GMR
The Original

COMPUTATIONAL AND AI-BASED DRUG REPURPOSING APPROACHES IN ANTI-AGING RESEARCH

Anand Babu K*[1], Naveen Kumaran V G[2], Naveen Kumar N[3], Mageswaran J[4], Dhatchinamoorthy B[5], Priyadharshini S[6], Thoshan Kumar E V[7], Karthick P[8], Meenakshi Sundharam R[9]

[1*]GRT Institute of Pharmaceutical Education and Research, GRT Mahalakshmi Nagar, Chennai- Tirupathi Highway, Tiruttani, Thiruvallur district - 631209, Tamil Nadu, India, E-mail: anandanalyst85@gmail.com
[2,3,4,5,6,7,8,9]GRT Institute of Pharmaceutical Education and Research, GRT Mahalakshmi Nagar, Chennai- Tirupathi Highway, Tiruttani, Thiruvallur district -631209, Tamil Nadu, India

ABSTRACT
Aging is a multilevel biological process characterized by the progressive loss of structural and functional integrity in tissues and organs, ultimately leading to various diseases. Advances in geroscience and computational biology have accelerated the discovery of potential anti-aging compounds, especially through drug repurposing approaches that utilise existing natural products and approved drugs for novel therapeutic applications.
In this review article, we summarize the current understanding of the molecular hallmarks of aging, including DNA damage, genomic instability, mitochondrial dysfunction, impaired proteostasis, and dysregulation of nutrient-sensing pathways. The review discussed the computational and AI approaches that have been used to systematically search for geroprotectors, including machine learning, deep learning, network-based and signature-based approaches, along with the high-throughput techniques that have enabled the rapid identification of compounds that extend lifespan.
In summary, the present review provides an updated framework to harness the advances in molecular biology and computational science for AI-assisted repurposing of anti-aging therapeutics.

KEYWORDS: Aging; Drug repurposing; Geroscience; Artificial intelligence; Natural anti-aging agents; Computational biology; DNA damage..

INTRODUCTION
Aging is the gradual deterioration of bodily functions and increased risk of disease and death. It was believed to be an immutable, universal, and inevitable process, but it is now clear that the process is modifiable. Metabolic, environmental, and genetic factors are responsible for this, and as a result, aging is no longer considered an inevitable degenerative process but a biological change that can be modified and treated [1-6].
In the last 10 years, the goal of aging research has changed from extending the lifespan to extending the healthspan (the number of years a person stays healthy). Out of various approaches to developing pharmaceuticals, drug repurposing is one of the most cost-effective. Finding new therapeutic uses for existing drugs that have already been proven to be safe can help ease the clinical approval for geroprotective therapies [7,8].
Therefore, this study aims to analyze current advancements in geroscience and computational drug repurposing, as well as to present a conceptual framework for AI-enabled precision gerotherapy. By combining molecular hallmarks of aging, multi-omics technologies, network pharmacology, explainable artificial intelligence, and translational clinical research, this review gives an in-depth vision of the future of individualized anti-aging therapy. It highlights the present scientific hurdles, identifies crucial information gaps, and depicts a translational roadmap to expedite the development of safe, efficacious, and personalized gerotherapeutic approaches.

2. BIOLOGICAL BASIS OF AGING
2.1. Molecular and Cellular Hallmarks
The main characteristics of aging consist of DNA damage, shortening of telomeres, changes in epigenetics, dysfunction of mitochondria, loss of proteostasis, depletion of stem cells, and persistent inflammation [5,7]. These molecular disruptions lead to a decrease in the physiological resilience of aging organisms.

2.2. DNA Damage and Genomic Instability
Genomic instability and DNA damage play crucial roles in the aging process. Reactive oxygen species, commonly referred to as ROS, are known to cause significant damage to DNA. These species originate from both internal metabolic activities and external influences like UV radiation and environmental toxins. Although cells have complex repair mechanisms, these systems generally become less effective as we grow older. This results in an increase in mutations, a decline in tissue regeneration, and the presence of older cells that are more susceptible to illness.[4,5,7]

2.3 Mechanistic Basis of Major Anti-Aging Pathways

The biological processes that govern aging consist of linked signaling pathways that manage cellular metabolism, stress response, autophagy, inflammation, and the balance of mitochondrial function [8-10]. Various pharmaceutical and natural substances demonstrate geroprotective properties by influencing these conserved molecular pathways.

2.3.1 AMPK Signaling Pathway

AMP-activated protein kinase (AMPK) acts as a cellular energy sensor that activates during metabolic stress and when ATP levels are low [11-12]. When AMPK activates, it encourages autophagy, mitochondrial biogenesis, glucose balance, and fatty acid oxidation. At the same time, it reduces anabolic processes linked to mTOR signaling [11-13]. Metformin, resveratrol, berberine, and EGCG are AMPK activators that have been linked to longer lifespans in experimental models. [12-14].

2.3.2 mTOR Pathway

The mechanistic target of rapamycin (mTOR) controls protein synthesis, nutrient sensing, cellular growth, and autophagy [15]. Long-term activation of mTOR speeds up aging by reducing autophagy and increasing cellular senescence [16]. Rapamycin and substances that mimic caloric restriction lower mTOR activity, which improves the removal of damaged proteins and organelles through autophagy. [17-18].

2.3.3 Sirtuin Signaling and Mitochondrial Protection

Sirtuins are NAD+-dependent deacetylases that play a role in genomic stability, oxidative stress regulation, and mitochondrial function [20]. Resveratrol, fisetin, and nicotinamide-related compounds activate SIRT1 signaling pathways. This activation improves mitochondrial efficiency and reduces ROS-mediated cellular injury. [21-23].

2.3.4 Cellular Senescence and SASP

Cellular senescence is characterized by an irreversible cell-cycle arrest, along with secretion of pro-inflammatory cytokines, chemokines and proteases collectively termed the senescence-associated secretory phenotype (SASP) [24].
Senescent cells persistently accumulate and have been accountable for the inflammaging, stem cell exhaustion, fibrosis, and organ degeneration [23-25]. Senolytic agents (dasatinib, quercetin, and fisetin) selectively clear senescent cells by targeting their anti-apoptotic survival pathways. [25–27].

2.3.4 Autophagy and Proteostasis

Lysosomal degradation of damaged organelles and dysfunctional proteins contributes to cellular proteostasis. Age-associated autophagy impairment leads to protein aggregation, mitochondrial dysfunction, and neurodegeneration. Spermidine, rapamycin, and caloric restriction enhance autophagic flux and cellular resilience in aging. (28-30)

2.3.5 Oxidative Stress and Nrf2 Pathway

Accumulation of reactive oxygen species (ROS) is one of the key factors contributing to DNA damage, lipid peroxidation and mitochondrial dysfunction throughout aging.
Activation of the Nrf2 antioxidant pathway results in overexpression of cytoprotective enzymes such as superoxide dismutase, catalase and glutathione peroxidase. Astaxanthin, curcumin, quercetin, and sulforaphane have been reported to modulate Nrf2 mediated antioxidant defense systems.(31-35)

3. ANTI-AGING STRATEGIES: CONCEPTS AND SCOPE

Current biomedical research on 'anti-aging' therapies seeks to modulate the biological mechanisms of aging, rather than treating its consequences. These approaches employ computational techniques, drugs, and changes in lifestyle for fighting age-related diseases and slowing down the loss of physical functions [6, 7]. Anti-aging research has evolved into a dynamic and progressive area of study, prioritizing prevention measures and the increase of resilience rather than a primary focus on the treatment of current disorders.

4. NATURAL COMPOUNDS WITH ANTI-AGING ACTIVITY

An increasing number of studies show that naturally occurring substances can increase lifespan by modulating conserved signaling pathways including as insulin/IGF-1, mTOR, AMPK, sirtuins and Nrf2 [6,7,36]. Bioactive compounds such as resveratrol, curcumin, quercetin, spermidine, astaxanthin and urolithins were shown to reduce oxidative stress, induce autophagy and maintain mitochondrial function in several experimental systems.
A comparative review of these substances, their target pathways and their biological effects is shown in Table No.1.

Table 1: Target pathways and their target and geroprotective effects

Drug	Clinical Indication	Primary antiaging targets	Geroprotective effects	Evidence level
Fisetin	Dietary flavonoid	Senolytic signaling, SIRT1 activation, antioxidant pathways	Reduced senescent cell burden, anti-inflammatory effects	Preclinical; early clinical
Spermidine	Nutraceutical/polyamine supplement	Autophagy induction, mitochondrial homeostasis	Cardioprotection, lifespan extension, improved proteostasis	Preclinical and observational
Resveratrol	Nutraceutical	SIRT1 activation, AMPK signaling	Improved mitochondrial function, oxidative	Extensive preclinical

			stress reduction	
GLP-1 receptor agonists	Type 2 diabetes and obesity	Insulin signaling, mitochondrial protection, anti-inflammatory pathways	Neuroprotection, cardiometabolic improvement, reduced inflammaging	Clinical and preclinical
Senolytics (Navitoclax)	Oncology	BCL-2 family inhibition	Selective elimination of senescent cells	Preclinical
NAD+ precursors (NR/NMN)	Metabolic supplementation	NAD+ restoration, sirtuin activation	Enhanced mitochondrial metabolism, DNA repair support	Early clinical and preclinical

5. DRUG REPURPOSING FOR GEROTHERAPY

5.1. Rationale

Drug repurposing employs existing pharmacological information to find new therapeutic uses for existing medications, tackling the challenges of time, cost and safety inherent in traditional drug discovery [8]. Gerotherapy seeks repurposed medicines that can alter molecular pathways that influence aging and thereby increase the healthspan of animals or humans . [8,11].

5.2. Evidence from Preclinical and Clinical Studies

Resources like the Drug REVIEW ARTICLE Age database and the Intervention Testing Program (ITP) have allowed for rigorous investigation of substances for lifespan modification [8,11]. Drugs like metformin, acarbose, rapamycin, beta-blockers, bisphosphonates, and GLP-1 receptor agonists have demonstrated substantial preclinical evidence for modulation of geroprotective pathways and improved outcomes in age-related disorders.

5.3. Senolytics and Senomorphics in Anti-Aging Therapy

Cellular senescence is a hallmark of aging and is defined as an irreversible cell-cycle arrest linked with the release of pro-inflammatory molecules, the senescence-associated secretory phenotype (SASP) [13,36]. Accumulation of senescent cells leads to persistent inflammation, tissue malfunction, stem cell exhaustion, and progression of age-related illnesses such as dementia, cardiovascular disease, osteoarthritis and metabolic dysfunction [27 and 38]. Therefore, senolytics and senomorphics have been recognized as potential therapeutic interventions for slowing biological aging and increasing healthspan. Senolytics are drugs that preferentially kill senescent cells by targeting pro-survival signaling pathways, whereas senomorphics reduce the detrimental SASP without triggering the death of senescent cells [28]. Several naturally occurring and repurposed chemicals have shown senolytic promise in experimental aging models. Among these, dasatinib with quercetin (D+Q), is one of the most studied senolytic combos, with reductions in senescent cell load and improvements in physical function in preclinical investigations [28,29]. Fisetin is a further naturally occurring flavonoid that showed substantial senotherapeutic efficacy by modulating oxidative stress, inflammatory signaling, and apoptosis-related pathways [38]. Differential effects on cellular senescence-associated signaling pathways have also been seen with navitoclax, rapamycin, metformin, and piperlongumine [39-41]. Senolytics primarily target anti-apoptotic survival networks, including BCL-2 family members, PI3K/AKT, p53/p21, and FOXO-mediated stress responses [27,29]. Persistent senescent cells resist apoptosis by activating senescent cell anti-apoptotic pathways (SCAPs) contributing to tissue deterioration and chronic low-grade inflammation described as "inflammaging" [26,38]. Removal of these defective cells can improve mitochondrial function, reduce release of inflammatory cytokines, restore regenerative capacity of stem cells and improve tissue homeostasis[28,37].

Recent breakthroughs in computational biology and artificial intelligence (AI) have sped the identification of novel senolytic drugs by transcriptome signature matching, molecular docking, network pharmacology and machine learning-assisted screening techniques. AI-enabled computational models may efficiently analyze multi-omics datasets to uncover molecular signatures associated with senescence and prioritize prospective senotherapeutics above conventional drug development methodologies [41]. Moreover, network-based pharmacology platforms can identify hub genes and signaling pathways implicated in cellular aging, which can aid in the creation of precision senotherapeutics targeting certain aging phenotypes [42,43].

6. Computational and AI-Based Strategies for Drug Repurposing

6.1. Network-Based and Systems Biology Approaches

Network medicine models aging as a failure of the biological networks that sustain cellular function. By mapping gene–disease–drug interactions, researchers can identify molecular “hubs” that serve as promising intervention points [9,12]. Protein–protein interaction (PPI) networks, along with pathway enrichment analyses, improve the functional grouping of genes linked to longevity. This, in turn, aids in the computational identification of potential candidates for repurposing, with the goal of promoting longevity.

6.2. Artificial Intelligence Approaches

Artificial intelligence has transformed biomedical research by quickly analyzing large and heterogeneous datasets. Machine learning (ML) and deep learning (DL) methods exploit multi-omics, phenotypic, and clinical data to discover

novel associations between medications and aging pathways [9,10]. These methods enhance the accuracy of drug target predictions, disease modeling, and compound prioritization, thereby accelerating the identification of new gerotherapeutic candidates.

6.3. Artificial Intelligence Tools and Computational Platforms in Geroscience

Artificial intelligence (AI)-based computational platforms have revolutionized geroscience by allowing integration, interpretation and analysis of large-scale biological datasets generated from genomics, transcriptomics, proteomics, metabolomics and clinical phenotypes, leading to accelerated identification of candidate geroprotective compounds and therapeutic targets associated with aging and longevity [41,44,45]. Molecular markers of aging, prioritization of therapeutic targets and prediction of drug-target interactions and computational drug repurposing are widely investigated using machine learning (ML), deep learning (DL) and network-based techniques [44,46]. These computational approaches have greatly contributed to the identification of candidate molecules modulating key longevity-associated pathways, such as AMPK, mTOR, SIRT1, FOXO, insulin/IGF-1 signaling, and autophagy, which control cellular metabolism, stress responses, and lifespan [46,48].

Among the available computational resources, network pharmacology platforms like STRING and Cytoscape are extremely useful for building protein-protein interaction (PPI) networks, discovering hub genes and visualizing complex signaling pathways involved in cellular senescence, mitochondrial dysfunction, oxidative stress, chronic inflammation and other hallmarks of aging [47–49]. These platforms offer important systems-level insights into aging biology, but are largely tools for biological interpretation and network analysis, rather than direct prediction of therapy efficacy. In contrast, transcriptomics-based platforms, such as the LINCS Connectivity Map (CMap), leverage disease-associated gene-expression signatures to compare with drug-induced transcriptional profiles, in an effort to identify compounds that can reverse aging-related molecular perturbations, and are thus highly valuable for AI-assisted drug repurposing [50,53,54]. Similarly, AlphaFold has transformed structure-based drug discovery by using deep learning to predict extremely accurate three-dimensional conformations of proteins, which in turn improves molecular docking, target identification, and rational drug design of longevity-associated proteins [51,55].

These computing platforms are remarkably capable, yet they have complementary rather than overlapping qualities. While AlphaFold is an excellent tool in structural biology for its ability to predict protein structures with high accuracy in target-based drug discovery, the LINCS Connectivity Map is one of the most powerful resources in transcriptomics-driven drug repurposing as it links disease-specific molecular signatures directly with candidate therapeutic compounds. In contrast, STRING and Cytoscape are still important systems pharmacology tools to find interaction networks and prioritize potential genes, but they do not predict clinical efficacy, biological age or lifetime extension on their own. Moreover, computational predictions obtained by these platforms are still constrained by cell-type specificity, limited biological datasets, false-positive network linkages, and lack of experimental or clinical validation. Thus, no single computer platform can forecast longevity in its entirety, nor can it discover universally successful gerotherapeutic therapies.

Thus, for future breakthroughs in AI-driven geroscience, it will be necessary to combine complementary computational platforms with multi-omics datasets, explainable artificial intelligence (XAI), digital twin technologies, longitudinal clinical cohorts and validated indicators of biological aging. Such an integrated computational ecosystem is expected to enhance model interpretability, increase prediction accuracy, support personalized therapeutic decision-making, and ultimately provide the basis for precision gerotherapy where individualized anti-aging interventions can be designed according to patient-specific molecular and biological aging profiles [41,44–46,52,56–60].

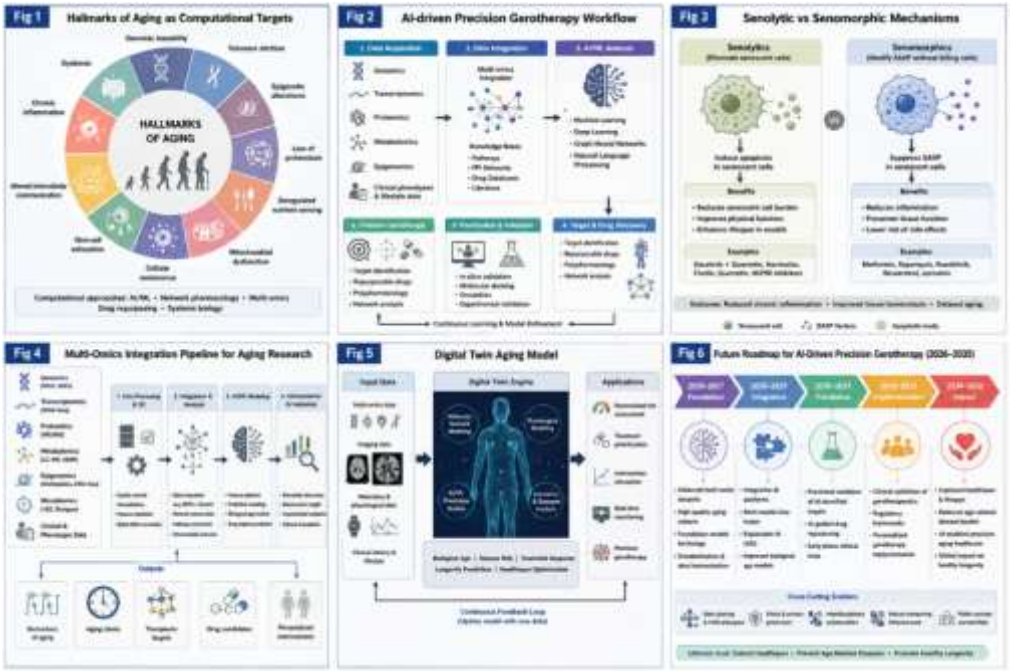
Table 2. Representative AI and Computational Tools Used in Anti-Aging Drug Discovery

Tool/Platform	Primary Application	Biological Data Used	Major Contribution
DeepAge	Biological age prediction	Transcriptomics, DNA methylation	Aging biomarker prediction
DrugAge	Geroprotective compound database	Lifespan experimental data	Drug prioritization
LINCS Connectivity Map	Signature matching	Gene expression profiles	Drug repurposing
STRING	Protein–protein interaction analysis	Proteomics	Network construction
Cytoscape	Network visualization and hub gene analysis	Multi-omics	Pathway identification
AlphaFold	Protein structure prediction	Amino acid sequences	Target interaction modeling
DeepPurpose	Drug–target interaction prediction	Chemical and genomic data	AI-driven screening
GeneMANIA	Functional gene association	Gene expression and interaction data	Gene prioritization

Table 3 : Comparative Evaluation of Computational Platforms in Geroscience

Platform	Primary Function	AI-Based	Application	Clinical Validation	False-Positive Risk	Suitability for Drug Repurposing

AlphaFold	Protein structure prediction	Yes (Deep Learning)	Protein structure determination, target identification, molecular docking	Indirectly validated through many experimentally confirmed protein structures, but not as a clinical decision tool	Low–Moderate (higher for intrinsically disordered proteins and protein complexes)	High
LINCS Connectivity Map (CMap)	Gene-expression signature matching	Uses AI/ML and statistical models	Drug repurposing, transcriptomic reversal, mechanism-of-action studies	Moderate (widely used in preclinical studies; few direct clinical validations)	Moderate–High (cell-line dependence and batch effects)	Very High
STRING	Protein–protein interaction analysis	No (knowledge-based with predictive scoring)	Identification of disease pathways and hub proteins	Indirect (supported by experimental and curated databases)	Moderate (predicted interactions may not occur in specific biological contexts)	Moderate–High
Cytoscape	Network visualization and analysis	No	Integration of omics data, hub-gene analysis, pathway visualization	Not applicable	Depends on input data rather than the software	Moderate



(This figure was created with the assistance of a generative AI tool and reviewed and verified by the authors)

7. DISCUSSION

The field of geroscience has evolved from descriptive studies of aging to a mechanistic and intervention-driven discipline, with drug repurposing emerging as a promising strategy. Traditional drug discovery is associated with high costs, protracted timelines and high attrition rates. Instead, drug repurposing makes use of existing safety and pharmacological data, drastically shortening the time required to uncover molecules with new therapeutic value. Conversely, medication repositioning harnesses current knowledge of safety and pharmacology in order to speed up the process of discovering compounds with innovative therapeutic applications. Such an approach has the potential to transform the discipline,

allowing researchers to test and confirm therapies against aging at an unparalleled speed and precision, especially when paired with contemporary computational and artificial intelligence capabilities.

The integration of systems biology, bioinformatics and machine learning (ML) has demonstrated the presence of complex biochemical links between aging pathways and druggable targets. AI systems can spot hidden connections between genes, pathways and medications by analyzing vast amounts of genomic, transcriptomic, metabolomic and proteomic data. Network-based models describe the interaction of proteins and genes to diseases. This allows us to identify hub molecules that control our life-span. These approaches enable logical compound ranking, interaction prediction and systematic study of naturally occurring or authorized medicines never shown to have geroprotective properties.

However, despite the rapid appreciation of computational advances, significant scientific and translational restrictions still exist. The study of aging is made difficult by the biological variability of model species, cell types, and individuals, sometimes making results inapplicable to human biology. In addition, the absence of validated biomarkers of aging hampers the correct assessment of intervention efficacy. Public repositories can include missing data or bias, which can make AI models less credible. This can lead to overfitting and spurious correlation. Good data curation, model interpretability and multi-omics validation are important to build reliable computational repurposing pathways for drug development.

Researchers encounter distinct problems in the ethical and therapeutic application of anti-aging medicines. Gerotherapeutics, which aim to modulate normal physiological processes rather than to cure disease, are faced with regulatory challenges and challenges in determining long-term safety. The changing demographics of the world to an aging population needs that the development of scientific knowledge be accompanied by the development of ethical norms, especially with respect to fair access and the impact on different groups in society.

However, the integration of artificial intelligence, network pharmacology, and molecular geroscience holds great promise. With more abundant biological data and improved analytical models, the precision gerotherapy based on individual aging trajectory is getting more feasible.

Future research should be directed on collaborative research infrastructure that incorporates computer scientists, molecular biologists and clinicians that will allow the translation of predictive algorithms into therapeutic outcomes.

8. CONCLUSION

The combination of molecular biology of aging and artificial intelligence is a giant leap forward in the search and development of therapies against the effects of aging. Computational drug repurposing provides an efficient data-driven approach to identify existing drugs and natural compounds that may modulate key lifespan-regulating pathways such as AMPK, mTOR and SIRT1. The combination of systems biology, deep learning and network modeling allows scientists to predict drug-target interactions that they could not have predicted with standard experimental methods.

The most crucial new idea for the future will be the integration of AI-driven multi-omics analysis with translational clinical research to discover safe, ethical, and successful approaches to assist people age. Scientists from molecular biology, computational science, pharmacology and biostatistics will need to collaborate to transform prediction models into real-life clinical situations.

Ultimately, computational repurposing is a revolution in both technology and concept for geroscience. It changes the focus from curing age-related disorders to actually managing aging. These new tools, developed through ongoing collaboration across different fields, have the potential to transform the quest for longer life from a general goal into a precisely designed way to extend healthy years.

ACKNOWLEDGEMENTS

The authors declare no acknowledgements

FUNDING

The authors declare no funding

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Naveen Kumaran V G

A collection of data from research and review articles is then arranged according to the review article formatting

Anand Babu K

Arranged review articles are checked for formatting, grammar, and plagiarism checking, then finalised for publication.

Naveen Kumar N

Check the manuscript for AI percentage.

Mageswaran J, Dhatchinamoorthy B, Priyadharshini S, Thoshan Kumar E V, Karthick P, Meenakshi Sundharam R

All of the above-listed authors contributed equally to the preparation of each subtype in this work.

REFERENCES

1. Rose, M.R., 1991. Evolutionary Biology of Aging. Oxford University Press, New York.
2. Comfort, A., 1979. The Biology of Senescence, 3rd ed. Churchill Livingstone, Edinburgh.

3. Arking, R., 1999. Biology of Aging: Observations and Principles, 2nd ed. Sinauer Associates, Sunderland.
4. Cannon, M.L., 2015. Ageing and disease. Disease-a-Month 61(11), 454–459.
5. Li, Y., Tian, X., Luo, J., Bao, T., Wang, S., Wu, X., 2024. Molecular mechanisms of aging and anti-aging strategies. Cell Communication and Signaling 22, 285.
6. 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, 408–446.
7. Liu, J.K., 2022. Antiaging agents: safe interventions to slow aging and healthy lifespan extension. Aging 12(1), 18.
8. Kulkarni, A.S., Aleksic, S., Berger, D.M., Sierra, F., Kuchel, G.A., Barzilai, N., 2022. Geroscience-guided repurposing of FDA-approved drugs to target ageing. Aging Cell 21(4), e13596.
9. Muniyappan, S., Rayan, A.X.A., Varrieth, G.T., 2024. DRADTiP: Drug repurposing for aging disease through drug–target interaction prediction. Computers in Biology and Medicine 182, 107093.
10. Keramida, P., Syrigos, N.K., Kouvela, M., Poulakou, G., Charpidou, A., Fiste, O., 2025. AI-driven drug repurposing: applications and challenges. Medicines 12(4), 28.
11. Leone, M., Barzilai, N., 2024. An updated prioritisation of geroscience-guided FDA-approved drugs repurposed to target ageing. European Journal of Medicine.
12. Donertas, H.M., Fuentealba-Valenzuela, M., Partridge, L., Thornton, J.M., 2018. Gene expression-based drug repurposing to target aging. Aging Cell 17(5), e12819.
13. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153(6):1194–1217.
14. López-Otín C, Kroemer G. Hallmarks of health. Cell. 2021;184(1):33–63.
15. Campisi J, Kapahi P, Lithgow GJ, et al. From discoveries in ageing research to therapeutics for healthy ageing. Nature. 2019;571:183–192.
16. Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. Nat Rev Mol Cell Biol. 2018;19:121–135.
17. Salminen A, Kaarniranta K, Kauppinen A. AMPK and HIF signaling pathways regulate both longevity and cancer growth. Cell Signal. 2016;28:561–572.
18. Garcia D, Shaw RJ. AMPK: mechanisms of cellular energy sensing and restoration of metabolic balance. Mol Cell. 2017;66:789–800.
19. Kulkarni SS, Cantó C. The molecular targets of resveratrol. Biochim Biophys Acta. 2015;1852:1114–1123.
20. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017;168:960–976.
21. Papadopoli D, Boulay K, Kazak L, et al. mTOR as a central regulator of lifespan and aging. F1000Res. 2019;8 Faculty Rev-998.
22. Blagosklonny MV. Rapamycin for longevity: opinion article. Aging. 2019;11:8048–8067.
23. Bonkowski MS, Sinclair DA. Slowing ageing by design: the rise of NAD+ and sirtuin-activating compounds. Nat Rev Mol Cell Biol. 2016;17:679–690.
24. Imai SI, Guarente L. It takes two to tango: NAD+ and sirtuins in aging/longevity control. NPJ Aging Mech Dis. 2016;2:16017.
25. Hubbard BP, Sinclair DA. Small molecule SIRT1 activators for the treatment of aging and age-related diseases. Trends Pharmacol Sci. 2014;35:146–154.
26. Childs BG, Durik M, Baker DJ, van Deursen JM. Cellular senescence in aging and age-related disease. Nat Med. 2015;21:1424–1435.
27. Kirkland JL, Tchkonia T. Cellular senescence: a translational perspective. EBioMedicine. 2017;21:21–28.
28. Zhu Y, Tchkonia T, Pirtskhalava T, et al. The Achilles' heel of senescent cells. Aging Cell. 2015;14:644–658.
29. Yousefzadeh MJ, Zhu Y, McGowan SJ, et al. Fisetin is a senotherapeutic that extends health and lifespan. EBioMedicine. 2018;36:18–28.
30. Levine B, Kroemer G. Biological functions of autophagy genes. Cell. 2019;176:11–42.
31. Hansen M, Rubinsztein DC, Walker DW. Autophagy as a promoter of longevity. Nat Rev Mol Cell Biol. 2018;19:579–593.
32. Eisenberg T, Abdellatif M, Schroeder S, et al. Cardioprotection and lifespan extension by spermidine. Nat Med. 2016;22:1428–1438.
33. Sies H, Jones DP. Reactive oxygen species and oxidative stress. Redox Biol. 2020;32:101471.
34. Tonelli C, Chio IIC, Tuveson DA. Transcriptional regulation by Nrf2. Antioxid Redox Signal. 2018;29:1727–1745.
35. Kasai S, Shimizu S, Tatara Y, et al. Regulation of Nrf2 by natural compounds in age-re-related diseases. Molecules. 2021;26:4597.
36. Campisi J. Aging, cellular senescence, and cancer. Annu Rev Physiol. 2013;75:685–705.
37. Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. J Intern Med. 2020;288(5):518–536.
38. Yosef R, Pilpel N, Tokarsky-Amiel R, et al. Directed elimination of senescent cells by inhibition of BCL-W and BCL-XL. Nat Commun. 2016;7:11190.
39. Correia-Melo C, Passos JF. Mitochondria: are they causal players in cellular senescence? Biochim Biophys Acta. 2015;1847:1373–1379.
40. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. Cell Metab. 2020;32(1):15–30.
41. Zhavoronkov A, Mamoshina P, Vanhaelen Q, et al. Artificial intelligence for aging and longevity research. Ageing Res Rev. 2019;49:49–66.

42. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019;18:41–58.
43. Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011;12:56–68.
44. Moskalev A, Aliper A, Smit-McBride Z, et al. Genetics and epigenetics of aging and longevity. Cell Cycle. 2014;13(7):1063–1077.
45. Claesson K, Hansen M. The hallmarks of aging and current strategies to counteract them. Exp Gerontol. 2022;167:111926.
46. Barzilai N, Cuervo AM, Austad S. Aging as a biological target for prevention and therapy. JAMA. 2018;320(13):1321–1322.
47. López-Otín C, Kroemer G. Hallmarks of health. Cell. 2021;184(1):33–63.
48. Szklarczyk D, Gable AL, Lyon D, et al. STRING v11: protein–protein association networks with increased coverage. Nucleic Acids Res. 2019;47:D607–D613.
49. Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for integrated biomolecular interaction networks. Genome Res. 2003;13:2498–2504
50. Subramanian A, Narayan R, Corsello SM, et al. A next-generation Connectivity Map. Cell. 2017;171(6):1437–1452.
51. Jumper J, Evans R, Pritzel A, et al. Highly accurate protein structure prediction with AlphaFold. Nature. 2021;596:583–589.
52. Pyrkov TV, Avchaciov K, Tarkhov AE, et al. Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit. Nat Commun. 2021;12:2765.
53. Varadi M, Anyango S, Deshpande M, Nair S, Natassia C, Yordanova G, et al. AlphaFold Protein Structure Database: massively expanding the structural coverage of protein-sequence space with high-accuracy models. Nucleic Acids Res. 2022;50(D1):D439–D444.
54. Musa A, Ghoraie LS, Zhang SD, Galzko G, Yli-Harja O, Dehmer M, et al. A review of connectivity map and computational approaches in pharmacogenomics. Brief Bioinform. 2018;19(3):506–523.
55. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein–protein association networks and functional enrichment analyses. Nucleic Acids Res. 2023;51(D1):D638–D646.
56. Paul D, Sanap G, Shenoy S, Kalyane D, Kalia K, Tekade RK. Artificial intelligence in drug discovery and development. Drug Discov Today. 2021;26(1):80–93.