aging treatments include embryonic stem cells (ESCs), adipose-derived stem cells (ASCs), and mesenchymal stem cells (MSCs), in general, and induced pluripotent stem cells (IPSCs). ESCs are pluripotent stem cells, meaning they come from embryos and have the ability to give rise to every cell type in the body. Recent studies have put in perspective the potential of stem cell-based treatments in tissue rejuvenation and the combat of aging. Mesenchymal stem cells derived from adipose tissue (ADSCs) and bone marrow (BMSCs) secrete extracellular vesicles and exosomes that enhance collagen production, fibroblast cell proliferation, and oxidative stress reduction. They are hence skin rejuvenation and wound healing agents [43]. These advances are towards stem cell therapy with an emphasis on epigenetic changes and gene editing as beneficial tools in the retardation of aging and treatment of age-related diseases. Therapies based on IPSCs are under clinical investigation regarding their potential for the regeneration of tissues and organs that have been damaged or aged. The safety of IPSC therapies remains to be resolved concerning tumor formation [44].

3.2.2 Tissue Engineering

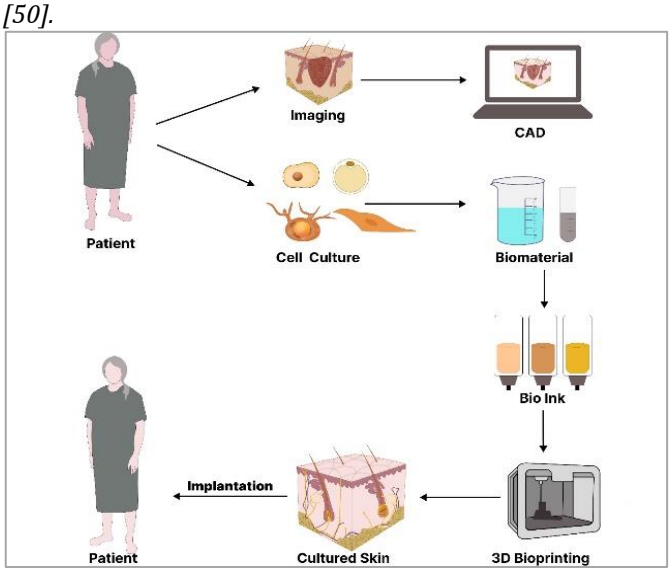
Tissue engineering is one of the relatively advanced fields of regenerative medicine, committed to repair, regeneration, or replacement with innovative methodologies such as 3D printing, scaffolding, and biomaterials. This technology has been applied in the restoration of aged tissue structure and function, particularly skin, as an advantageous marker for anti-aging [45].

3.2.2.1 3D Bioprinting

Three-dimensional bioprinting is a novel technology capable of attaining some of the biological materials with precise detail, such as cells, biomaterials, and bioactive factors, assembling into functional tissues and organs layer by layer [46]. In anti-aging treatment, 3D bioprinting can do much for skin regeneration and rejuvenation. It can also print skin grafts or patches designed from autologous cells, which are cell material taken from the patient themselves, thereby minimizing the possibility of an immune response against a foreign material [47]. The anti-aging skin tissues that are bioprinter fill in the loss of elasticity, structure, and firmness associated with aging. The bioprinter tissue in this tissue would contain skin with its extracellular matrix, which is architecturally similar to that of its natural counterpart and is thus responsible for many of the skin's mechanical properties, such as elasticity and strength. Applications may involve areas where elasticity has been lost due to aging or other types of damage to the skin, such as wrinkles, scars, or skin thinning [48]. During the bioprinting process, the application of growth factors induces cell proliferation and collagen production in the dermis under such a crucial skin rejuvenation process. 3D bioprinting in the future might be able to speed up the healing process of wounds with individually tailored skin grafts that optimally integrate with the patient's skin for faster healing and thus preserve the youthful appearance of the skin [49]. Figure 1 depicts the process of 3D Bioprinting for skin regeneration.

Figure 1

The procedure begins with the imaging of the patient's skin and the application of computer-aided design (CAD) to create a precise model. Meanwhile, the patient's cells are cultured and combined with biomaterials to create the bio-ink. A tailored skin construct is printed by the 3D bioprinter, which is implanted in a patient, a promising procedure for wound healing and skin tissue engineering [50].



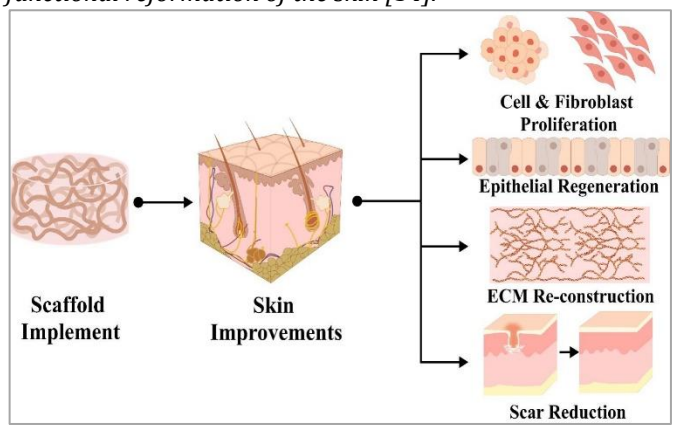
3.2.2.2 Scaffolding

Scaffolding in tissue engineering is a three-dimensional framework that gives cells a base to attach, grow, and consequently regenerate. These normally come in the form of natural or synthetic biomaterials, which mimic the extracellular matrix that provides support to cells in tissues [51]. The scaffolds in skin regeneration provide a platform on which the new skin cells grow, collagen develops, and the tissue is later repaired. Growth factors and stem cells can also be added to scaffolds to increase their stimulatory effects on cells, e.g., proliferation and differentiation. This stimulation not only contributes to the growth of new skin cells but also to the production of structural proteins, which are crucial in skin structure, i.e., collagen and elastin. Hence, it is very useful in providing the skin with its firmness and elasticity. The cells stretch and expand to the scaffold until the material structure is exhausted or recaptured by the body, and the new tissue is formed [52]. Bioactive materials or nanomaterials can also be added to advanced scaffolds, whereupon a further enhancement of the regeneration of skin is promoted. Such biomaterials can be designed to release growth factors or drugs in a regulated mode, thus producing an optimistic microenvironment for cell growth and healing of defective skin. More to the point, scaffolds should be composed of biodegradable materials,

the main benefit of which is that the body will absorb them in consequence with no negative effects and leaving behind a newly formed tissue. Nanoparticle-eluting collagen-chondroitin sulfate scaffold with anti-aging gene therapy β-Klotho for enhanced wound healing in human ADSCs. The presented β-Klotho gene-activated scaffold augmented the regenerative capability of the ADSCs themselves through positive regulations of transcription factors like Oct-4 and TGF-β3 in critical periods of the healing process. This was further manifested by enhanced basement membrane regeneration as expressed by the deposition of laminin and collagen IV, whereas scar-associated proteins were reduced. In summary, the turned-on scaffold of the β-Klotho gene is much more effective in wound healing and therefore stands at an important place in rejuvenation therapy with the use of stem cells [53]. Biomaterial Scaffolds for Skin Regeneration are illustrated in Figure 2.

Figure 2

Biomaterial Scaffolds for Skin Regeneration: The scaffold is a three-dimensional support that enables cell adhesion, migration, and proliferation, facilitating critical regenerative processes such as fibroblast activation, epithelial regeneration, ECM reconstruction, and scar tissue remodeling. The process enhances the recovery of wounds by facilitating organized tissue regeneration and functional reformation of the skin [54].



3.2.2.3 Bioactive Materials

Bioactive materials used in tissue engineering for anti-aging therapies include hydrogels and nanomaterials. Such materials are designed to interactively act with biological systems for enhanced healing and regeneration of tissues, thus having a reverse effect on the damage related to aging [55]. Hydrogels are a class of highly absorbent polymers that can retain a great amount of water in their structure, thus creating a moist environment that is ideal for tissue growth and regeneration. Due to their excellent biocompatibility, hydrogels are preferred for carrying cells, nutrients, and growth factors in tissue engineering. Hence, they have a very distinctive role to play in anti-aging techniques when it comes to the rejuvenation and repair of damaged or aged tissues [56]. Concerning skin aging, the hydrogels are designed to stimulate cell proliferation and collagen synthesis. These, in fact, represent the two major contributors to maintaining firmness and elasticity in the skin. Collagen is the main structural protein of skin, which provides it strength and elasticity; however, its production decreases with age, causing wrinkles or sagging skin. Hydrogels can be engineered to provide growth factors and other active agents, offering a suitable microenvironment for the action of fibroblasts, which are specialized cells responsible for the synthesis of collagen. This process helps to reverse the signs of aging through the reduction of wrinkles. The hydrogels can be designed to release bioactive molecules over sometime, ensuring sustainable local effects. This mechanism of controlled release favors the maintenance of optimum conditions for tissue regeneration for a longer period and turns them into a formidable tool in long-term skin rejuvenation [57].

Nanomaterials have been able to introduce a new level of accuracy in the field of tissue engineering. These materials are designed at the nanoscale and are capable of interacting with cells and tissues on the molecular level. This is particularly useful in enhancing cellular interactions because of their size; they can easily penetrate into tissues, incorporating into biological systems. For anti-aging uses, nanomaterials are designed to transport particular molecules, e.g., growth factors, peptides or drugs, directly to the target cells, e.g., fibroblasts in the skin. This offers a very focused delivery system that guarantees the accurate delivery of signals to the correct cells, resulting in improved collagen production and the other regenerative systems. Nanomaterials may be developed through imitating the natural ECM elements, hence, promoting cell adhesion, migration, and differentiation [58]. Because of their close mimicry with the in vivo environment, nanomaterials can support cells to reconstruct tissues in a way that their normal function and appearance are maintained. Similarly, their ability to interact at a molecular level also enables them to trigger certain cellular pathways, including wound healing and collagen formation [59].

3.3 Development of Anti-aging Compounds

Therapies that target biological mechanisms of aging include cellular senescence, mitochondrial dysfunction, telomere attrition, and genomic instability. The research aims to develop small molecules, peptides, and biologics that enhance lifespan and treat aging diseases.

3.3.1 Current Research on Anti-aging Medications

Cells stop dividing and enter the state of permanent growth arrest in the process of Cellular senescence. Senescent cells accumulate with age and release pro-inflammatory factors, causing tissue dysfunction and chronic inflammation known as senescence-associated secretory phenotype (SASP). These senescent cells cause tissue degeneration and other age-related disorders like cardiovascular disease, osteoarthritis, and pulmonary fibrosis [60]. Senolytic drug therapies, including dasatinib and quercetin, are designed to eliminate senescent cells. Dasatinib is a tyrosine kinase inhibitor, while quercetin is a flavonoid with anti-inflammatory properties. A combination of these drugs has been shown to reduce senescent cells in aged mice. A combination of dasatinib and quercetin is one of the best-documented interventions known to extend life span and delay the

onset of age-related diseases in a wide variety of species, from yeast to worms, flies, and mammals [61]. Biochemists and gerontologists acknowledge that it is not easy to apply long-term CR in human beings. Because of this limitation, researchers have actively been developing CR mimetics-CRMs, or compounds that can effectively mimic all the beneficial effects of CR without the need for actual food restriction [62]. The two most well-known CRMs are resveratrol and nicotinamide riboside (NR). Resveratrol is a plant polyphenol derived from grape and berry skin, which has been identified as a natural activator of the SIRT1 pathway implicated in cellular resistance to stress and longevity [63]. Preclinical studies have shown the efficacy of resveratrol in improving mitochondrial function and metabolic health, with animal lifespan extension. Nicotinamide riboside (NR) is a nicotinamide adenine dinucleotide+ (NAD+) precursor associated with energy metabolism, DNA repair, and cell survival. NAD+ was found to decrease with age, just like mitochondrial impairment, thus declining metabolic health [64]. NR supplementation helps in rebuilding NAD+, thus improving mitochondrial function, reducing oxidative stress, and promoting longevity in animal models. In humans, administration of NR supplements resulted in improvement of metabolic health markers and reductions of inflammation [65].

3.3.2 Notable Compounds in Anti-aging Medication

A large number of compounds are being studied for their ability to extend lifespan and healthy aging, including metformin and rapamycin. Metformin, a drug used in the treatment of type 2 diabetes, has been shown to activate AMP-activated protein kinase (AMPK), which improves mitochondrial function, reduces oxidative stress, and enhances insulin sensitivity [66]. Clinical trials such as targeting aging with metformin (TAME), with the potential to delay age-related diseases, are ongoing. Rapamycin is an immunosuppressive drug that works through inhibition of the mTOR pathway, responsible for maintaining cell growth and metabolism. It also holds a great promise for life span extension, as shown in animal studies previously [67].

3.3.2.1 Metformin

Metformin is one of the most frequently administered drugs for the management of type 2 diabetes. However, in recent studies, it has been indicated that this drug may have anti-aging potential and thus can be considered drug repurposing [26]. Its anti-aging properties are mainly mediated through AMP-activated protein kinase, the enzyme involved in the regulation of cellular energy. This drug activates AMPK and promotes healthy aging. AMPK activation reduces the production of reactive oxygen species that can cause cellular damage and stimulate aging. It also promotes mitochondrial efficiency and biogenesis, eventually improving the production of cellular energy. Metformin induces autophagy, in which damaged organelles and proteins are removed, contributing to cellular rejuvenation. The capability of metformin to lower blood sugar and increase insulin sensitivity eventually reduces the risks of metabolic disorders such as diabetes associated with accelerated aging [68]. The clinical trial "TAME" trial has evolved for the broader pharmacological potential of metformin in preventing age-related diseases. This large-scale clinical study has been designed to assess the ability of the medication to delay the onset of age-related conditions, including cardiovascular disease, cancer, and cognitive decline. Since these represent some of the most prevalent pathologies related to aging, the TAME trial seeks to position metformin as a seroprotective agent that delays aging and extends the health span [69].

3.3.2.2 Rapamycin

The development of rapamycin as a leading compound in anti-aging research began originally as an antifungal agent and later was used as an immunosuppressant in organ transplant patients. The anti-aging potential of this drug has been found due to its ability to inhibit one important pathway known as the mechanistic target of rapamycin (mTOR). The mTOR pathway is the key regulator for cellular growth, metabolism, and protein synthesis, playing an important role in balancing anabolic and catabolic processes in cells [70]. Inhibition of mTOR has also been demonstrated to extend the life span in organisms from yeast to mice [71]. There are two complexes of the mTOR pathway: mTORC1 and mTORC2. Rapamycin largely inhibits mTORC1, which diminishes cell growth and proliferation and promotes repair processes such as autophagy. This shift away from growth toward maintenance is considered one avenue in which the process of aging may be delayed by the avoidance of accumulation of cellular damage [72]. This drug, given even at an advanced age in mice, has been shown to extend their lives by 9–14%, thus supporting the hypothesis that mTOR inhibition works even if initiated at an advanced age [73]. It has also been demonstrated that rapamycin decreases the incidence of cancer, neurodegeneration, and cardiovascular disease during aging at least partly due to the enhancement of cellular repair mechanisms and diminishment of inflammation [74]. Human clinical trials are currently underway with rapamycin as a prophylactic against age-related pathology, for example, against neurodegenerative conditions like Alzheimer's and Parkinson's disease. This drug has also been considered to reduce the progression of these diseases. Its immune-modulating effects can also enhance immune responses in the elderly against infections to reduce age-related immune decay [75].

3.3.2.3 NAD+ Precursors

Anti-aging research focuses on using precursor compounds to raise levels of NAD+, nicotinamide mononucleotide, and nicotinamide riboside. The NAD+ is the abbreviation of nicotinamide adenine dinucleotide coenzyme, which is the most essential in the rate-limiting processes of cellular energy production, DNA repair, and cellular homeostasis. As NAD+ levels decline over time, aging symptoms such as mitochondrial malfunction, a diminished capacity for DNA repair, and a slowed metabolic rate occur. These are symptoms of aging [76]. Researchers employ NAD+ precursors, such as nicotinamide mononucleotide (NMN) and nicotinamide

riboside (NR), to replenish reduced NAD+ levels in aged cells and restore cellular function. NAD+ itself is also indispensable in mitochondrial health; restoration of NAD+ level has been associated with improved energy production and reduced cellular damage. For the activation of enzymes participating in DNA repair, such as PARPs, the presence of NAD+ is required [77]. An increased availability of NAD+, therefore, might lead to an enhanced cellular capacity to repair damaged DNA. This increases resistance to stress by activating enzymes known as sirtuins, which are key regulators of biological processes ranging from stress responses and inflammation to metabolism. NMN and NR supplementation may enhance cellular resistance to oxidative stress and other insults by the activation of sirtuins [74]. Early studies have shown promising results with NMN and NR, including optimum metabolic health, increased endurance, and markers reduced for aging in humans. Clinical trials are ongoing to examine the hypothesis that diseases associated with aging can be prevented by long-term administration of NAD+ precursors, thus promoting a healthy and longer life span [78].

3.4 Personalized Medicine in Anti-aging

In anti-aging research, personalized treatments are designed and tailored to an individual's genetic profile, physiological status, and health conditions. In this approach, treatment is directed at unique causes of aging in a person, emphasizing intervention at the levels of specific biological processes: DNA repair, oxidative stress, and inflammation. Genomic data and biomarkers can be used to tailor therapies in personalized medicine in such a way that aging will be slowed or reversed more effectively than it would be with generic or broad-spectrum solutions [79]. Aging is indeed a very complex process. It relates to genetic and epigenetic factors, as well as many other environmental ones [80]. Personalized medicine against aging consists of the elaboration of therapies in relation to the particular genetic background of an individual. A detailed knowledge about how specific genes modulate particular cellular processes relevant to aging, including DNA repair, oxidative stress, and inflammation, will allow the formulation of therapies directed toward precise problems contributing to slowing down or reversing certain features of aging [81].

3.4.1 Genetic Profiling in Anti-aging

It involves the sequencing of the DNA of an individual's genome to search for genes believed to influence aging. Generally, personalized anti-aging treatment targets two kinds of genes, which are either involved in telomere length maintenance or the management of oxidative stress. Telomeres are the protective caps at the end of chromosomes that get shortened with every cell division [82]. The enzyme telomerase rebuilds them, while the TERT gene encodes the latter. This simple mechanism is underlain by mutations or reduced activity in this gene, accelerating telomere shortening and leading to early cellular senescence and hence contributing to aging. Therefore, personalized therapies could disturb the activity of these pathways by facilitating telomerase activity and thus act toward maintaining the length of telomeres and extending cellular lifespan [83]. Oxidative stress occurs due to an imbalance between free radicals and antioxidants in the body, to such a level that even cell damage occurs. SOD2 encodes an enzyme responsible for the neutralization of free radicals. Variants in this gene increase the susceptibility to oxidative damage, thus accelerating aging. Once these variants are identified, targeted antioxidant therapies can be devised that decrease oxidative stress and help protect cells [84, 85].

3.4.2 Epigenetics in Personalized Anti-aging Therapies

Epigenetics is the alteration in gene expression that does not involve variations/alterations in the DNA sequence but might be caused by diet, lifestyle routine, aging, or any other environmental factor. With the advance of age, epigenetic modifications generally alter gene expression by silencing these genes and switching on others in a fashion that promotes aging [86]. There are a few major epigenetic modifications that usually result in the silencing of genes. During aging, there is an altered pattern of DNA methylation leading to gene silencing for maintaining cellular function. Inhibitors of DNA methylation could be administered to promote personalized anti-aging therapies that would counteract such age-related changes for the induction of youthful gene expression. For example, the restoration of the expression of genes involved in DNA repair contributes to genomic stability and therefore slows down aging [87]. Modifications to histones can stimulate or shut off gene expression. As histone modifications change with age, normal gene regulation goes away. The application of drugs to modify n-histones, known as HDAC inhibitors, can rejuvenate cells by restoring healthy patterns of gene expression. This activation of genes involved in survival and repair may slow down the aging process [88].

3.4.3 Integrating Genetic and Epigenetic Approaches

The idea behind personalized anti-aging medicine would now be to involve both genetic profiling and epigenetic markers, for instance, therapies regarding telomerase activation, senolytic drugs, antioxidants, and epigenetic modulators together may address the multidimensionality of aging in one stroke, for example, if someone has a mutation in the TERT gene, causing shorter-than-normal telomeres, a personalized treatment can be devised involving a telomerase activator to extend their telomeres. If, at the same time, epigenetic modifications take place that shut down the expression of the DNA repair genes, they might further benefit from the use of an HDAC inhibitor to restore the expression of such genes. Involving both genetic and epigenetic aspects, personalized anti-aging treatments may well be a holistic and more effective approach to delaying aging and longevity [89].

3.5 Role of Biomarkers in Personalized Therapies

Biomarkers have a crucial role in personalized medicine in the context of evaluation of the biological process of aging, identification of risks for age-related diseases, and

management adaptation. Such measurable indicators allow us to observe various biological processes: cellular aging, inflammation, oxidative stress, and degradation of proteins, which have effects on the general aging process in humans. The following is the detailed description of a few key biomarkers used in anti-aging therapies [90].

3.5.1 Telomere Length

The protective caps at the ends of chromosomes are known as telomeres; these are meant to protect against the loss of vital genetic material during cell division. Every time a cell divides, its telomeres get shortened. Once telomeres reach a critically short length, the cell enters either a state of senescence or it loses the ability to divide. Telomere shortening has been recognized as one of the hallmarks of biological aging [91]. The measurement of the length of the telomeres gives an idea about the biological age, which may or may not be exactly accurate with chronological aging. Short telomeres have been associated with the heightened possibility of age-related diseases such as cardiovascular disease, cancer, and neurodegenerative diseases. Thus, the length of the telomeres has become a reliable biomarker to predict not only the aging condition but also the susceptibility to aging-related diseases. Telomerase is an enzymatic activity that can extend telomeres. Since most adult somatic cells lack expression of telomerase, numerous regenerative medicine therapies are pursuing activation of telomerase to slow down or reverse telomere shortening. For those whose telomeres are critically short, telomerase activators are tried as possible treatments aimed at extending cellular lifespan. Another regenerative approach is the use of stem cell therapy, where damaged or senescent cells are replaced with new, healthy cells having longer telomeres. In this regard, by the introduction of young cells with intact telomeres, researchers seek to improve tissue repair and postpone aging at the cellular level [92].

3.5.2 Inflammatory Markers

Inflammation is the term used to describe the process of chronic, low-grade inflammation, which increases in intensity with the passage of time, contributing to the development of age-related diseases: cardiovascular disease, arthritis, and neurodegenerative conditions such as Alzheimer's disease [93]. It is usually driven by cellular damage, the accumulation of senescent cells, and an overactive immune system. IL-6 is a pro-inflammatory cytokine that is implicated in immune response and inflammation. High concentrations of IL-6 have been associated with frailty, disability, and chronic diseases in older age. CRP, a liver-derived protein, is secreted in response to inflammation. It is the most commonly measured marker of systemic inflammation and is associated with high risks of cardiovascular diseases and other aging-related conditions. If IL-6 or other pro-inflammatory cytokines are high, medications against inflammation may be recommended to reduce chronic inflammation and improve health in older individuals, including cytokine blockers-e.g., inhibitors of IL-6 [94].

3.5.3 Oxidative Stress

Oxidative stress occurs when the production of free radicals, very reactive molecules damaging to the cells, falls out of balance with the antioxidant defenses of the body. This leads to the accumulation of oxidative lesions to DNA, proteins, and lipids, thus contributing to aging and age-related diseases [95]. The product of lipid peroxidation is used as a marker of oxidative damage to cell membranes. 8-Hydroxy-2'-deoxyguanosine (8-OHdG): 8-OHdG is the biomarker of oxidative DNA damage. In this case, these metabolites occur in higher amounts within either blood or urine, thus making oxidative stress with DNA damage obvious, leading to accelerated aging and cancer [96]. Conditions involving a high level of oxidative stress could be subjected to antioxidant supplementation such as vitamins C and E, Coenzyme Q10, or N-acetylcysteine. The purpose of antioxidant therapy is to neutralize free radicals and thus prevent cellular damage caused by free radicals. Antioxidant therapy can be tailored according to the type of biomarkers found in the patient. Oxidative stress can be regulated by personalized lifestyle changes such as regular exercise and a balanced diet rich in antioxidants [97].

3.5.4 Advanced Glycation Products

Glycation involves the non-enzymatic attachment of sugars to proteins, lipids, or nucleic acids, forming injurious compounds known as advanced glycosylation end-products, or AGEs. The latter accumulate over time, contributing to the hardening and malfunction of tissues, leading to chronic diseases such as diabetes, cardiovascular pathology, and even senile dementia [98]. AGE levels might be measured in the blood or tissues to give an idea about the extent of glycation and the resulting damage. High levels of AGEs have been linked to aging and the development of degenerative conditions. One of the most scientifically valid ways to reduce the formation of AGEs is dietary modification [99]. Cooking on high heat, grilling, and roasting can result in the production of AGEs in food. Individualized dietetic practice aimed at taking steamed or boiled foods with a lower glycation index might lower the burden of advanced glycosylation products in the human body. Meanwhile, limiting the use of refined sugar and processed food intake can also slow the glycation process [100]. Investigations are going on to discover some pharmaceutical interventions that may include drugs inhibiting the formation of AGEs or breaking down already-formed AGEs. These can be prescribed, depending on a person's biomarker profile, to diminish the negative effect of glycation on aging [101].

4. Impact of Anti-Aging Research on Human Health

The potential of anti-aging research in improving lifespan, especially healthy duration and quality of life, is a cut above the rest. According to the UN report on World Population Aging 2023, the number of individuals above 60 years is expected to increase to 2.1 billion in 2050, according to the UN Report 2023. This is due to developments in medicine and improvements in food quality, especially in developed countries [102].

4.1 Improvement in Lifespan and Quality of Life

Anti-aging research mainly focuses on enhancing healthy lifespan and longevity. Anti-aging researchers are trying to reduce aging-related diseases, maintaining good cognitive and physical activities in later life rather than reversing the biological processes of aging. Most of the recent research focuses on fundamental mechanisms of aging, such as genetic instability, mitochondrial dysfunction, cellular senescence, and telomerase shortening [103]. By targeting the above-mentioned fundamental mechanisms of aging researchers are hoping to slow down the gradual functional decline that leads to compromised health and the onset of different diseases such as Alzheimer's disease (AD), cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), osteoarthritis (OA), chronic obstructive pulmonary disease (COPD), and nonalcoholic fatty liver disease (NAFLD). Anti-aging research has led to reduced incidence of the above-mentioned aging-related diseases [104]. It is due to focus of anti-aging research on various physiological, pathological, and biophysical conditions is the key to maintaining health. Till now, many products such as diets, supplements and medications are available in markets claiming to have anti-aging properties. But there are no proven ways of slowing the aging process at the moment. There is a lot of scope for research on how quality of life can be improved in the future [105].

4.2 Socioeconomic Implications

According to the WHO report, the population aged 65 years or above has outnumbered the youth aged 15 years or less, largely due to improvements in healthy aging. Thus, countries worldwide are facing the enormous challenge of building and maintaining the healthcare sector to counter such a huge number. The total cost for healthcare spending on dementia/AD is about $594 billion and is estimated to increase to $1.3 trillion in 2025 [106]. In the USA, healthcare spending for PD is estimated to rise from $51.9 billion to $79 billion by 2050 [107]. For CVD in the EU, costs reached $327 billion as of 2023 [108]. While these are estimated costs, the actual burden can be quite high. However, if people are given a comfortable environment where they can work and maintain their health, it will provide a great boost for the economy as well as a relief for the strained health-care system. Thus, interest in anti-aging research will continue to grow, but its complications can be addressed through several diverse approaches. Moreover, as the public interest in aging increases, public demand for aging consultations and management will also increase significantly. Anti-aging research will be able to play a critical role in mitigating various policies, environmental, and social challenges posed by the current aging population. As a result, interest in anti-aging medication has grown to be a problem with the potential for further growth and an essential complication for which there are several possible approaches to provide answers. Furthermore, anti-aging drugs can address the environmental, policy, and public challenges posed by the existing aging population by increasing public interest in consultation and support for aging management. Moreover, as the public interest in aging increases, public demand for aging consultations and management [109].

5. Current Struggles in Anti-Aging Research

5.1 Ethical and Regulatory Challenges

The ethics of anti-aging research are complex, as it requires redefining the boundary between aging and disease. This change could also mean that anti-aging treatments, which are now considered cosmetics by the FDA and EMA, will be classed as medicines in the new guidelines and need more regulations and stringent testing. This regulatory gap has raised concerns over some cosmetic anti-aging treatments for not being safe or effective, yet being marketed [110]. Currently, there is no single body controlling the regulation of medicinal drugs globally, but rather controlled by countrywide or regional bodies, i.e. FDA in the USA and the EMA in the EU. Although guidelines by the FDA are followed in most parts of the world, there is still a need for a universal regulator, which can be fulfilled by the International Council for Harmonization (ICH). But as of now, the mandate of ICH is just the harmonization of standards across the USA, EU and Japan, etc. [111].

In addition, ethical issues regarding the research participation of older people with cognitive impairment may also arise. Such individuals must be shielded from compulsion or undue influence; thus, contemporary guidelines are needed. At the same time, it is necessary to make sure their participation in research, as they are the most vulnerable individuals [112]. Another ethical issue is the equitable access to anti-aging research for the benefit of all, not just those who can afford it. Currently, anti-aging treatments are expensive, leading to disparity, while lifestyle changes and exercise can be adopted by everyone [113]. The ethical issues regarding genetic enhancement are significant, particularly where the goal of the intervention is aimed at conferring superiority over others by selective changes. Also, modifications of the germline cause heritable changes that are passed on to the new generations. This may interfere with human evolution, unintended changes over longtime and moral obligation due to the inability to obtain consent from future generations [114]. The potential of anti-aging research in increasing lifespan raises questions in a few societies about diminishing resources more quickly, in addition to increased pressure on already strained healthcare systems, especially in third-world countries [112].

5.2 Scientific and Technical Hurdles

Aging, being a multi-factorial complex biological process, has many major hurdles in anti-aging research. The efficacy of current therapies against factors, including epigenetics and lifestyle, has not yet been determined. The results of aging research are insufficiently conclusive to determine whether they can only prevent or delay the development of aging-related disorders [115]. The dependence of aging on medical conditions, genetic origins and environmental exposures also complicates the situation. This heterogeneity further complicates the innovation of universal therapies, and the chances of

success of any standard solution are very low. This heterogeneity favors the need for personalized and targeted therapies, which are still in their early stage of development [116].

5.3 Balancing Efficacy and Safety in Treatments

The development of therapies to achieve an optimal balance between effectiveness and safety is the key challenge of anti-aging research. Although the goal of anti-aging research is to prolong health span and lifespan, most side effects are poorly understood, and research is still ongoing. Many proposed medications have the potential to create unintended results, particularly in older people already suffering from multiple health issues. Another challenge is the development of anti-aging therapies with not only possible benefits but also fewer side effects, which require extensive clinical trials with a stringent evaluation of immediate and long-term consequences. This process is often met with funding and procedural challenges, making it undesirable for companies [117].

5.4 Public Perception and Misinformation

The general public has the wrongful perception of anti-aging research that has generated not just confusion but also unrealistic expectations. The ideas of heavenly (eternal) youth, power, and health are the major ones that attract the general public, which usually doesn't focus on the scientific and ethical challenges involved in such research. This has led to scams and unproven and untested therapies that affect the masses. This has not just deprived them of their money but also their trust in scientific research. Furthermore, research agendas and funding are also determined by societal attitudes. Ageism and stigmatization of older people may lead to changes in such research, leading to the regressing of anti-aging research that otherwise would have made great progress [110]. Altogether, anti-aging research faces financial, ethical, scientific, and societal challenges. These problems must be handled by the key players, including scientists, decision-makers, and the general public, to have a significant impact [118].

6. Interactions between Aging Research and Diseases

6.1 Aging as a Risk Factor for Chronic Diseases

The major impact of aging on chronic disease is due to a disruption in biological function. In aging, sub-cellular capacity is lost in restoring DNA damage, maintaining cellular homeostasis, and regenerating new tissues. This contributes to the accumulation of senescent cells secreting pro-inflammatory cytokines, thereby promoting chronic inflammation or "Inflammaging" [119]. Mitochondrial dysfunction causes excessive oxidative stress, resulting in neurodegenerative diseases such as Parkinson's and Alzheimer's disease due to dysfunction of lipids, DNA and proteins. Telomere shortening acts as a counteract against telomerase shortening in the replication, while impaired autophagy impairs the ability to clear cellular components. The factors mentioned above lead to susceptibility to CVDs and metabolic disorders. Cellular senescence, inflammation, and mitochondrial dysfunction together provide a complex network that accelerates aging-related diseases and complicates their management [114]. One of the major risk factors for neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases, is the process of aging. Neurodegenerative disease, one such type, leads to the buildup of amyloid-beta plaques and tau protein tangles, which can disrupt synaptic function, eventually leading to cognitive decline in Alzheimer's. Over time, these protein aggregates lead to neuronal death and loss of brain tissue, with a special impact on areas most responsible for memory and cognition hippocampus. As discussed earlier, accumulation of oxidative stress due to aging increases these pathological features, creating damage to proteins, lipids, and DNA [120].

6.2 Anti-aging Therapies' Effects on Disease Prevention and Management

Aging plays a significant role in the development of cardiovascular diseases. Over time, blood vessels tend to lose some of their elasticity, eventually stiffening the arteries. This consequently produces a plausible chance for atherosclerosis, in which the deposit of some sort of fatty residue within the arterial lining narrows the passageway that blood would have to pass through. These latter changes of arterial stiffening and narrowing contribute to hypertension, forcing the heart to work harder to pump blood [121]. After many years, this extra work for the heart leads to the failure of the heart and increases the chances of heart attacks and strokes. Chronic vascular inflammation, common in aging individuals, also contributes to the development of these diseases [122].

Metabolic processes deteriorate with the aging of the body, hence metabolic disorders such as type 2 diabetes and metabolic syndrome start to appear [123]. Cells gradually become insensitive to insulin until blood sugar levels go up, which, in general, is intertwined with a state of chronic, low-grade inflammation that in turn promotes metabolic impairment [124]. This general impairment of mitochondrial activity in old age further facilitates dysregulation of energy metabolism and correlates with increased weight gain, fat deposition and dyslipidemia. Taken together, these changes increase the predisposition to metabolic syndrome that puts an individual at risk of heart disease, stroke, and diabetes. The condition of oxidative stress, chronic inflammation and cellular dysfunction of the age-related processes is inseparably intertwined with diseases and, thus, predetermines so many chronic diseases in the elderly to be so complicated to treat [125]. Chronic back pain is one of the common conditions associated with aging. Though it is a multifactorial effect, its main reason is intervertebral disc degeneration accumulated over time [126]. Proper functioning of the intervertebral disc is necessary for movement, flexibility and is composed of three compartments. A change in any of the compartments affects the functions of the other, leading to back pain. There is evidence that senolytic drugs reduce intervertebral disc degeneration caused by aging in mouse models. This can be seen as a new avenue opened by anti-aging research [127].

Anti-aging therapies might therefore contribute significantly to the prevention of age-related diseases, especially cardiovascular and metabolic disorders. Anti-aging therapies may help by targeting the very basic mechanisms of oxidative stress and chronic inflammation in maintaining vascular elasticity and reducing arterial stiffness to lower the risk for atherosclerosis and hypertension. Physical activities, together with antioxidant- and anti-inflammatory-rich nutrition, support medications like statins or inhibitors of angiotensin-converting enzymes in protecting the cardiovascular system. Other novel senolytics and NAD+ boosters are emerging treatments that aim to restore the vitality of mitochondria [128, 129]. This, in turn, improves insulin sensitivity and hence metabolic dysfunction, which contributes to type 2 diabetes and metabolic syndrome. Collectively, they contribute to a decrease in such cases of heart attack, stroke, and other chronic conditions related to aging [130].

6.3 Comorbidities and the Complexity of Treating Aging-Related Diseases

Comorbidity is explained as the co-existence of more than one chronic disease in one person at the same time; therefore, treatment is more challenging in comparison with the treatment for one disease. In older people, comorbidities are very common because aging frequently influences more than one physiological system at the same time. For example, many aged individuals suffer from Cardiovascular Disease (CVD) and simultaneously have several conditions like diabetes, osteoarthritis or cognitive impairment. Overlapping conditions thus present some complications during diagnosis and treatment [130]. Managing multiple chronic diseases usually involves polypharmacy, or the use of multiple medications. While this may be necessary, it carries the risk of drug interactions when medications interfere with the efficacy of other drugs or produce harmful side effects. For example, blood thinners, used in the treatment of heart disease, may interact negatively with anti-inflammatory medications, resulting in severe side effects such as gastrointestinal bleeding. All these interactions make the optimization of treatment regimens quite challenging. In older patients, the liver and kidneys are usually the two organs that do not function as well, and these are the sites involved with drug metabolism and excretion, respectively [131]. Treating chronic conditions in elderly patients is challenging, as therapies for one disease often worsen another due to age-related systemic decline. Reduced physiologic reserves in organs like the heart, liver, and kidneys increase the risk of poor treatment outcomes. For example, cancer therapies may cause cardiovascular issues, while heart treatments can harm kidney function. Diabetes management also impacts other systems, as insulin-induced weight gain raises blood pressure and cardiovascular risks [132]. Precision medicine offers hope by tailoring treatments to genetic, environmental, and lifestyle factors, but its application in aging remains limited. Genetic diversity influences disease progression and drug responses, yet personalized treatments face obstacles due to comorbidities, biological variability, high diagnostic costs, and a lack of comprehensive datasets for older populations [133].

7. Future Directions in Anti-Aging Research

Gene editing, therapies involving stem cells and nanotechnology hold great promise in anti-aging research. Tools such as CRISPR-Cas9 allow scientists to edit genes linked to aging and may provide ways to defer or even reverse cellular damage. In addition, treatments involving the replacement of stem cells aim at rejuvenating tissues with new cells from outside sources, restoring the youthfulness of tissues. Nanotechnology can finally provide focused treatments at the molecular level for specific mechanisms of aging, including oxidative stress or inflammation [134]. As anti-aging research becomes more available and effective, it increases the health span of people. This demands changes in current social and economic policies. Increased health span will eventually lead to a higher pension burden and changes in employment dynamics [135]. Certain rules about retirement ages and shifting aged populations to fewer demanding jobs will be needed. Easing retirement ages will benefit countries with a high population past the retirement age. It will also help retain experts who can be productive for a longer time [136]. Anti-aging research is becoming increasingly interdisciplinary, integrating biotechnology, pharmacology, genomics, and bioinformatics. These collaborations provide deeper insights into aging at the molecular level and accelerate the development of targeted interventions [137]. In addition, partnerships between academia-government-private sector may also serve as a driving force for innovation in this field. The future of anti-aging interventions will focus on the extension of health span and quality of life, rather than just lifespan. In translation, it will focus on reducing age-related diseases like Alzheimer's, cardiovascular conditions, and arthritis. In the future, regenerative medicine may substitute aged organs and tissues with freshly generated ones with the help of stem cells and tissue engineering [138].

8. CONCLUSION

Anti-aging research from ancient theories to the cutting-edge science all stem from the human desire to increase the life and health span. Studies focused on unravelling the genetic basis of the aging process lead the way. Still, research in regenerative medicine, complemented with anti-aging pharmacology, is leading towards therapies that have an impact on every aspect of aging. Among these are optimistic prospects such as personalized medicine, stem cell therapies, and anti-aging drugs such as metformin and rapamycin in treating age-related diseases to enhance the quality of life, thereby decreasing the burden on the health system and the economy. Despite these advancements, anti-aging research faces a multitude of challenges: ethical, scientific, and problematic regulations and policies. Public perception and misinformation, along with the complexity of aging-related disease, as well as rising research, are continuously adding to challenges. Despite these advancements, anti-aging research faces a plethora of challenges, ranging from ethical, scientific, public

perception, misinformation, and problematic rules and regulations. The multifaceted nature of aging is also making the research in this field complex. However profound effects of anti-aging research on human health cannot be denied, as it has to play a crucial role in halting aging, and even preventing many age-related chronic disorders, as well as enhancing longevity.

In the future, anti-aging interventions based on emergent technologies and interdisciplinary collaborations will continue to evolve. Through a holistic vision involving scientists, policy makers, sustained financing, and most importantly, the involvement of the people, this field is set to deliver a lot in the paradigms that have been hard to change in the aging field and provide life-transforming benefits as well as economic stability.

REFERENCES

1. Fialová, D., & Desplenter, F. (2016). Aging of the population, clinical pharmacy services, and interdisciplinary cooperation in the optimization of pharmacotherapy in older patients. *Drugs & Aging*, *33*(3), 163-167. https://doi.org/10.1007/s40266-016-0361-6
2. Javed, A. (2022). Mental health of older adults: An agenda for action. *Consortium Psychiatricum*, *3*(1), 6-7. https://doi.org/10.17816/cp156
3. Augusto, S., Kaelber, D. C., & Tang, W. W. (2025). Testosterone therapy in patients with heart failure and protein-calorie malnutrition: Insights from a propensity-matched cohort study. *Current Problems in Cardiology*, *50*(7), 103070. https://doi.org/10.1016/j.cpcardiol.2025.103070
4. Alegre, G. F., & Pastore, G. M. (2023). NAD+ Precursors nicotinamide Mononucleotide (NMN) and nicotinamide Riboside (NR): Potential dietary contribution to health. *Current Nutrition Reports*, *12*(3), 445-464. https://doi.org/10.1007/s13668-023-00475-y
5. Aliper, A., Jellen, L., Cortese, F., Artemov, A., Karpinsky-Semper, D., Moskalev, A., Swick, A. G., & Zhavoronkov, A. (2017). Towards natural mimetics of metformin and rapamycin. *Aging*, *9*(11), 2245-2268. https://doi.org/10.18632/aging.101319
6. Allen, J. O. (2015). Ageism as a risk factor for chronic disease. *The Gerontologist*, *56*(4), 610-614. https://doi.org/10.1093/geront/gnu158
7. Amorim, J. A., Coppotelli, G., Rolo, A. P., Palmeira, C. M., Ross, J. M., & Sinclair, D. A. (2022). Mitochondrial and metabolic dysfunction in aging and age-related diseases. *Nature Reviews Endocrinology*, *18*(4), 243-258. https://doi.org/10.1038/s41574-021-00626-7
8. Anisimov, V. N. (2013). Metformin: Do we finally have an anti-aging drug? *Cell Cycle*, *12*(22), 3483-3489. https://doi.org/10.4161/cc.26928
9. Apetroaei, M., Fragkiadaki, P., Velescu, B. Ş., Baliou, S., Renieri, E., Dinu-Pirvu, C. E., Drăgănescu, D., Vlăsceanu, A. M., Nedea, M. I., Udeanu, D. I., Docea, A. O., Tsatsakis, A., & Arsene, A. L. (2024). Pharmacotherapeutic considerations on telomere biology: The positive effect of pharmacologically active substances on telomere length. *International Journal of Molecular Sciences*, *25*(14), 7694. https://doi.org/10.3390/ijms25147694
10. Arriola Apelo, S. I., Pumper, C. P., Baar, E. L., Cummings, N. E., & Lamming, D. W. (2016). Intermittent administration of Rapamycin extends the life span of female C57BL/6J mice. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *71*(7), 876-881. https://doi.org/10.1093/gerona/glw064
11. Ashraf, H. (2002). Older people must be on the health and development policy agenda. *The Lancet*, *359*(9314), 1321. https://doi.org/10.1016/s0140-6736(02)08331-9
12. Baghdadi, M., Nespital, T., Monzó, C., Deelen, J., Grönke, S., & Partridge, L. (2024). Intermittent rapamycin feeding recapitulates some effects of continuous treatment while maintaining lifespan extension. *Molecular Metabolism*, *81*, 101902. https://doi.org/10.1016/j.molmet.2024.101902
13. Balch, W. E., Morimoto, R. I., Dillin, A., & Kelly, J. W. (2008). Adapting Proteostasis for disease intervention. *Science*, *319*(5865), 916-919. https://doi.org/10.1126/science.1141448
14. Duarte, L. F. (2020). The vitality of vitalism in contemporary anthropology: Longing for an evergreen tree of life. *Anthropological Theory*, *21*(2), 131-153. https://doi.org/10.1177/1463499620923546
15. Kalache, A. (2009). Towards age-friendly societies: From research to policy, from policy to society. *International Journal of Integrated Care*, *9*(5). https://doi.org/10.5334/ijic.388
16. Latorre Barragán, M. F., García Cárdenas, F. R., & Culqui Sánchez, M. V. (2024). Stimulation of cellular longevity using CRISPR-cas9 in aging-associated genes. *Interamerican Journal of Health Sciences*, *4*, 98. https://doi.org/10.59471/ijhsc202498
17. Beerman, I., & Rossi, D. J. (2014). Epigenetic regulation of hematopoietic stem cell aging. *Experimental Cell Research*, *329*(2), 192-199. https://doi.org/10.1016/j.yexcr.2014.09.013
18. Bellu, E., Medici, S., Coradduzza, D., Cruciani, S., Amler, E., & Maioli, M. (2021). Nanomaterials in skin regeneration and rejuvenation. *International Journal of Molecular Sciences*, *22*(13), 7095. https://doi.org/10.3390/ijms22137095
19. Bernardes de Jesus, B., Vera, E., Schneeberger, K., Tejera, A. M., Ayuso, E., Bosch, F., & Blasco, M. A. (2012). Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. *EMBO Molecular Medicine*, *4*(8), 691-704. https://doi.org/10.1002/emmm.201200245
20. BJORNSSON, H. (2004). An integrated epigenetic and genetic approach to common human disease. *Trends in Genetics*, *20*(8), 350-358. https://doi.org/10.1016/j.tig.2004.06.009
21. Bonomini, F., Rodella, L. F., & Rezzani, R. (2015). Metabolic syndrome, aging and involvement of oxidative stress. *Aging and disease*, *6*(2), 109. https://doi.org/10.14336/ad.2014.0305
22. Bové, J., Martínez-Vicente, M., & Vila, M. (2011). Fighting neurodegeneration with rapamycin: Mechanistic insights. *Nature Reviews Neuroscience*, *12*(8), 437-452. https://doi.org/10.1038/nrn3068
23. Cai, R., Gimenez-Camino, N., Xiao, M., Bi, S., & DiVito, K. A. (2023). Technological advances in three-dimensional skin tissue engineering. *REVIEWS ON ADVANCED MATERIALS SCIENCE*, *62*(1). https://doi.org/10.1515/rams-2022-0289
24. Cantó, C., Houtkooper, R., Pirinen, E., Youn, D., Oosterveer, M., Cen, Y., Fernandez-Marcos, P., Yamamoto, H., Andreux, P., Cettour-Rose, P., Gademann, K., Rinsch, C., Schoonjans, K., Sauve, A., & Auwerx, J. (2012). The NAD+ precursor nicotinamide Riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell Metabolism*, *15*(6), 838-847. https://doi.org/10.1016/j.cmet.2012.04.022

25. Caobi, A., Dutta, R. K., Garbinski, L. D., Esteban-Lopez, M., Ceyhan, Y., Andre, M., Manevski, M., Ojha, C. R., Lapierre, J., Tiwari, S., Parira, T., & El-Hage, N. (2020). The impact of CRISPR-cas9 on age-related disorders: From pathology to therapy. *Aging and disease*, *11*(4), 895. https://doi.org/10.14336/ad.2019.0927
26. Cătană, C., Atanasov, A. G., & Berindan-Neagoe, I. (2018). Natural products with anti-aging potential: Affected targets and molecular mechanisms. *Biotechnology Advances*, *36*(6), 1649-1656. https://doi.org/10.1016/j.biotechadv.2018.03.012
27. Chan, B. P., & Leong, K. W. (2008). Scaffolding in tissue engineering: General approaches and tissue-specific considerations. *European Spine Journal*, *17*(S4), 467-479. https://doi.org/10.1007/s00586-008-0745-3
28. Chen, C., Zeldich, E., Li, Y., Yuste, A., & Abraham, C. R. (2018). Activation of the anti-aging and cognition-enhancing gene Klotho by CRISPR-dcas9 transcriptional effector complex. *Journal of Molecular Neuroscience*, *64*(2), 175-184. https://doi.org/10.1007/s12031-017-1011-0
29. Chen, X., Liu, F., Song, X., Wang, Z., Dong, Z., Hu, Z., Lan, R., Guan, W., Zhou, T., Xu, X., Lei, H., Ye, Z., Peng, E., Du, L., & Zhuang, Q. (2010). Rapamycin regulates Akt and ERK phosphorylation through mTORC1 and mTORC2 signaling pathways. *Molecular Carcinogenesis*, *49*(6), 603-610. https://doi.org/10.1002/mc.20628
30. Mokdad, H. (2024). Burden of disease scenarios by state in the USA, 2022-50: a forecasting analysis for the Global Burden of Disease Study 2021. *Lancet (London, England)*, *404*(10469), 2341–2370. https://doi.org/10.1016/S0140-6736(24)02246-3
31. Conti, P. (2020). Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by COVID-19: Anti-inflammatory strategies. *Journal of Biological Regulators and Homeostatic Agents*, *34*(2), 1. https://doi.org/10.23812/conti-e
32. Conway, M. E. (2021). Emerging moonlighting functions of the branched-chain Aminotransferase proteins. *Antioxidants & Redox Signaling*, *34*(13), 1048-1067. https://doi.org/10.1089/ars.2020.8118
33. Daikuara, L. Y., Chen, X., Yue, Z., Skropeta, D., Wood, F. M., Fear, M. W., & Wallace, G. G. (2021). 3D Bioprinting constructs to facilitate skin regeneration. *Advanced Functional Materials*, *32*(3). https://doi.org/10.1002/adfm.202105080
34. Datta, H. S., Mitra, S. K., Paramesh, R., & Patwardhan, B. (2011). Theories and management of aging: Modern and ayurveda perspectives. *Evidence-Based Complementary and Alternative Medicine*, *2011*(1). https://doi.org/10.1093/ecam/nep005
35. De Araújo, R., Lôbo, M., Trindade, K., Silva, D., & Pereira, N. (2019). Fibroblast growth factors: A controlling mechanism of skin aging. *Skin Pharmacology and Physiology*, *32*(5), 275-282. https://doi.org/10.1159/000501145
36. Morris, B. J., Willcox, D. C., Donlon, T. A., & Willcox, B. J. (2015). FOXO3: A Major Gene for Human Longevity - A Mini-Review. *Gerontology*, *61*(6), 515-525. https://doi.org/10.1159/000375235
37. El Assaad, N., Chebly, A., Salame, R., Achkar, R., Bou Atme, N., Akouch, K., Rafoul, P., Hanna, C., Abou Zeid, S., Ghosn, M., & Khalil, C. (2024). Anti-aging based on stem cell therapy: A scoping review. *World Journal of Experimental Medicine*, *14*(3). https://doi.org/10.5493/wjem.v14.i3.97233
38. Elbaky, N. A., El-Orabi, N. F., Fadda, L. M., Abd-Elkader, O. H., & Ali, H. M. (2018). Role of N-acetylcysteine and coenzyme Q10 in the amelioration of myocardial energy expenditure and oxidative stress, induced by carbon tetrachloride intoxication in rats. *Dose-Response*, *16*(3). https://doi.org/10.1177/1559325818790158
39. Feng, R., Wu, S., Li, R., Huang, K., Zeng, T., Zhou, Z., Zhong, X., Songyang, Z., & Liu, F. (2023). Mtorc1-induced bone marrow-derived Mesenchymal stem cell exhaustion contributes to the bone abnormalities in *klotho*-deficient mice of premature aging. *Stem Cells and Development*, *32*(11-12), 331-345. https://doi.org/10.1089/scd.2022.0243
40. Ferrucci, L., & Fabbri, E. (2018). Inflammaging: Chronic inflammation in aging, cardiovascular disease, and frailty. *Nature Reviews Cardiology*, *15*(9), 505-522. https://doi.org/10.1038/s41569-018-0064-2
41. Finkel, T., & Holbrook, N. J. (2000). Oxidants, oxidative stress and the biology of aging. *Nature*, *408*(6809), 239-247. https://doi.org/10.1038/35041687
42. Flachsbart, F., Caliebe, A., Kleindorp, R., Blanché, H., Von Eller-Eberstein, H., Nikolaus, S., Schreiber, S., & Nebel, A. (2009). Association of *FOXO3A* variation with human longevity confirmed in German centenarians. *Proceedings of the National Academy of Sciences*, *106*(8), 2700-2705. https://doi.org/10.1073/pnas.0809594106
43. Flynn, J. M., & Melov, S. (2013). SOD2 in mitochondrial dysfunction and neurodegeneration. *Free Radical Biology and Medicine*, *62*, 4-12. https://doi.org/10.1016/j.freeradbiomed.2013.05.027
44. Fülöp, T., Larbi, A., & Witkowski, J. (2019). Human Inflammaging. *Gerontology*, *65*(5), 495-504. https://doi.org/10.1159/000497375
45. Fulop, T., Larbi, A., Witkowski, J. M., McElhaney, J., Loeb, M., Mitnitski, A., & Pawelec, G. (2010). Aging, frailty and age-related diseases. *Biogerontology*, *11*(5), 547-563. https://doi.org/10.1007/s10522-010-9287-2
46. Gandhi, L., Camidge, D. R., Ribeiro de Oliveira, M., Bonomi, P., Gandara, D., Khaira, D., Hann, C. L., McKeegan, E. M., Litvinovich, E., Hemken, P. M., Dive, C., Enschede, S. H., Nolan, C., Chiu, Y., Busman, T., Xiong, H., Krivoshik, A. P., Humerickhouse, R., Shapiro, G. I., … Rudin, C. M. (2011). Phase I study of Navitoclax (ABT-263), a novel bcl-2 family inhibitor, in patients with small-cell lung cancer and other solid tumors. *Journal of Clinical Oncology*, *29*(7), 909-916. https://doi.org/10.1200/jco.2010.31.6208
47. Gao, G., & Cui, X. (2015). Three-dimensional bioprinting in tissue engineering and regenerative medicine. *Biotechnology Letters*, *38*(2), 203-211. https://doi.org/10.1007/s10529-015-1975-1
48. García-García, V. A., Alameda, J. P., Page, A., & Casanova, M. L. (2021). Role of NF-κb in aging and age-related diseases: Lessons from genetically modified mouse models. *Cells*, *10*(8), 1906. https://doi.org/10.3390/cells10081906
49. Gems, D. (2011). Tragedy and delight: The ethics of decelerated aging. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *366*(1561), 108-112. https://doi.org/10.1098/rstb.2010.0288
50. Giannakou, M. E., & Partridge, L. (2004). The interaction between FOXO and SIRT1: Tipping the balance towards survival. *Trends in Cell Biology*, *14*(8), 408-412. https://doi.org/10.1016/j.tcb.2004.07.006
51. Gkogkolou, P., & Böhm, M. (2012). Advanced glycation end products. *Dermato-Endocrinology*, *4*(3), 259-270. https://doi.org/10.4161/derm.22028
52. Griñán-Ferré, C., Bellver-Sanchis, A., Guerrero, A., & Pallàs, M. (2024). Advancing personalized medicine in neurodegenerative diseases: The role of epigenetics and

pharmacoepigenomics in pharmacotherapy. *Pharmacological Research*, *205*, 107247. https://doi.org/10.1016/j.phrs.2024.107247
53. Grinin, L., Grinin, A., & Korotayev, A. (2024). Global aging and the medicine of the future. *World Futures*, *81*(1), 35-62. https://doi.org/10.1080/02604027.2024.2424723
54. Guarasci, F., D'Aquila, P., Montesanto, A., Corsonello, A., Bellizzi, D., & Passarino, G. (2019). Individual DNA methylation profile is correlated with age and can be targeted to modulate healthy aging and longevity. *Current Pharmaceutical Design*, *25*(39), 4139-4149. https://doi.org/10.2174/1381612825666191112095655
55. Guo, J., Huang, X., Dou, L., Yan, M., Shen, T., Tang, W., & Li, J. (2022). Aging and aging-related diseases: From molecular mechanisms to interventions and treatments. *Signal Transduction and Targeted Therapy*, *7*(1). https://doi.org/10.1038/s41392-022-01251-0
56. Halim, M., & Halim, A. (2019). The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *13*(2), 1165-1172. https://doi.org/10.1016/j.dsx.2019.01.040
57. Han, F., Meng, Q., Xie, E., Li, K., Hu, J., Chen, Q., Li, J., & Han, F. (2023). Engineered biomimetic micro/nano-materials for tissue regeneration. *Frontiers in Bioengineering and Biotechnology*, *11*. https://doi.org/10.3389/fbioe.2023.1205792
58. Harman, D. (2002). Aging: A theory based on free radical and radiation chemistry. *Science of Aging Knowledge Environment*, *2002*(37). https://doi.org/10.1126/sageke.2002.37.cp14
59. 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
60. Hayflick, L., & Moorhead, P. (1961). The serial cultivation of human diploid cell strains. *Experimental Cell Research*, *25*(3), 585-621. https://doi.org/10.1016/0014-4827(61)90192-6
61. Hayflick, L. (2003). Modulating aging, longevity determination and the diseases of old age. *Modulating Aging and Longevity*, 1-15. https://doi.org/10.1007/978-94-017-0283-6_1
62. Hosseini, M., & Shafiee, A. (2021). Engineering Bioactive scaffolds for skin regeneration. *Small*, *17*(41). https://doi.org/10.1002/smll.202101384
63. Huidobro, C., Fernandez, A. F., & Fraga, M. F. (2013). Aging epigenetics: Causes and consequences. *Molecular Aspects of Medicine*, *34*(4), 765-781. https://doi.org/10.1016/j.mam.2012.06.006
64. Hull, E. E., Montgomery, M. R., & Leyva, K. J. (2016). HDAC inhibitors as epigenetic regulators of the immune system: Impacts on cancer therapy and inflammatory diseases. *BioMed Research International*, *2016*, 1-15. https://doi.org/10.1155/2016/8797206
65. Johnson, S., & Imai, S. (2018). NAD+ biosynthesis, aging, and disease. *F1000Research*, *7*, 132. https://doi.org/10.12688/f1000research.12120.1
66. Kang, M. S., Jang, J., Jo, H. J., Kim, W., Kim, B., Chun, H., Lim, D., & Han, D. (2022). Advances and innovations in 3D Bioprinting skin. *Biomolecules*, *13*(1), 55. https://doi.org/10.3390/biom13010055
67. Kenyon, C., Chang, J., Gensch, E., Rudner, A., & Tabtiang, R. (1993). A C. elegans mutant that lives twice as long as wild type. *Nature*, *366*(6454), 461-464. https://doi.org/10.1038/366461a0
68. Kenyon, C. (2011). The first long-lived mutants: Discovery of the insulin/IGF-1 pathway for aging. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *366*(1561), 9-16. https://doi.org/10.1098/rstb.2010.0276
69. Keshavarz, M., Xie, K., Schaaf, K., Bano, D., & Ehninger, D. (2022). Targeting the "hallmarks of aging" to slow aging and treat age-related disease: Fact or fiction? *Molecular Psychiatry*, *28*(1), 242-255. https://doi.org/10.1038/s41380-022-01680-x
70. Khorsandi, D., Moghanian, A., & Nazari, R. (2016). Personalized medicine: Regulation of genes in human skin aging. *Journal of Allergy & Therapy*, *07*(06). https://doi.org/10.4172/2155-6121.1000245
71. 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
72. Laiva, A. L., O'Brien, F. J., & Keogh, M. B. (2021). Anti-aging β-klotho gene-activated scaffold promotes Rejuvenative wound healing response in human adipose-derived stem cells. *Pharmaceuticals*, *14*(11), 1168. https://doi.org/10.3390/ph14111168
73. Lamming, D. W., Ye, L., Sabatini, D. M., & Baur, J. A. (2013). Rapalogs and mTOR inhibitors as anti-aging therapeutics. *Journal of Clinical Investigation*, *123*(3), 980-989. https://doi.org/10.1172/jci64099
74. Li, Y., Hao, J., Hu, Z., Yang, Y., Zhou, Q., Sun, L., & Wu, J. (2022). Current status of clinical trials assessing mesenchymal stem cell therapy for Graft versus host disease: A systematic review. *Stem Cell Research & Therapy*, *13*(1). https://doi.org/10.1186/s13287-022-02751-0
75. Lombardi, F., Augello, F. R., Ciafarone, A., Ciummo, V., Altamura, S., Cinque, B., & Palumbo, P. (2024). 3D models currently proposed to investigate human skin aging and explore preventive and reparative approaches: A descriptive review. *Biomolecules*, *14*(9), 1066. https://doi.org/10.3390/biom14091066
76. Lopes-Paciencia, S., Saint-Germain, E., Rowell, M., Ruiz, A. F., Kalegari, P., & Ferbeyre, G. (2019). The senescence-associated secretory phenotype and its regulation. *Cytokine*, *117*, 15-22. https://doi.org/10.1016/j.cyto.2019.01.013
77. Luengo-Fernandez, R., Walli-Attaei, M., Gray, A., Torbica, A., Maggioni, A. P., Huculeci, R., Bairami, F., Aboyans, V., Timmis, A. D., Vardas, P., & Leal, J. (2023). Economic burden of cardiovascular diseases in the European Union: A population-based cost study. *European Heart Journal*, *44*(45), 4752-4767. https://doi.org/10.1093/eurheartj/ehad583
78. Lutz, M. (2023). Ethical challenges in research regarding aging population. *Medwave*, *23*(08), e2714-e2714. https://doi.org/10.5867/medwave.2023.08.2714
79. Sanada, F., Hayashi, S., & Morishita, R. (2025). Targeting the hallmarks of aging: Mechanisms and therapeutic opportunities. *Frontiers in Cardiovascular Medicine*, *12*. https://doi.org/10.3389/fcvm.2025.1631578
80. Mannick, J. B., & Lamming, D. W. (2023). Targeting the biology of aging with mTOR inhibitors. *Nature Aging*, *3*(6), 642–660. https://doi.org/10.1038/s43587-023-00416-y
81. Martens, C. R., Denman, B. A., Mazzo, M. R., Armstrong, M. L., Reisdorph, N., McQueen, M. B., Chonchol, M., & Seals, D. R.

(2018). Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults. *Nature Communications*, *9*(1). https://doi.org/10.1038/s41467-018-03421-7
82. Mcdonald, R., & Ramsey, J. (2010). Honoring Clive McCay and 75 years of calorie restriction research. *SciVee*. https://doi.org/10.4016/18433.01
83. Mitchell, E., & Walker, R. (2020). Global aging: Successes, challenges and opportunities. *British Journal of Hospital Medicine*, *81*(2), 1-9. https://doi.org/10.12968/hmed.2019.0377
84. Mor, V. (2005). The compression of morbidity hypothesis: A review of research and prospects for the future. *Journal of the American Geriatrics Society*, *53*(9s). https://doi.org/10.1111/j.1532-5415.2005.53496.x
85. Iqbal, Q. M., Iqbal, Z., Iqbal, S., Aftab, M. T., & Rashid, A. (2025). A comprehensive study of BTD: Total reported variants, in-silico analyses and overview of functional studies. *Indus Journal of Bioscience Research*, *3*(10), 1-9. https://doi.org/10.70749/ijbr.v3i10.2372
86. Morris, B. J., Willcox, D. C., Donlon, T. A., & Willcox, B. J. (2015). FOXO3: a major gene for human longevity-a mini-review. *Gerontology*, *61*(6), 515-525. https://doi.org/10.1159/000375235
87. Nobili, A., Garattini, S., & Mannucci, P. M. (2011). Multiple diseases and polypharmacy in the elderly: Challenges for the internist of the third millennium. *Journal of Comorbidity*, *1*(1), 28-44. https://doi.org/10.15256/joc.2011.1.4
88. North, B. J., & Sinclair, D. A. (2012). The intersection between aging and cardiovascular disease. *Circulation Research*, *110*(8), 1097-1108. https://doi.org/10.1161/circresaha.111.246876
89. Risbud, M., Novais, E., Tran, V., Darris, K., Roupas, A., Sessions, G., Shapiro, I., & Diekman, B. (2021). Long-term treatment with senolytic drugs Dasatinib and quercetin ameliorates age-dependent intervertebral disc degeneration in mice. https://doi.org/10.21203/rs.3.rs-123815/v1
90. Novais, P., Silva, P. M., Amorim, I., & Bousbaa, H. (2021). Second-generation Antimitotics in cancer clinical trials. *Pharmaceutics*, *13*(7), 1011. https://doi.org/10.3390/pharmaceutics13071011
91. Novelle, M. G., Ali, A., Diéguez, C., Bernier, M., & De Cabo, R. (2016). Metformin: A hopeful promise in aging research. *Cold Spring Harbor Perspectives in Medicine*, *6*(3), a025932. https://doi.org/10.1101/cshperspect.a025932
92. Nowak, A., Zagórska-Dziok, M., Perużyńska, M., Cybulska, K., Kucharska, E., Ossowicz-Rupniewska, P., Piotrowska, K., Duchnik, W., Kucharski, Ł., Sulikowski, T., Droździk, M., & Klimowicz, A. (2022). Corrigendum: Assessment of the anti-inflammatory, antibacterial and anti-aging properties and possible use on the skin of hydrogels containing epilobium angustifolium L. extracts. *Frontiers in Pharmacology*, *13*. https://doi.org/10.3389/fphar.2022.991766
93. Ferrucci, L., & Fabbri, E. (2018). Inflammaging: Chronic inflammation in aging, cardiovascular disease, and frailty. *Nature Reviews Cardiology*, *15*(9), 505-522. https://doi.org/10.1038/s41569-018-0064-2
94. Ocampo, A., Reddy, P., Martinez-Redondo, P., Platero-Luengo, A., Hatanaka, F., Hishida, T., Li, M., Lam, D., Kurita, M., Beyret, E., Araoka, T., Vazquez-Ferrer, E., Donoso, D., Roman, J. L., Xu, J., Rodriguez Esteban, C., Nuñez, G., Nuñez Delicado, E., Campistol, J. M., … Izpisua Belmonte, J. C. (2016). In vivo amelioration of age-associated hallmarks by partial reprogramming. *Cell*, *167*(7), 1719-1733.e12. https://doi.org/10.1016/j.cell.2016.11.052
95. Ok, S. (2022). Insights into the anti-aging prevention, diagnostic medicine, and healthcare. *Diagnostics*, *12*(4), 819. https://doi.org/10.3390/diagnostics12040819
96. Pacinella, G., Ciaccio, A. M., & Tuttolomondo, A. (2022). Endothelial dysfunction and chronic inflammation: The cornerstones of vascular alterations in age-related diseases. *International Journal of Molecular Sciences*, *23*(24), 15722. https://doi.org/10.3390/ijms232415722
97. Kohly, R., Zajner, C., Huang, R., Popovic, M., Kertes, P., & Muni, R. (2025). Associations between cataract and cognitive impairment in a sample of the United States population. https://doi.org/10.21203/rs.3.rs-7189919/v1
98. Peng, Y., Ding, L., Song, M., Xiao, Z., Lv, J., & Liu, G. (2023). Acting on ethics and governance of aging research. *Trends in Molecular Medicine*, *29*(6), 419-421. https://doi.org/10.1016/j.molmed.2023.03.004
99. Pestieau, P., & Ponthiere, G. (2013). Policy implications of changing longevity. *CESifo Economic Studies*, *60*(1), 178-212. https://doi.org/10.1093/cesifo/ifs042
100. Pezone, A., Olivieri, F., Napoli, M. V., Procopio, A., Avvedimento, E. V., & Gabrielli, A. (2023). Inflammation and DNA damage: Cause, effect or both. *Nature Reviews Rheumatology*, *19*(4), 200-211. https://doi.org/10.1038/s41584-022-00905-1
101. Pezzola, A., & Sweet, C. M. (2016). Global pharmaceutical regulation: The challenge of integration for developing states. *Globalization and Health*, *12*(1). https://doi.org/10.1186/s12992-016-0208-2
102. Poljsak, B., & Milisav, I. (2016). NAD+ as the link between oxidative stress, inflammation, caloric restriction, exercise, DNA repair, longevity, and health span. *Rejuvenation Research*, *19*(5), 406-413. https://doi.org/10.1089/rej.2015.1767
103. Popescu, I., Deelen, J., Illario, M., & Adams, J. (2023). Challenges in anti-aging medicine–trends in biomarker discovery and therapeutic interventions for a healthy lifespan. *Journal of Cellular and Molecular Medicine*, *27*(18), 2643-2650. https://doi.org/10.1111/jcmm.17912
104. Afraz, E. S., Hoseinikhah, S. A., & Moradikor, N. (2025). Recent advances in aging-related diseases: Accelerated aging, molecular mechanisms, interventions, and therapies. *Aging and disease*, *16*(4), 1785. https://doi.org/10.14336/ad.2025.10618
105. Qian, M., & Liu, B. (2018). Pharmaceutical intervention of aging. *Advances in Experimental Medicine and Biology*, 235-254. https://doi.org/10.1007/978-981-13-1117-8_15
106. Ramunas, J., Yakubov, E., Brady, J. J., Corbel, S. Y., Holbrook, C., Brandt, M., Stein, J., Santiago, J. G., Cooke, J. P., & Blau, H. M. (2015). Transient delivery of modified mRNA encoding TERT rapidly extends telomeres in human cells. *The FASEB Journal*, *29*(5), 1930–1939. https://doi.org/10.1096/fj.14-259531
107. Ranjbar, N., Raeisi, M., Barzegar, M., Ghorbanihaghjo, A., Shiva, S., Sadeghvand, S., Negargar, S., Poursistany, H., & Raeisi, S. (2023). The possible anti-seizure properties of Klotho. *Brain Research*, *1820*, 148555. https://doi.org/10.1016/j.brainres.2023.148555
108. RATTAN, S. I. (2000). Biogerontology: The next step. *Annals of the New York Academy of Sciences*, *908*(1), 282-290. https://doi.org/10.1111/j.1749-6632.2000.tb06655.x
109. Rattan, S. I. S. (2018). Biogerontology: research status, challenges and opportunities. *Acta Bio Medica : Atenei Parmensis*, *89*(2), 291–301.

https://doi.org/10.23750/abm.v89i2.7403
110. Renault, V. M., Rafalski, V. A., Morgan, A. A., Salih, D. A., Brett, J. O., Webb, A. E., Villeda, S. A., Thekkat, P. U., Guillerey, C., Denko, N. C., Palmer, T. D., Butte, A. J., & Brunet, A. (2009). FoxO3 regulates neural stem cell homeostasis. *Cell Stem Cell*, *5*(5), 527-539. https://doi.org/10.1016/j.stem.2009.09.014
111. Rogina, B., & Tissenbaum, H. A. (2024). SIRT1, resveratrol and aging. *Frontiers in Genetics*, *15*. https://doi.org/10.3389/fgene.2024.1393181
112. Sancar, A., Lindsey-Boltz, L. A., Ünsal-Kaçmaz, K., & Linn, S. (2004). Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. *Annual Review of Biochemistry*, *73*(1), 39-85. https://doi.org/10.1146/annurev.biochem.73.011303.073723
113. Ros, M., & Carrascosa, J. M. (2020). Current nutritional and pharmacological anti-aging interventions. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1866*(3), 165612. https://doi.org/10.1016/j.bbadis.2019.165612
114. Saliev, T., & Singh, P. (2025). Age reprogramming: Innovations and ethical considerations for prolonged longevity (Review). *Biomedical Reports*, *22*(6), 1-15. https://doi.org/10.3892/br.2025.1974
115. Dominguez-Hernandez, E., Salaseviciene, A., & Ertbjerg, P. (2018). Low-temperature long-time cooking of meat: Eating quality and underlying mechanisms. *Meat Science*, *143*, 104-113. https://doi.org/10.1016/j.meatsci.2018.04.032
116. Schumacher, B., Pothof, J., Vijg, J., & Hoeijmakers, J. H. (2021). The central role of DNA damage in the aging process. *Nature*, *592*(7856), 695-703. https://doi.org/10.1038/s41586-021-03307-7
117. Sheon, R. P. (1991). Injuries of the lower extremity, painful lesions, compartment syndrome, and soft tissue calcification. *Current Opinion in Rheumatology*, *3*(2), 203-206. https://doi.org/10.1097/00002281-199104000-00002
118. Rashid et al., (2025). Aging Anxiety in Pakistani Gen Z: AAS Scores and Perceptions of Genetic Influence. *Journal of Health, Wellness and Community Research*, e859. https://doi.org/10.61919/5gxjrh15
119. Zhao, Y., Simon, M., Seluanov, A., & Gorbunova, V. (2022). DNA damage and repair in age-related inflammation. *Nature Reviews Immunology*, *23*(2), 75-89. https://doi.org/10.1038/s41577-022-00751-y
120. 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
121. Sun, Z. (2015). Aging, arterial stiffness, and hypertension. *Hypertension*, *65*(2), 252-256. https://doi.org/10.1161/hypertensionaha.114.03617
122. Sun, Z. (2015). Aging, arterial stiffness, and hypertension. *Hypertension*, *65*(2), 252-256. https://doi.org/10.1161/hypertensionaha.114.03617
123. Talbourdet, S., Sadick, N. S., Lazou, K., Bonnet-Duquennoy, M., Kurfurst, R., Neveu, M., Heusèle, C., André, P., Schnebert, S., Draelos, Z. D., & Perrier, E. (2007). Modulation of gene expression as a new skin anti-aging strategy. *Journal of Drugs in Dermatology: JDD*, *6*(6 Suppl), s25-33. https://pubmed.ncbi.nlm.nih.gov/17691207/
124. Tan, S. H., Chua, D. A., Tang, J. R., Bonnard, C., Leavesley, D., & Liang, K. (2022). Design of hydrogel-based scaffolds for in vitro three-dimensional human skin model reconstruction. *Acta Biomaterialia*, *153*, 13-37. https://doi.org/10.1016/j.actbio.2022.09.068
125. Luen Tang, B. (2016). Sirt1 and the mitochondria. *Molecules and Cells*, *39*(2), 87-95. https://doi.org/10.14348/molcells.2016.2318
126. Tenchov, R., Sasso, J. M., Wang, X., & Zhou, Q. A. (2024). Antiaging strategies and remedies: A landscape of research progress and promise. *ACS Chemical Neuroscience*, *15*(3), 408-446. https://doi.org/10.1021/acschemneuro.3c00532
127. Unnikrishnan, A., Freeman, W. M., Jackson, J., Wren, J. D., Porter, H., & Richardson, A. (2019). The role of DNA methylation in epigenetics of aging. *Pharmacology & Therapeutics*, *195*, 172-185. https://doi.org/10.1016/j.pharmthera.2018.11.001
128. Valdoz, J. C., Johnson, B. C., Jacobs, D. J., Franks, N. A., Dodson, E. L., Sanders, C., Cribbs, C. G., & Van Ry, P. M. (2021). The ECM: To scaffold, or not to scaffold, that is the question. *International Journal of Molecular Sciences*, *22*(23), 12690. https://doi.org/10.3390/ijms222312690
129. Von Nordheim, F., & Kvist, J. (2022). Regulating the retirement age—Lessons from nordic pension policy approaches. *Regulation & Governance*, *17*(3), 644-657. https://doi.org/10.1111/rego.12475
130. Walters, H. (2024). Pharmacological TERT activation attenuates phenotypes of natural aging. *Nature Aging*, *4*(7), 904-904. https://doi.org/10.1038/s43587-024-00673-5
131. Wang, C., Chen, B., Feng, Q., Nie, C., & Li, T. (2020). Clinical perspectives and concerns of metformin as an anti-aging drug. *AGING MEDICINE*, *3*(4), 266-275. https://doi.org/10.1002/agm2.12135
132. Wang, S., Madu, C. O., & Lu, Y. (2019). Telomere and its role in diseases. *Oncomedicine*, *4*, 1-9. https://doi.org/10.7150/oncm.28210
133. Wątroba, M., & Szukiewicz, D. (2016). The role of sirtuins in aging and age-related diseases. *Advances in Medical Sciences*, *61*(1), 52-62. https://doi.org/10.1016/j.advms.2015.09.003
134. Woo, J., Archard, D., Au, D., Bergstresser, S., Erler, A., Kwok, T., Newman, J., Tong, R., & Walker, T. (2019). Ethical perspectives on advances in biogerontology. *AGING MEDICINE*, *2*(2), 99-103. https://doi.org/10.1002/agm2.12061
135. Xu, L., Freeman, G., Cowling, B. J., & Schooling, C. M. (2013). Testosterone therapy and cardiovascular events among men: A systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Medicine*, *11*(1). https://doi.org/10.1186/1741-7015-11-108
136. Yang, W., Hamilton, J. L., Kopil, C., Beck, J. C., Tanner, C. M., Albin, R. L., Ray Dorsey, E., Dahodwala, N., Cintina, I., Hogan, P., & Thompson, T. (2020). Current and projected future economic burden of Parkinson's disease in the U.S. *npj Parkinson's Disease*, *6*(1). https://doi.org/10.1038/s41531-020-0117-1
137. Zhang, T., Zhou, L., Makarczyk, M. J., Feng, P., & Zhang, J. (2025). The anti-aging mechanism of metformin: From molecular insights to clinical applications. *Molecules*, *30*(4), 816. https://doi.org/10.3390/molecules30040816
138. Zhang, W., Zhou, W., Luo, Z., Huang, Y., & Zhang, H. (2024). Anti-aging therapeutics for the musculoskeletal and cardiovascular systems: The role of regular exercise. *The Innovation Medicine*, *2*(3), 100085. https://doi.org/10.59717/j.xinn-med.2024.100085