Anti-Aging Polypharmacology

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PREFACE

Welcome to "Anti-Aging Polypharmacology: Unlocking the Secrets to Lifelong Health and Vitality," an in-depth exploration of the revolutionary field of polypharmacology and its potential to transform our understanding of aging and longevity. In an era defined by unprecedented advancements in biomedicine and a growing desire to extend the human healthspan, the principles of polypharmacology offer a paradigm-shifting approach to combating age-related decline and promoting optimal aging.

This book represents the culmination of years of research, collaboration, and interdisciplinary inquiry, drawing upon the expertise of leading scientists, clinicians, and thought leaders at the forefront of anti-aging research. Our goal is to provide readers with a comprehensive understanding of the underlying mechanisms of aging, as well as the innovative pharmacological strategies and interventions that hold promise for extending healthspan and lifespan.

At its core, "Anti-Aging Polypharmacology" seeks to unravel the complexities of aging by examining the intricate interplay of cellular processes, molecular pathways, and environmental factors that contribute to age-related degeneration. From the molecular hallmarks of aging, such as genomic instability, telomere attrition, and epigenetic alterations, to the systemic manifestations of aging, including inflammation, metabolic dysfunction, and neurodegeneration, we explore the multifaceted nature of the aging process and the myriad opportunities for intervention.

Central to our exploration is the concept of polypharmacology—a strategic approach that harnesses the synergistic effects of multiple pharmacological agents to target diverse aspects of aging and age-related diseases. By leveraging the power of polypharmacology, we can simultaneously intervene at multiple levels of biological organization, modulating cellular signaling pathways, metabolic processes, and regulatory mechanisms to promote resilience against age-related stressors and enhance overall well-being.

Throughout the pages of this book, we delve into the latest scientific discoveries, clinical trials, and therapeutic interventions that are reshaping our understanding of aging and revolutionizing the practice of anti-aging medicine. From natural compounds and dietary supplements to synthetic drugs and emerging biotechnologies, we explore a diverse array of pharmacological agents and their potential roles in promoting healthy aging and extending lifespan.

But “Anti-Aging Polypharmacology” is more than just a compendium of scientific knowledge—it is a call to action, inspiring readers to embrace a proactive approach to aging and to become active participants in their own healthspan journey. Through evidence-based recommendations, practical insights, and personalized strategies for optimizing aging, we empower individuals to take control of their health and vitality, regardless of age or background.

“Anti-Aging Polypharmacology” is designed to be both informative and actionable, offering practical insights, evidence-based recommendations, and personalized approaches to anti-aging interventions. Whether you are a healthcare professional, researcher, or individual seeking to optimize your own aging journey, this book serves as a valuable resource for understanding the complexities of aging and implementing effective strategies for longevity and vitality.

As we embark on this transformative journey together, let us embrace the spirit of curiosity, innovation, and collaboration in our quest to unlock the secrets of longevity and vitality. May “Anti-Aging Polypharmacology” serve as a guiding light in our pursuit of a healthier, more vibrant future—one in which aging is not merely a process of decline, but an opportunity for growth, resilience, and flourishing. May it also serve as a beacon of hope and knowledge in our quest to defy the limitations of time and age.

Warm regards,
Zhiguo Wang

CHAPTER 1

PANDECT

The decade of 2020–2030 was termed by the World Health Organization (WHO) as the "Decade of Healthy Aging", with the target of sustainably extending healthspan (WHO, 2020). WHO predicts that by 2050, 2.1 billion people worldwide will be over 60 years old, a drastic increase from only 1 billion in 2019 (WHO, 2020). Considering these numbers, strategies to ensure an extended "healthspan" or healthy longevity are urgently needed. Strategies to improve healthy aging include lifestyle modification (to limit the effects of risk behaviors, namely tobacco consumption, and alcohol abuse), regenerative medicine and tissue/organ engineering, manipulation of genes and pathways associated with longevity, and pharmacological compounds to extend healthy lifespan (Jin et al. 2014, 1–5; Rajado et al. 2023, 3191–3217).

Anti-aging pharmacology is a field of research focused on developing pharmaceutical interventions to slow down or reverse the aging process and its associated diseases. While there has been significant progress in understanding the biology of aging and identifying potential targets for intervention, there is still much work to be done before effective anti-aging drugs are widely available. Several clinical trials are underway to evaluate the safety and efficacy of potential anti-aging interventions in humans. These trials often focus on repurposing existing drugs that target aging-related pathways.

Recently, anti-aging research has witnessed a paradigm shift towards Polypharmacology, emphasizing the multifaceted nature of aging processes and the need for comprehensive interventions. Polypharmacology in the context of anti-aging refers to the use of multiple drugs or compounds that target multiple pathways involved in the aging process. This is because aging is a universal biological process that encompasses a myriad of interconnected factors, shaping the trajectory of human health and longevity. From cellular senescence to systemic inflammation, the aging process is inherently multifactorial, defying simplistic explanations or singular interventions.

In this pandect, I delve into the intricacies of aging, explore the rationale behind adopting a Polypharmacological approach, and outline the objectives and structure of a monograph focusing on "Anti-Aging Polypharmacology" by synthesizing the current understanding of anti-aging Polypharmacology, encompassing diverse therapeutic modalities aimed at extending healthspan and lifespan. Through a systematic examination of pharmacological agents, nutraceuticals, lifestyle interventions, and emerging technologies, this monograph explores the intricate interplay of molecular pathways underlying aging and the potential synergies afforded by Polypharmacological approaches. The rationale behind this approach is that aging is a complex and multifactorial process involving various interconnected pathways, and targeting multiple pathways simultaneously may have synergistic effects in slowing down or reversing aging-related decline.

This book endeavors to address the emerging demand for Anti-Aging Polypharmacology as a distinct sub-discipline within Pharmacology. It not only delves into a burgeoning field of pharmacological inquiry but also represents a fresh frontier in drug discovery. Its contents span a comprehensive exploration of current understanding regarding human aging and longevity, Polypharmacology principles, anti-aging drugs and supplements, novel conceptual frameworks, innovative technologies, and translational and clinical applications. Through showcasing state-of-the-art anti-aging strategies and cutting-edge technologies, the book aims to advance Polypharmacology-based approaches in the quest for anti-aging drug discovery.

1.1 Overview of Aging as a Multifactorial Process

Aging unfolds through a complex interplay of genetic, environmental, and lifestyle factors, manifesting at cellular, tissue, and organismal levels. Key hallmarks of aging include telomere shortening, mitochondrial dysfunction, genomic instability, epigenetic alterations, and cellular senescence (please refer to Chapter 2 for detail on 12 hallmarks of aging). Furthermore, age-related changes in inflammation, oxidative stress, hormonal signaling, and metabolic dysregulation contribute to the progressive decline in physiological function observed with advancing age. Importantly, these hallmarks are not isolated phenomena but rather interconnected nodes in a vast network of molecular pathways governing the aging process.

1.2 Rationale for Adopting a Polypharmacological Approach

Given the multifaceted nature of aging, a single-target intervention is unlikely to suffice in mitigating its complexities effectively. Traditional pharmacological approaches often target individual pathways or mechanisms associated with aging, yielding limited efficacy or unintended consequences. In contrast, Polypharmacology embraces the concept of multitarget interventions, leveraging the synergistic effects of multiple compounds or modalities to address the diverse aspects of aging simultaneously (Hopkins 2007, 1110–1111; Hopkins 2008, 682–690; Wang and Yang 2002). By targeting multiple pathways implicated in aging, Polypharmacological interventions offer the potential for enhanced efficacy, resilience against resistance mechanisms, and reduced side effects compared to monotherapies.

Polypharmacology aligns with the systems biology perspective of aging, which recognizes the intricate interconnectedness of biological processes and the need for holistic interventions to modulate aging trajectories comprehensively (Hopkins 2007, 1110–1111; Hopkins 2008, 682–690; Wang and Yang 2002). By simultaneously targeting multiple hallmarks of aging, Polypharmacological approaches aim to restore homeostasis, promote cellular resilience, and extend healthspan—the period of life free from age-related diseases and disabilities.

Notably, the anti-aging agents with experimental verification in animal models and supporting evidence from clinical observation and trials to date are exclusively multitarget compounds that can simultaneously act on multiple aging-related molecules or signaling pathways.

1.3 Objectives and Structure of “Anti-Aging Polypharmacology” Monograph

The monograph on “Anti-Aging Polypharmacology” seeks to elucidate the principles, strategies, and potential applications of Polypharmacological interventions in combating age-related decline and promoting healthy aging. Its objectives are threefold:

1.3.1 Comprehensive Review

The monograph will provide a comprehensive review of the molecular mechanisms underpinning aging, highlighting the interconnected pathways and hallmarks implicated in the aging process (López-Otín et al. 2023, 243–

278). By elucidating the biological basis of aging, readers will gain insights into the rationale for adopting Polypharmacological approaches to target multiple facets of aging simultaneously.

1.3.2 Exploration of Polypharmacological Strategies

Building upon the foundation of aging biology, the monograph will explore diverse Polypharmacological strategies aimed at extending healthspan and lifespan (Wang and Yang, 2022). From pharmacological agents and nutraceuticals to lifestyle interventions and emerging technologies, readers will discover the synergistic potential of multimodal approaches in rejuvenating aging tissues and systems.

1.3.3 Stimulating Research Interest on Anti-Aging Polypharmacology

Stimulating interest in research on anti-aging Polypharmacology involves fostering curiosity, enthusiasm, and engagement among researchers, clinicians, and stakeholders in exploring the potential of Polypharmacological approaches to address age-related decline and promote healthy aging. This endeavor is essential for advancing scientific understanding, developing innovative interventions, and ultimately improving the quality of life for aging populations. Several strategies can be employed to stimulate interest in research on anti-aging Polypharmacology:

Highlighting the potential impact: Emphasize the significance of anti-aging Polypharmacology research in addressing the global challenge of an aging population. By highlighting the potential impact of Polypharmacological interventions in extending healthspan, reducing the burden of age-related diseases, and enhancing quality of life in old age, researchers can generate interest and enthusiasm for this field of study.

Showcasing success stories: Share success stories and breakthroughs in anti-aging Polypharmacology research to inspire and motivate researchers to explore this field further. Highlighting examples of Polypharmacological interventions that have demonstrated promising results in preclinical or clinical studies can serve as compelling evidence of the potential efficacy of this approach.

Promoting interdisciplinary collaboration: Encourage interdisciplinary collaboration between researchers from diverse fields, including pharmacology, gerontology, biochemistry, genetics, and computational biology. Collaboration fosters cross-fertilization of ideas, expertise, and methodologies, leading to innovative approaches and synergistic discoveries in anti-aging Polypharmacology research.

Providing funding and resources: Allocate funding and resources to support research initiatives focused on anti-aging Polypharmacology. Funding agencies, philanthropic organizations, and government institutions play a crucial role in incentivizing and supporting research in this field by providing grants, fellowships, and research infrastructure.

Facilitating knowledge exchange: Facilitate knowledge exchange and dissemination of research findings through conferences, workshops, seminars, and publications. Creating platforms for researchers to present their work, exchange ideas, and engage in discussions fosters a vibrant research community and promotes collaboration in anti-aging Polypharmacology.

Investing in education and training: Invest in education and training programs to develop the next generation of researchers and clinicians with expertise in anti-aging Polypharmacology. Providing opportunities for undergraduate and graduate students, postdoctoral fellows, and early-career researchers to gain hands-on experience in this field cultivates a skilled workforce and ensures the continuity of research efforts.

Addressing ethical and societal implications: Address ethical, legal, and societal implications associated with anti-aging Polypharmacology research to build public trust and support. Engage stakeholders, including policymakers, ethicists, patient advocacy groups, and the general public, in discussions about the potential benefits, risks, and ethical considerations of Polypharmacological interventions for aging.

Overall, stimulating interest in research on anti-aging Polypharmacology requires a concerted effort to raise awareness, foster collaboration, provide resources, promote education and training, facilitate knowledge exchange, and address ethical and societal considerations. By harnessing collective expertise and enthusiasm, researchers can accelerate progress in this dynamic and promising field of study.

1.3.4 Translational Perspectives

In addition to discussing the theoretical framework of anti-aging Polypharmacology, the monograph will explore translational perspectives, including challenges, opportunities, and future directions in the field. By bridging the gap between basic science and clinical application, the monograph aims to catalyze the development of innovative therapies and interventions to address the challenges of global aging populations.

In conclusion, aging represents a multifactorial phenomenon characterized by the interplay of diverse biological processes and environmental influences. Embracing the complexity of aging, a Polypharmacological approach offers a promising avenue for mitigating age-related decline and promoting healthy aging. Through comprehensive reviews, exploration of Polypharmacological strategies, and translational perspectives, the monograph on "Anti-Aging Polypharmacology" endeavors to unravel the intricacies of aging and pave the way for transformative interventions in the quest for prolonged healthspan and longevity.

1.4 Contents of "Anti-Aging Polypharmacology"

1.4.1 Introduction to Molecular Basis and Hallmarks of Aging Process

The initial step in comprehending Anti-Aging Polypharmacology involves revisiting our understanding of the molecular basis of aging, encompassing concepts, mechanisms, and phenomena associated with the aging process. This includes elucidating the hallmarks of aging (López-Otín et al. 2023, 243–278), exploring aging-related diseases, examining aging theories, understanding principles of healthy aging, and investigating the relationships between aging and longevity. Understanding the molecular basis of aging is of paramount importance for several reasons (please see details in Chapters 2 and 3):

Developing interventions for healthy aging: By elucidating the underlying molecular mechanisms driving aging, researchers can identify potential targets for interventions aimed at promoting healthy aging and extending lifespan. These interventions may include pharmacological compounds, lifestyle modifications, and dietary interventions designed to modulate specific pathways associated with aging and age-related diseases.

Prevention and treatment of age-related diseases: Many age-related diseases, such as cancer, cardiovascular disease, neurodegenerative disorders, and metabolic syndromes, share common molecular pathways with aging. By understanding the molecular basis of aging, researchers can identify targets for the prevention and treatment of these diseases. Therapeutic interventions that target aging processes directly may offer a broad-spectrum approach to combating multiple age-related diseases simultaneously.

Identifying biomarkers of aging: Molecular markers of aging, including epigenetic modifications, telomere length, and circulating factors, can serve as biomarkers for assessing biological age and predicting age-related health outcomes. These biomarkers enable early detection of age-related changes and disease risk, facilitating personalized interventions and healthcare strategies tailored to an individual's aging trajectory.

Advancing personalized medicine: Understanding the molecular basis of aging contributes to the development of personalized medicine approaches that take into account an individual's genetic makeup, environmental exposures, and lifestyle factors. By integrating information about aging-related molecular pathways, healthcare providers can tailor preventive measures, screening protocols, and therapeutic interventions to address each individual's unique aging profile and health needs.

Promoting healthspan extension: While extending lifespan is a long-standing goal of aging research, equally important is the extension of healthspan—the period of life free from age-related diseases and disabilities. By targeting the molecular mechanisms underlying aging, interventions can aim not only to prolong lifespan but also to enhance healthspan, enabling individuals to maintain functional independence and quality of life as they age.

Informing public health policy: Insights into the molecular basis of aging can inform public health policies aimed at promoting healthy aging and reducing the burden of age-related diseases on society. By addressing modifiable risk factors associated with aging, such as diet, physical activity, and environmental exposures, policymakers can implement preventive strategies and healthcare initiatives that promote healthy aging across populations.

In summary, understanding the molecular basis of aging is essential for developing interventions to promote healthy aging, preventing age-related diseases, advancing personalized medicine, and informing public health policies. By unraveling the complex molecular mechanisms underlying aging, researchers can pave the way for innovative strategies to enhance healthspan, improve quality of life in old age, and address the societal challenges associated with global aging populations.

The molecular basis of aging refers to the underlying cellular and biochemical processes that contribute to the progressive decline in physiological function and increased susceptibility to age-related diseases observed with advancing age. Aging is a multifaceted phenomenon influenced by a complex interplay of genetic, environmental, and lifestyle factors. Understanding the molecular mechanisms underlying aging is crucial for developing interventions to promote healthy aging and extend lifespan.

Several key hallmarks of aging have been identified at the molecular level (López-Otín et al. 2023, 243–278). These hallmarks represent common features or pathways that are dysregulated during the aging process.

While each hallmark can contribute independently to aging, they are often interconnected and mutually reinforcing. Understanding these molecular hallmarks of aging provides insights into the underlying mechanisms driving age-related decline and disease. Targeting these pathways holds promise for developing interventions to promote healthy aging and extend lifespan. Strategies such as caloric restriction, pharmacological interventions, and lifestyle modifications aim to modulate these molecular processes to promote longevity and reduce the burden of age-related diseases. For detailed information on 12 hallmarks of aging, please refer to Chapter 2.

1.4.2 Introduction to Polypharmacology

The subsequent phase in grasping Anti-Aging Polypharmacology involves gaining fundamental insights into the basics of Polypharmacology (Hopkins 2007, 1110–1111; Hopkins 2008, 682–690; Wang and Yang 2002). This encompasses understanding its concept, principles, characteristics, mission, and objectives, as well as acknowledging the opportunities it presents and the challenges it poses. Understanding the basics of Polypharmacology is crucial for advancing anti-aging Polypharmacology for several reasons (please see details in Chapter 4):

Multifactorial nature of aging: Aging is a complex process influenced by multiple interconnected factors. Polypharmacology recognizes this multifactorial nature and offers a holistic approach by targeting multiple pathways simultaneously. Understanding the basics of Polypharmacology enables researchers to identify synergistic combinations of compounds that can effectively modulate various aspects of aging, such as inflammation, oxidative stress, and cellular senescence.

Enhanced efficacy: Polypharmacological interventions have the potential to achieve greater efficacy compared to single-target therapies. By targeting multiple molecular pathways involved in aging, Polypharmacological approaches can produce additive or synergistic effects, leading to more profound improvements in healthspan and longevity. Understanding the principles of Polypharmacology allows researchers to design rational combinations of compounds that maximize therapeutic benefits.

Delaying resistance and adaptation: One of the challenges in anti-aging therapy is the development of resistance or adaptation to single-target interventions over time. Polypharmacology can mitigate this issue by simultaneously targeting multiple points of vulnerability in aging pathways, making it more difficult for cells or organisms to develop resistance. By understanding the characteristics of Polypharmacology, researchers can design interventions that delay or prevent the onset of resistance, thereby prolonging the effectiveness of anti-aging treatments.

Comprehensive intervention: Aging is characterized by the dysregulation of numerous biological processes, including DNA repair, mitochondrial function, and cellular senescence. Polypharmacological interventions offer a comprehensive approach by addressing multiple hallmarks of aging simultaneously. Understanding the mission and tasks of Polypharmacology enables researchers to develop integrated strategies that comprehensively modulate aging processes, leading to more profound and lasting effects on healthspan and lifespan.

Optimizing safety and tolerability: Polypharmacological interventions may involve the simultaneous administration of multiple compounds, raising concerns about safety and tolerability. However, a thorough understanding of Polypharmacology principles allows researchers to identify combinations of compounds that minimize adverse effects and maximize therapeutic benefits. By balancing the potential risks and benefits of Polypharmacological interventions, researchers can optimize safety and tolerability profiles, ensuring that anti-aging therapies are well-tolerated and suitable for long-term use.

In summary, understanding the basics of Polypharmacology is essential for advancing anti-aging Polypharmacology by enabling researchers to design rational, comprehensive, and effective interventions that target multiple aspects of aging simultaneously. By harnessing the principles of Polypharmacology, researchers can develop innovative strategies to promote healthy aging and extend lifespan, ultimately improving the quality of life for aging populations.

1.4.3 Introduction to Overall Anti-Aging Interventions

The third step towards better understanding Polypharmacology in anti-aging therapy is to acquire general knowledge about overall anti-aging interventions that have been experimentally tested and validated for their potential efficacies (Teut and Ortiz 2021, 383–386; Knowles et al. 2016, 467–476). In other words, understanding overall anti-aging interventions is crucial for gaining insight into Polypharmacology as a pharmacological intervention for several reasons (please see details in Chapter 5):

Contextualization of Polypharmacology: Polypharmacology, as a pharmacological approach, involves the simultaneous targeting of multiple molecular pathways or targets to achieve therapeutic effects. By understanding overall anti-aging interventions, researchers can contextualize Polypharmacology within the broader framework of aging biology and therapeutic strategies. This contextualization enables researchers to identify relevant targets and pathways implicated in aging and design Polypharmacological interventions that address multiple aspects of age-related decline comprehensively.

Identification of synergistic targets: Overall anti-aging interventions encompass a diverse array of modalities, including pharmacological compounds, dietary interventions, lifestyle modifications, and behavioral strategies. By examining the mechanisms of action and therapeutic targets of these interventions, researchers can identify synergistic targets and pathways that may be amenable to Polypharmacological modulation. Understanding how different interventions interact and converge on common pathways provides valuable insights into the rational design of Polypharmacological interventions for aging.

Integration of multiple modalities: Polypharmacology offers the flexibility to integrate multiple modalities and compounds to achieve synergistic effects and enhance therapeutic outcomes. By understanding overall anti-aging interventions, researchers can identify complementary approaches that target different aspects of aging biology and combine them synergistically in Polypharmacological interventions. For example, combining pharmacological agents that target inflammation with dietary interventions that modulate metabolism may produce additive or synergistic effects in mitigating age-related inflammation and metabolic dysfunction.

Optimization of therapeutic strategies: Overall anti-aging interventions provide a wealth of knowledge about effective strategies for promoting healthy aging and extending lifespan. By analyzing the efficacy, safety, and tolerability of different interventions, researchers can optimize Polypharmacological strategies to maximize therapeutic benefits while minimizing adverse effects. This optimization process involves selecting the most promising compounds, determining appropriate dosages and treatment regimens, and monitoring outcomes to ensure optimal outcomes for individuals undergoing Polypharmacological interventions.

Translational potential: Understanding overall anti-aging interventions enhances the translational potential of Polypharmacology by informing the development of evidence-based interventions for aging-related conditions. By leveraging insights from clinical trials and observational studies on overall anti-aging interventions, researchers can design rigorous clinical trials to evaluate the safety and efficacy of Polypharmacological interventions in human populations. This translational research is essential for advancing Polypharmacology as a viable therapeutic approach for promoting healthy aging and extending healthspan in clinical practice.

In summary, understanding overall anti-aging interventions is integral to gaining a deeper understanding of Polypharmacology as a pharmacological intervention for aging (Teut and Ortiz 2021, 383–386; Knowles et al. 2016, 467–476). By contextualizing Polypharmacology within the broader landscape of aging biology and therapeutic strategies, researchers can identify synergistic targets, integrate multiple modalities, optimize therapeutic strategies, and enhance the translational potential of Polypharmacological interventions for aging-related conditions.

1.4.4 Introduction to Basics, Strategies, Therapeutic Targets, and Technologies of Anti-Aging Polypharmacology

Understanding the basics, strategies, therapeutic targets, and technologies of anti-aging Polypharmacology is essential for gaining a comprehensive understanding of anti-aging Polypharmacology (Wang and Yang 2002). Specifically, these aspects encompass designing rational interventions, identifying potential therapeutic targets, optimizing treatment outcomes, and advancing translational research efforts aimed at promoting healthy aging and extending healthspan. By leveraging this knowledge, researchers can develop innovative Polypharmacological interventions with the potential to transform the landscape of anti-aging medicine and improve outcomes for aging populations.

Foundational knowledge: Acquiring a solid understanding of the basics of pharmacology, including drug-receptor interactions, pharmacokinetics, and pharmacodynamics, provides a foundational framework for comprehending Polypharmacology. Understanding these fundamental principles allows researchers to appreciate the complexities of Polypharmacological interventions and their potential effects on biological systems.

Strategic design: Understanding the strategies employed in Polypharmacology is crucial for designing effective interventions. Polypharmacological approaches may involve targeting multiple pathways simultaneously, exploiting synergistic interactions between compounds, or modulating diverse biological processes to achieve desired therapeutic outcomes. Familiarity with these strategies enables researchers to design rational and strategic Polypharmacological interventions for anti-aging purposes (Wang and Yang 2002).

Identification of therapeutic targets: Knowledge of the molecular targets involved in aging and age-related diseases is essential for identifying potential therapeutic targets for Polypharmacological interventions. Aging is a multifactorial process involving the dysregulation of numerous molecular pathways, including those related to inflammation, oxidative stress, mitochondrial function, and cellular senescence. Understanding the underlying mechanisms of aging enables researchers to identify key targets for intervention and design Polypharmacological approaches that address multiple aspects of age-related decline (Wang and Yang 2002).

Optimization of therapeutic outcomes: Understanding the basics, strategies, and therapeutic targets of anti-aging Polypharmacology facilitates the optimization of therapeutic outcomes. By strategically targeting multiple pathways implicated in aging, Polypharmacological interventions have the potential to produce synergistic effects, enhance efficacy, and minimize adverse effects compared to single-target therapies. Knowledge of therapeutic targets enables researchers to select appropriate compounds, optimize dosing regimens, and monitor treatment responses to achieve optimal outcomes for individuals undergoing anti-aging interventions.

Translational research: A thorough understanding of anti-aging Polypharmacology is essential for translational research aimed at bringing Polypharmacological interventions from the laboratory to clinical practice. Translating Polypharmacological interventions requires rigorous preclinical studies to elucidate mechanisms of action, assess efficacy and safety profiles, and optimize treatment protocols. Knowledge of basic principles, strategies, and therapeutic targets informs the design and implementation of translational research studies, accelerating the translation of promising interventions into clinical applications for aging populations.

In Chapters 6 and 7, the perspectives on understanding the basics, strategies, and therapeutic targets for anti-aging Polypharmacology are introduced. This chapter serves as a pivotal point in the monograph, providing readers with foundational knowledge and strategic insights essential for comprehending the complexities of Polypharmacological interventions in the context of anti-aging therapy.

Within Chapters 6 and 7, readers delve into the fundamental principles of pharmacology, including drug-receptor interactions, pharmacokinetics, and pharmacodynamics, laying the groundwork for understanding Polypharmacology (Wang and Yang 2002). Additionally, the chapter explores the strategic approaches employed in Polypharmacology, such as targeting multiple pathways simultaneously and exploiting synergistic interactions between compounds. By elucidating these strategies and methodologies, readers gain insights into the rational design and strategic implementation of Polypharmacological interventions for anti-aging purposes (Wang and Yang 2002).

Moreover, Chapters 6 and 7 delve into the identification of therapeutic targets implicated in aging and age-related diseases. Readers explore the multifactorial nature of aging, encompassing dysregulation of molecular pathways such as inflammation, oxidative stress, mitochondrial function, and cellular senescence. Understanding these underlying mechanisms is paramount for identifying potential therapeutic targets and designing Polypharmacological interventions that comprehensively address age-related decline.

Through Chapters 6 and 7, readers are equipped with the knowledge and strategic insights necessary for optimizing therapeutic outcomes and advancing translational research efforts in anti-aging Polypharmacology. By leveraging the perspectives introduced in this chapter, researchers can develop innovative Polypharmacological interventions with the potential to transform the landscape of anti-aging medicine and improve outcomes for aging populations.

1.4.5 Introduction to Currently Available Multitarget Anti-Aging Agents

In Chapters 8 through 19, I will introduce multitarget anti-aging agents that have undergone experimental testing and validation. Some of these agents are further supported by clinical observations and trials, while others hold significant potential to evolve into anti-aging medicines in the future. The arrangement of these chapters is primarily structured around the commonly accepted 12 hallmarks of aging (López-Otín et al. 2023, 243–278). Due to the multitargeting nature of both exogenous compounds and endogenous factors involved in anti-aging mechanisms, the agents are grouped into specific categories based on their primary mechanisms of action. Each category of multitarget anti-aging agents is introduced with discussions on their primary, secondary, and tertiary actions, among others. The contents of these chapters constitute the main body of this Anti-Aging Polypharmacology monograph and also serve as illustrative examples for the concepts, principles, strategies, and technologies of Polypharmacology.

Collectively, this pandect underscores the transformative potential of Anti-Aging Polypharmacology in reshaping our approach towards extending healthspan and lifespan. By embracing the complexity of aging processes and harnessing the synergistic effects of multimodal interventions, we can aspire to redefine aging as a modifiable risk factor, ushering in an era of proactive and personalized longevity medicine.

1.5 Scope of "Anti-Aging Polypharmacology"

The scope of this book is designed to appeal to diverse audiences, encompassing scientists engaged in pharmacological research and drug development, university educators and students in medical schools or schools of pharmacy, as well as medical doctors and healthcare practitioners committed to promoting healthy aging across the global population. By addressing these varied readerships, the book aims to contribute to the promotion of healthy aging across the global population.

Aging and longevity have long been subjects of widespread interest. The pursuit of extending chronological age has evolved into advocating for healthy aging or prolonging healthspan—the years individuals remain healthy, free from disease and disabilities. Aging, a degenerative process influenced by multiple genetic and environmental factors, is not a disease but a therapeutic target that can be pharmacologically addressed to promote healthy aging and extend healthspan, thereby contributing to longevity. Given its multifaceted nature, aging can be optimally managed through Polypharmacology-based treatments.

Anti-aging Polypharmacology emerges as a new subdiscipline within Pharmacology, encompassing and integrating novel concepts and fundamental knowledge about human aging and Polypharmacology. It showcases innovative anti-aging strategies, state-of-the-art technologies, creative approaches, and cutting-edge methodologies for Polypharmacology-based anti-aging drug discovery. The primary emphasis is on rationally designed Polypharmacology, also known as "multi-target drug (MTD)" pharmacology, which represents the predominant future direction of pharmacological research and drug discovery.

The book is enriched with illustrations and tables to facilitate better understanding of the concepts and technologies related to Polypharmacology.

It offers a clear roadmap to guide readers in comprehensively understanding the new concepts, principles, strategies, and technologies of Anti-aging Polypharmacology, as well as navigating the challenges in their research and applications.

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CHAPTER 2

AGING AND HEALTHY AGING

2.1 Aging

Aging or decrepitude is a topic of a commonplace talk of an old scholar, but there is no unified definition of aging. On the contrary, different people have different interpretations of aging, but none of them can encompass all aspects of aging process because it involves omnibearing alterations of an organism.

Here, I attempt to provide comprehensive descriptions of aging by condensing it into 7 distinct "Ds," allowing readers to formulate their own definitions based on these descriptions. Aging represents a universal, intrinsic, inevitable, and unalterable progression marked by the following phenomena:

1. **Destruction:** Aging entails the gradual degradation of both molecular (microscopic) and anatomical (macroscopic) structures, which typically peak during an individual's developmental and maturation stages within a given species.
2. **Decomposition:** It involves the breakdown of organismic complexity.
3. **Deterioration:** Aging results in the decline of physiological functions across all levels, including the molecular, cellular, tissue, organ, and organismic levels.
4. **Degradation:** This manifests as the deterioration of intercellular materials, such as a reduction in the number of elastic fibers and cross-links of collagen fibers in the dermis.
5. **Deregulation:** Aging disrupts the internal balance and homeostasis of an organism.
6. **Decline:** It encompasses the reduction in fecundity, leading to the failure of normal biological activities and metabolic processes within an individual.
7. **Degeneration:** Aging is marked by a decline in utility, encompassing both biological and societal aspects, and is characterized

demographically by an age-dependent increase in the risk of morbidity and the probability of mortality.

In essence, aging is a complex, multifactorial, multifaceted, multidimensional, multilayered, hierarchical process that resists easy dissection into discrete subprocesses. Biological aging represents a series of functional, structural, and biochemical changes that affect cells and organs, disrupt the body's homeostasis, contribute to the onset of diseases and disability, and ultimately culminate in mortality.

2.2 Aging Process

The aging process is typically divided into four distinct phases: the initial/healthy phase, the intermediate/subhealthy phase, the advanced/diseased phase, and the near-death/terminal phase.

2.2.1 Asymptomatic Stage of Aging Process

The initial stage of aging is asymptomatic and even imperceptible, despite that the overall health state of an individual decreases gradually with increasing age. This phase generally begins from an age of 25~30, nearly double the 1time (3~14 years) required for sexual maturity, in humans.

2.2.2 Subhealthy Stage of Aging Process

The intermediate stage is a phase characterized by suboptimal health status or subhealth status. Subhealth can be defined as a state marked by disturbances in psychological behaviors and/or physical characteristics, or by certain suboptimal indicators in medical examinations, without typical pathological features. Individuals in a subhealthy state may experience a range of discomforts or symptoms, but they do not manifest any obvious and illnesses detectable through standard medical observation methods (Li 2013, 446–462). This phase of the aging process typically commences from the age of 35, coinciding with the emergence of the first of three waves of aging (Lehallier et al. 2019, 1843–1850). The combined duration of healthy and subhealthy phases is equivalent to healthspan, a concept that will be introduced in the final subsection of this chapter.

2.2.3 Diseased Stage of Aging Process

The advanced phase is the pathological stage or diseased stage of aging process accompanied by one or more of morbidities, particularly the noncommunicable chronic diseases such as cardiovascular diseases, cancer, hypertension, diabetes, obesity, chronic kidney failure, osteoporosis, arthritis, Alzheimer's disease, and chronic obstructive pulmonary disease. It should be noted, however, individuals suffering from these diseases without definite sings or hallmarks of aging may not necessarily be in the aging process. The diseased stage commonly commences from ages of 55 or 60 years old, corresponding to the second of three waves of aging (Lehallier et al. 2019, 1843–1850). The length of this phase is equivalent to morbidity lifespan (Blagosklonny 2021, 110–119).

2.2.4 Near-death Stage of Aging Process

The terminal phase of aging refers to the situation where individuals entering the near-death stage. About half of those over 85 are disabled (defined as the inability to use public transportation). Over 75% of people >85 years have 3~9 pathological conditions, and the cause of death for these people is frequently unknown.

Interestingly, Lehallier et al. investigated undulating changes during the human lifespan by measuring 2,925 plasma proteins from 4,263 young adults to nonagenarians (18~95 years old) (Lehallier et al. 2019, 1843–1850). They identified three waves of changes in the proteome with differentially expressed proteins at ages 34, 60, and 78, which reflects distinct biological pathways and revealed differential associations with the genome and proteome of age-related diseases and phenotypic traits. These changes are the result of clusters of proteins moving in distinct patterns, culminating in the emergence of 3 waves of aging. These clusters are often part of shared biological pathways, particularly cellular signaling.

It should be noted that different parts of the body may age at different ages with different rates.

2.3 Symptoms of Aging

Though aging is presently not considered a disease in scientific community, it has certain “symptoms”. In developed countries, typical age changes mainly include two categories: non-lethal changes and lethal changes. For example, graying of hair is a symptom of aging, but graying does not increase likelihood of mortality. Morbidities in some core systems or organs such as acute cardiovascular events or cancers are deadly.

The typical symptoms of aging include the following:

(1) A loss of hearing ability, particularly for higher frequencies.

(2) There is a decline in the ability to taste salt and bitter (sweet and sour are much less affected).
(3) There is a reduction of the thymus gland to 5~10% of its original mass by age 50.
(4) Levels of antibodies increase with aging.
(5) One third of men and half of women over 65 report some form of arthritis.
(6) About half of those aged 65 have lost all teeth.
(7) The elderly require twice as much insulin to achieve the glucose uptake of the young. There is reduced sensitivity to growth factors and hormones due to fewer receptors and dysfunctional post-receptor pathways.
(8) The temperature needed to separate DNA strands increases with age.
(9) Weight declines after age 55 due to loss of lean tissue, water and bone (cell mass at age 70 is 36% of what it is at age 25).
(10) Body fat increases to age 60.
(11) Muscle strength for men declines 30~40% from age 30 to age 80.
(12) Reaction time declines 20% from age 20 to 60.
(13) Elderly people tend to sleep more lightly, more frequently and for shorter periods—with a reduction in rapid eye-movement (REM) sleep.
(14) Neurogenesis in the hippocampus declines with age.
(15) Degree of saturation of fats drops by 26% in the brains of old animals.
(16) Presbyopia (reduced ability to focus on close-up objects) occurs in 42% of people aged 52~64, 73% of those 65~74 and 92% of those over age 75. Most people over age 75 have cataracts.
(17) About half of those over 85 are disabled (defined as the inability to use public transportation).
(18) Over 75% of people over 85 have 3~9 pathological conditions, and the cause of death for these people is frequently unknown.

Aging changes are frequently associated with an increase in likelihood of mortality. Aging changes which are not associated with a specific disease, but which are associated with a generalized increase in mortality would qualify as biomarkers of aging and would distinguish biological age from chronological age (to be discussed below). Biomarkers would be better predictors of the increased likelihood of mortality (independent of specific disease) than the passage of time (chronological age). Cross-linking of collagen, insulin resistance and lung expiration capacity have been proposed as candidates but, as yet, no biomarkers of aging have been validated and universally accepted. This concept was first proposed in a seminal paper published in 2013 by López-Otín et al. (2013, 1194–1217), which identified nine hallmarks of aging. These hallmarks represent interconnected biological processes that play a role in the aging process.

2.4 Hallmarks of Aging

In the context of aging, "hallmarks" refer to a set of fundamental biological processes or characteristics that are associated with aging and age-related diseases. The concept of hallmarks of aging was introduced to provide a framework for understanding the underlying mechanisms that contribute to the aging process and its associated health decline. It was first proposed in a seminal paper published in 2013 by López-Otín et al., which identified nine hallmarks of aging (López-Otín et al. 2013, 1194–1217), and revised by the same authors 10 years later in 2023 with addition of three new hallmarks (López-Otín et al. 2023, 243–278). These 12 hallmarks represent interconnected biological processes that play a role in the aging process, and thus increasingly recognized as potential therapeutic targets for aging and aging-related diseases (Partridge 2020, 5513–532). They are introduced below primarily based upon the article by López-Otín et al. (López-Otín et al. 2023, 243–278) (**Figure 2-1**).

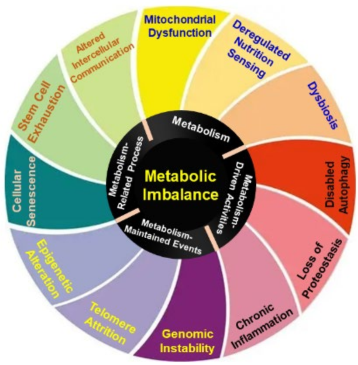

Figure 2-1. The 12 Hallmarks of Aging Proposed by López-Otín et al. (López-Otín et al. 2023, 243–278)

2.4.1 Genomic Instability

According to López-Otín *et al*. (López-Otín et al. 2023, 243–278), throughout life, genome integrity and stability are pervasively threatened and damaged from various sources, including exposure to exogenous chemicals, toxins, and radiations, as well as to endogenous challenges such as DNA replication errors, chromosome segregation defects, oxidative stress, and metabolic byproducts. The wide range of genetic lesions caused by these extrinsic or intrinsic sources of damage include point mutations, deletions, translocations, telomere shortening, single- and double-strand breaks, chromosomal rearrangements, defects in nuclear architecture, and gene disruption caused by the integration of viruses or transposons. All these molecular alterations and the resulting genomic mosaicism can cause natural and pathological aging. Accordingly, organisms have evolved a complex array of DNA repair and maintenance mechanisms to deal with the damage inflicted to nuclear and mitochondrial DNA (mtDNA) and to ensure the appropriate chromosomal architecture and stability. These DNA repair networks, however, lose efficiency with age, which accentuates the accumulation of genomic damage and the ectopic accumulation of DNA in the cytosol, impairing cellular function and leading to aging and age-related diseases.

Damages to genomic instability mainly include the following three aspects:

2.4.1.1 Nuclear DNA (nDNA)

Cells from aged humans and model organisms accumulate somatic mutations at nDNA. These nDNA alterations may affect essential genes and transcriptional pathways, resulting in dysfunctional cells that may finally compromise tissue and organismal homeostasis. This is especially relevant when nDNA damage impacts on stem cells, hampering their role in tissue renewal or leading to their exhaustion, which in turn promotes aging and increases susceptibility to age-related pathologies.

2.4.1.2 Mitochondrial DNA (mtDNA)

Mitochondria are organelles within cells that are responsible for energy production through oxidative phosphorylation. They have their own DNA (mtDNA), separate from the nuclear DNA, which is solely inherited from the mother. mtDNA and its role in aging have been the subject of significant scientific interest.

mtDNA is strongly impacted by aging-associated mutations and deletions due to its high replicative index, the limited efficiency of its repair mechanisms, its oxidative microenvironment, and the lack of protective histones embracing this small DNA molecule. Over time, mtDNA accumulate mutations more rapidly than nDNA due to several factors. Mitochondria generate reactive oxygen species (ROS) as a byproduct of energy production, and this can lead to oxidative damage to mtDNA. Additionally, mitochondria lack certain DNA repair mechanisms present in the nucleus, making mtDNA more vulnerable to mutations. The accumulation of mtDNA mutations can impair mitochondrial function, leading to energy deficits and increased oxidative stress, which are associated with aging. Indeed, somatic mtDNA damages increase across human tissues during aging, but it remains unclear whether this increase truly impacts the aging process at the functional level. Mitochondrial dysfunction contributes to various age-related diseases and conditions, such as neurodegenerative disorders, cardiovascular diseases, metabolic disorders, and frailty.

Mitochondria and the nuclear genome work closely together, with interactions and communications between them. Dysfunction in either the mitochondrial or nuclear genome can impact the other, affecting overall cellular function and contributing to aging. Disrupted mitochondrial-nuclear crosstalk can lead to a cascade of effects, including impaired energy metabolism, increased oxidative stress, and altered gene expression, which contribute to the aging process. Targeting mitochondrial dysfunction and exploring interventions to preserve mitochondrial health are areas of interest for potential strategies to promote healthy aging and mitigate age-related diseases.

Nonetheless, the causal implication of mtDNA mutations in driving aging has been difficult to assess because of ‘‘heteroplasmy,’’ which refers to the presence of a mixture of normal and mutated mtDNA within the same cell. Moreover, experimental evidence demonstrating deceleration of aging by gain of function in mtDNA repair mechanisms is also largely missing.

2.4.1.3 Nuclear architecture

Defects in the nuclear lamina, which constitutes a scaffold for tethering chromatin and protein complexes, can generate genome instability (López-Otín et al. 2023, 243–278). Accelerated aging syndromes such as the Hutchinson-Gilford and the Néstor-Guillermo progeria syndromes are caused by mutations in genes LMNA and BANF1 encoding protein components of nuclear lamina.

Alterations of the nuclear lamina and production of an aberrant prelamin A isoform called progerin are also characteristics of normal human aging, and lamin B1 levels decline during cellular senescence. The causal implication of nuclear lamina abnormalities in premature aging has been